One step forward: Successful end-of-treatment outcomes of drug-resistant TB patients who received concomitant bedaquiline and delamanid in Mumbai, India

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Summary: Concomitant use of Bedaquiline and Delamanid for ambulatory treatment of drug-resistant tuberculosis patients beyond 24 weeks has been found safe, feasible and successful in TB programme run by Médecins Sans Frontières in Mumbai, India.

Abstract

Background

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 programme data. In clinic, treatment regimens are designed based on culture-drug sensitivity test patterns, previous drug-exposures and are provided for 20-22 months. The 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 February2016-February2018 were included.

Result

Of the 70 patients included, the median (IQR) age was 25(22-32) years and 56% were females. All except one were fluoroquinolone resistant. The median(IQR) duration of exposure to BDQ and DLM was 77(43-96) weeks. Thirty-nine episodes of serious-adverse-events(SAEs) were reported among 30(43%) patients, including five instances of QTc prolongation-assessed as possibly related to BDQ and/or DLM. 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.

Conclusion

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

Keywords: all-oral regimen; aDSM; CDST; carbapenem; XDR-TB

INTRODUCTION

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

Bedaquiline (BDQ) and Delamanid (DLM)- are two new drugs recommended for treatment of drug-resistant tuberculosis (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 on-going [12,13], however the interim outcomes of DELIBERATE (NCT02583048) trial 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 for DR-TB including BDQ and DLM [14–17]. However, studies reporting end-of-treatment outcomes including adverse events are still limited. In addition, patients are usually offered DR-TB regimen including BDQ and DLM for 24 weeks, however, in some circumstances the removal of BDQ and DLM may lead to a sub-optimal regimen. Though the safety of using BDQ beyond 24 weeks has been highlighted in the recent WHO consolidated DR-TB guidelines-2019, 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 more than 24 weeks[19].

Médecins Sans Frontières (MSF) has been providing treatment for patients with DR-TB (Pre-extensively drug resistant TB-PreXDR-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 (including QTcF>500ms) during DR-TB treatment including BDQ and DLM. The study also analysed treatment outcomes and SAEs in the subgroup of patients who received BDQ and DLM for more than 24 weeks. We believe this 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 is 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 10621 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 (NTEP) has updated its guidelines in line with WHO recommendations, to include BDQ among Group A drugs, to be used for all patients with DRTB; and DLM to Group C, recommended when an effective regimen cannot be designed with only drugs from group A and B [22,25]. The concomitant administration of BDQ and DLM in DR-TB treatment regimen is carried out in selected healthcare institutions on compassionate grounds for patients among whom four-drug effective treatment regimen cannot be prepared with Group A and B drugs [16,25,26].

The Médecins Sans Frontières (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 enrolment in MSF clinic, patients already have complex TB disease with advanced TB drug resistance. Majority of them are exposed to the second and third line TB drugs and have only one-two 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 assay (LPA), and culture- drug susceptibility testing (C-DST). If these evaluations were carried out three months prior to referral, then they are accepted for treatment preparation. Chest X-rays are done if requested by the pulmonologist. Treatment regimens are individualised 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 complete their treatment successfully.

Individualised 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 (group of clinicians including pulmonologists and infectious diseases specialists) before treatment initiation. The extended use of BDQ and DLM beyond 24 weeks are based on 'WHO guidelines for off-label of Bedaquiline and Delamanid for DR-TB treatment' [6] and other international guidelines [30]. The criteria for extended use of new TB drugs beyond 24 weeks are: i) lack of four effective TB drugs (without new TB drugs) to form an effective regimen; ii) lack of culture conversion at the end of month three; iii) non-improvement of clinical condition of patient (persistent symptoms, no weight gain, chest X-ray abnormalities etc.), as assessed by doctors committee.

Monitoring consists of regular clinical follow up, sputum culture, blood analysis including liver and renal functions and other recommended tests. When the treatment is initiated, the clinical and laboratory follow up [including electrocardiogram (ECG) monitoring for assessing cardio-toxicity] is carried out every two weeks for first three months. After three months or once the patient is comfortable with the treatment, whichever is later, monthly routine clinical and laboratory (haematological, culture, biochemistry, ECG) follow-ups are carried out. The QTcF 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 feel any adverse event. All adverse event episodes are clinically managed in a step-wise manner - first managed symptomatically; later, if required, lowering the dose; followed by intermittent stopping of the likely associated drug. Serious adverse events (SAE) (following international guidelines [30]) are recorded by clinical team. The grading of SAE 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 MSF Pharmacovigilance (PV) unit based in Geneva, Switzerland. The PV team reviews the categorisation 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 four weeks during treatment) in the MSF Clinic during February 2016-February 2018 were included in the study. All patients had end of treatment outcome by November 2019.

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

Operational definitions:

1. **DR-TB Resistance profiles:** Standard definitions of pre-extensively drug-resistant tuberculosis (Pre-XDR TB) and; extensively drug-resistant tuberculosis (XDR-TB) was used [30].
2. **Serious adverse event (SAE):** Any untoward medical occurrence, regardless of its cause (including TB-related events), leading to patient's death, life-threatening experience, hospitalisation or prolongation of hospitalisation, significant disability/incapacity, congenital anomaly or any other situation requiring a significant intervention (qualified as 'medically important') [30]. In our study, SAE notably included Grade 3, Grade 4 adverse events and any other life threatening event [31].
3. **Cardio toxicity (Prolonged QTc):** i) Grade 3 prolonged QTc include average QTcF ≥ 501 ms without signs/symptoms of serious arrhythmia. ii) Grade 4 prolonged QTc include average QTcF ≥ 501 ms and one 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, HIV status, 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 end-of-treatment outcome were collected. The selected data from patient files and MSF TB programme databases (electronic medical records: Bahmni [32]) were exported into and analysed using STATA (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 summarise the analytic output (treatment outcomes, episodes of SAEs). Kaplan Meier curve was used to describe the culture progression over time.

Ethics

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 (IQR) age was 25 (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-co-infected. The median (IQR) body mass index (BMI) was 17.2 (15.2-19.6)kg/m^2. Most patients were resistant to fluoroquinolone (Pre-XDR TB=27 and XDR-TB=42). All had a history of previous episode of TB, and 64 (91%) had previously received one or more episodes of DR-TB treatment (12=only DR-TB treatment; 52=both DS-TB and DR-TB treatment). The median (IQR) duration of previous TB treatments (all episodes combined) for patients (n=19) was 84 (40-116) weeks. All the patients had resistance to Rifampicin and Isoniazid (Figure 1). More than 90% patients had additional resistance to Ethambutol, Streptomycin and Ofloxacin. The resistance to Clofazamine 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 majority of the patients received Clofazamine and Linezolid (94% and 76% respectively) in their treatment regimens. About 59% patients received Imipenem and Amoxicillin/Clavunate during DR-TB treatment. The most common four drugs in treatment regimen (in 71% of patients) were BDQ, DLM, Clofazamine and Linezolid administered along with other TB drugs (Amoxicillin/Clavunate and Imipenem, Moxifloxacin etc.). The doses of these drugs were: a) BDQ= for week 1-2: 400mg daily and week 3 onwards: 200 mg day dose (100 mg twice a day) three times per week. b) DLM= 200mg/day, c)

Clofazamine= 100mg/day, d) Linezolid= 600mg/day. The median duration of treatment was 77 (IQR: 43-96) weeks (Table 1). The median (IQR) exposure to individual BDQ, individual DLM, and concomitant use of BDQ and DLM was 77 (42-88) weeks, 92 (70-97) weeks and 76 (42-87) weeks respectively.

Serious adverse events

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

Culture conversion

Majority (69%, 22 of 32) patients with positive culture at baseline had culture conversion before 24 weeks. The median (IQR) time for culture conversion was 9 (7-16) weeks. Figure 3 shows the Kaplan Meier curve of time to culture conversion after treatment initiation in patients (n=32).

End-of-treatment outcome

The end-of-treatment outcome was successful for 49 (70% of 70) (Table 3). Thirty-eight patients were cured while 11 completed the treatment. Among the rest, 13 (19%) died, three (4%) were lost to follow up (LTFU) and five (7%) failed treatment. Of the 32 patients who were culture positive at baseline, the patients who had culture conversion by month two (n=14) and by month four (n=20); 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 longer than 24 weeks (Table 3). Among the remaining nine patients, the treatment was stopped before 24 weeks because of death (7/9) or patients being loss to follow-up (2/9). Of 39 SAE episodes, 12 (31%) episodes (in 10 patients) occurred after 24 weeks of treatment (non-tabulated).

DISCUSSION

Our study describes one of the largest global cohorts of patients with difficult to treat drug-resistant TB who received regimens including Bedaquiline (BDQ) and Delamanid (DLM) for more than 24 weeks. To our knowledge, this is also among the first studies in India to report end-of-treatment outcomes in patients treated with extended combined use of BDQ and DLM. Sixty-one (87%) patients received BDQ and DLM for more than 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 MSF Clinic in Mumbai [15]; we believe our study reporting end-of-treatment 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).

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 standard TB treatment package [29].

The safety and/or effectiveness of extended use of BDQ and DLM (individual or concomitant) beyond 24 weeks has been documented in previous studies [14,16,19]. In light of our study results and recent evidences [11,18], the national TB programmes should consider all oral regimen including extended use of BDQ and DLM beyond 24 weeks for the patients with complex TB resistance profiles to design an effective four 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 the cohort (43% of 70) experienced one 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 prolongation were reported and assessed as possibly related to BDQ and DLM. Among patients who received BDQ and DLM for longer than 24 weeks, 16% (10 of 61) experienced any SAE after the first 24 weeks of treatment. Though, our study reports 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 those reported in a recent systematic review on combined use of BDQ and DLM in DR-TB treatment and interim results of DELIBERATE clinical trial (16% vs

26% vs 26%) [13,14]. Thus, the SAE results in our study are encouraging for concomitant administration of BDQ and DLM in DR-TB patients.

The culture conversion rate at 24 weeks for the study cohort was 69% (22 of 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 conversion rates[36]. Among patients who had positive culture at baseline, majority of the patients who had culture conversion by month two (64%) and month four (70%) had successful end-of-treatment outcomes. Therefore, culture conversion at months two and four may be considered a proxy for end-of-treatment outcome for patients receiving concomitant BDQ and DLM [37] . Patients who had culture conversion before six months continued extended BDQ and DLM, since only two out of three 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 regimen including concomitant use of BDQ and DLM.

Majority of patients (seven in ten) had successful end of treatment outcome, among whom three-fourth were cured. The study results are encouraging considering that these patients were extremely difficult to treat and poor treatment outcomes have been reported among Pre-XDR-TB or XDR-TB patients 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 MSF Clinic. We believe 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 programme will minimise 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 known DR-TB hotspot with evidence of complex TB resistance profiles. Thus, the results will help in contributing towards evidence for similar DR-TB patients in need for combined administration of BDQ and DLM in their treatment regimen.

The study has following limitations. We document a resource intensive TB programme with individualised care offered to patients that would need additional resource allocation for national TB programmes to replicate. However, we believe individualised 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 more than 24 weeks during DR-TB treatment in routine programme settings. We also believe the findings cannot be generalised 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 one 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 profile show that regimens including concomitant use of BDQ and DLM are effective and extended use beyond 24 weeks is safe and well tolerated. More studies including DR-TB patients receiving BDQ and DLM (including patients co-infected with HIV) will help in adding the evidence around use of new TB drugs. We strongly recommend National TB programmes to 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.

Author contributions

MD, AD, CL, GF, and PI conceived and designed the study. FM, RP, TM, HM and ACM provided clinical services and PS, SR, NL, SC, SK and FNH collaborated in the implementation of clinical activities. MD, SR and ACM collected and analysed the study data. MD, CL, AD, GF and PI interpreted the results and drafted the manuscript. All the authors have contributed in revisions of the manuscript and approved the final manuscript.

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Conflict of interests

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Table 1. Demographic and clinical characteristics of patients with DR-TB who received treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019

Characteristic	Number	Percentage
Total	**70**	**(100)**
Age group (in years)		
13-17	2	(3)
18-24	29	(41)
25-34	25	(36)
35-44	6	(9)
45 and above	8	(11)
Sex		
Male	31	(44)
Female	39	(56)
HIV status		
Positive	1	(1)
Negative	69	(99)
Baseline BMI (Median, IQR, kg/m^2)	17.2 (15.2-19.6)	
TB site		
Pulmonary	61	(87)
Extra-pulmonary	9	(13)
Culture at baseline		
Positive	32	(46)
Negative	38	(54)
TB resistance profile		
Pre-XDR TB*	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) (Median, IQR, weeks) (n=19)	84 (40-116)	

Treatment duration (Median, IQR, weeks)	
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)

BMI: Body mass index (weight in kilograms divided by the square of the height in meters); *Pre-XDR TB: Pre-extensively resistant TB (27=Rifampicin+Isoniazid+fluoroquinolone resistant; 1=Rifampicin+Isoniazid+second line injectable resistant); XDR-TB: Extensively resistant TB; DS-TB: Drug susceptible TB; DR-TB: Drug-resistant TB; BDQ- Bedaquiline, DLM- Delamanid

Table 2. Serious adverse events among patients with DR-TB who received treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019

SAE including Grade 3 and 4 (n=episodes)	Categories	Number of episodes/ patients	Likely associated with only BDQ/DLM*	Likely associated other with TB drug(s)*
Grade 4 (n=28)	QTc prolongation	3/3	2- BDQ & DLM 1- DLM	-
	Death due to disease progression	8/8	-	-
	Cardio-pulmonary/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
	Anaemia	1/1	-	Imp, Lzd
	Haemoptysis	1/1	-	-
	Increase in Lipase/Transaminase	2/1	1- BDQ & DLM	-
Total episodes		**39**		

Grading of Adverse event (Based on Division of AIDS-Table for Grading the Severity of Adult and Pediatric Adverse Events): SAE: Serious Adverse Events reported in this cohort include Grade 3 and Grade 4. 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; BDQ- Bedaquiline; DLM- Delamanid; ; Ethio- Ethionamide; Lzd- Linezolid;; Cs- Cycloserine; Imp- Imipenem;; *The adverse events mentioned as '-' were not associated with BDQ, DLM or other TB drug(s) but due to advanced diseased condition of the patient .

Table 3. End-of-treatment outcomes of patients with DR-TB who received treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019, N=70

End-of-treatment outcome	Patients who received BDQ and DLM (concomitant) for any duration		Patients who received BDQ and DLM (concomitant) for less or equal to 24 weeks		Patients who received BDQ and DLM (concomitant) more than 24 weeks	
	Number	**(%)**	**Number**	**(%)**	**Number**	**(%)**
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)
Lost to follow up	3	(4)	2	(22)	1	(1)
Failed	5	(7)	-		5	(8)

Figure Legends

Figure 1. Proportion of patients with resistance to TB drugs at baseline among those who received DR-TB treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019, N=70

Proportion of patients with resistance to TB drugs at baseline among DR-TB patients who received treatment including concomitant Bedaquiline and Delamanid from February 2016 to November 2019 in MSF Clinic, Mumbai, India

Figure 2. Distribution of median QTcF (IQR) measurements during treatment in patients with DR-TB who received treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019, N=70

Months	0	1	2	3	4	5	6	7	8	9	10	11	12
N	70	68	65	58	57	58	54	51	50	53	48	42	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)

Figure 3. Culture positive probability in patients with DR-TB (culture positive at baseline) who received treatment including concomitant Bedaquiline and Delamanid in MSF Clinic, Mumbai, India, February 2016- November 2019, N=32

Proportion of patients with positive sputum culture over time among DR-TB patients who received treatment including concomitant Bedaquiline and Delamanid from February 2016 to November 2019 in MSF Clinic, Mumbai, India

Weeks from treatment initiation (Interval)	Number of patients at risk (n)	Proportion remaining culture positive (%)	95% Confidence Interval
0	32	-	-
4-5	32	0.97	(0.80-0.99)
8-9	24	0.62	(0.43-0.76)
12-13	15	0.49	(0.30-0.65)
16-17	12	0.38	(0.21-0.54)
21-22	6	0.24	(0.10-0.42)
26-27	5	0.20	(0.07-0.37)
32-33	4	0.15	(0.04-0.32)
46-47	2	0.10	(0.02-0.26)
58-59	1	0.10	(0.02-0.26)

Figure_1

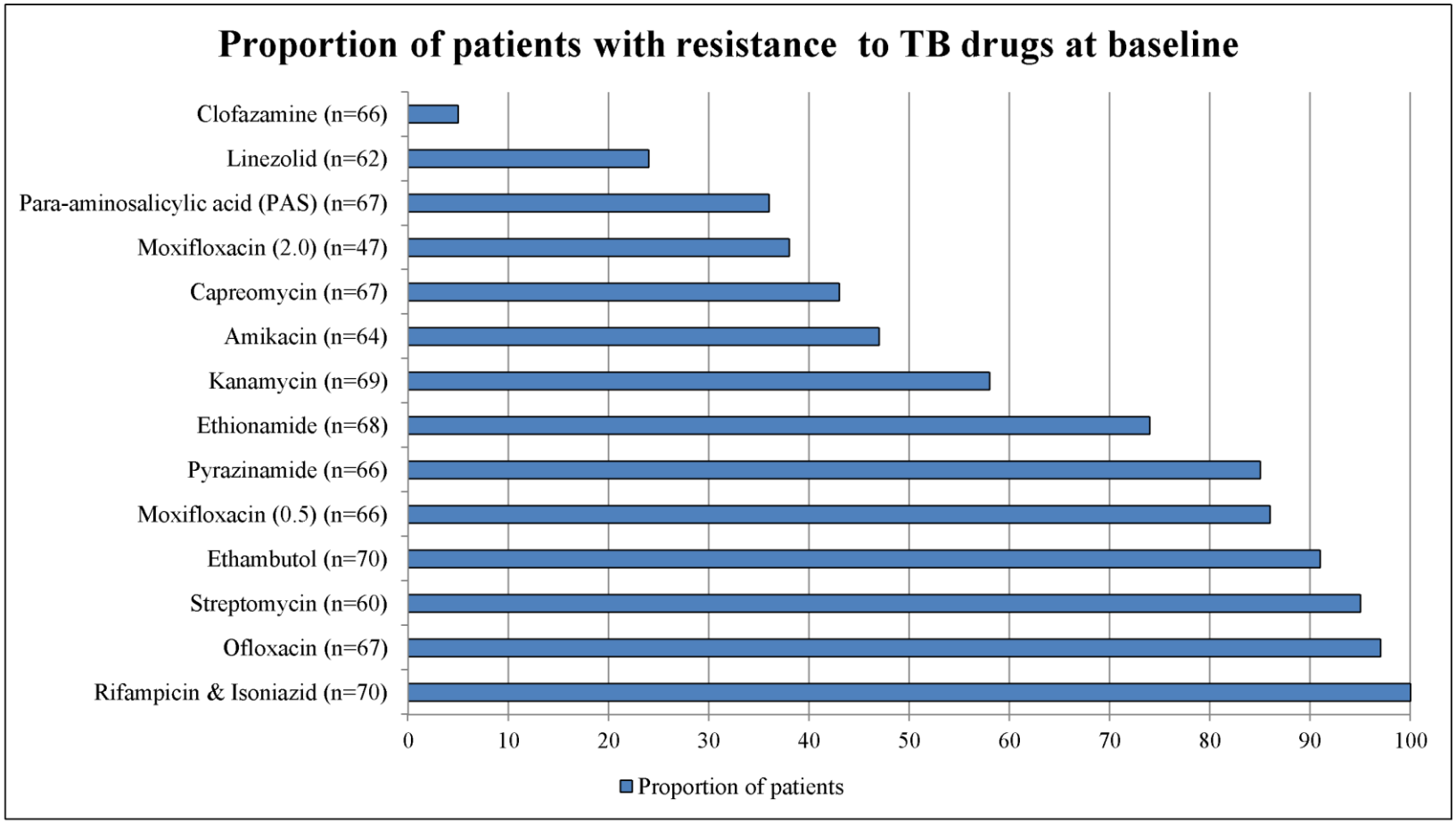

Figure 2

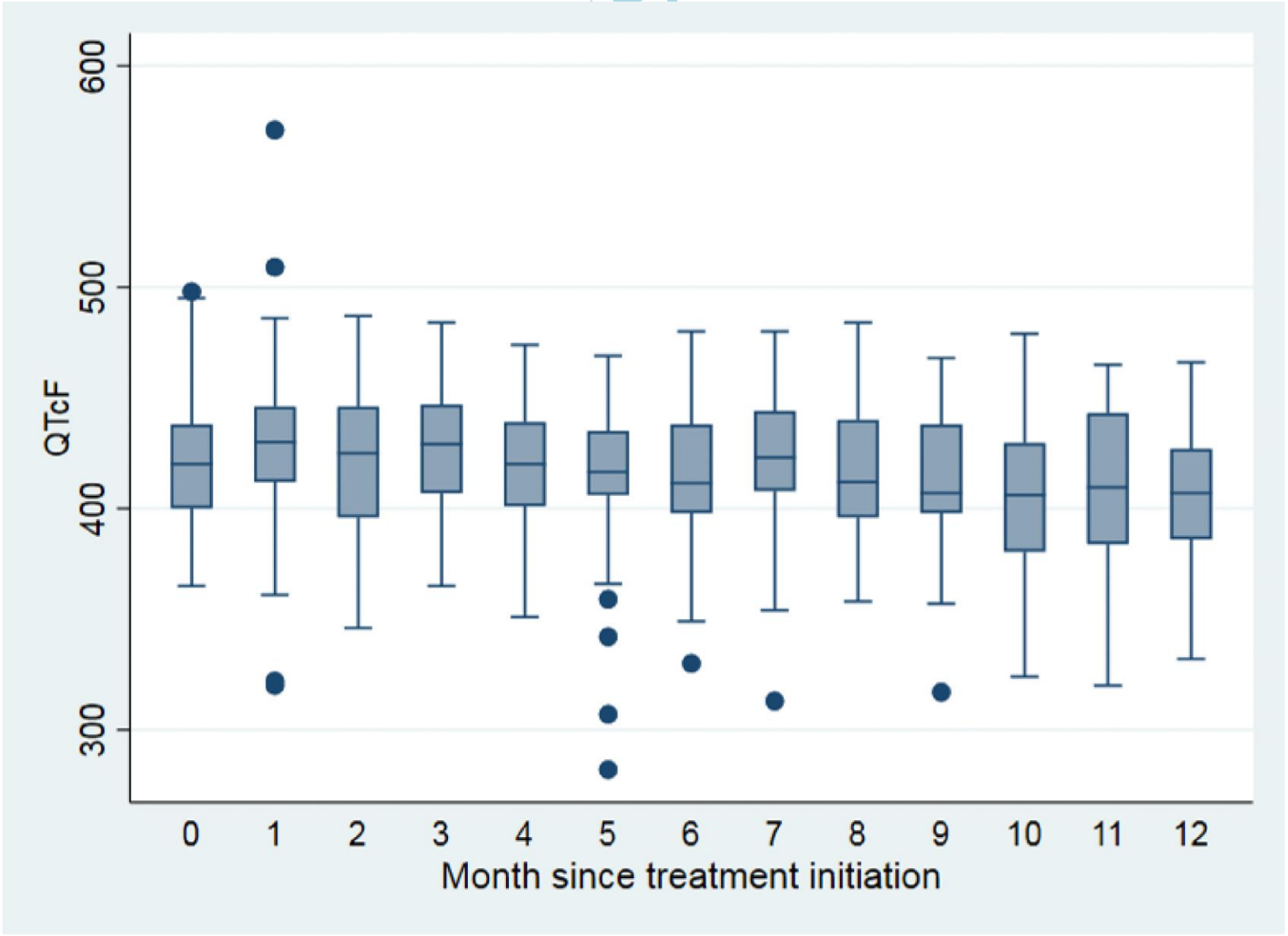

Figure 3