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MAJOR ARTICLE

Bedaquiline Resistance and Treatment Outcomes Among Patients With Tuberculosis Previously Exposed to Bedaquiline in India: A Multicentric Retrospective Cohort Study

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Background. Bedaquiline (BDQ) resistance presents a critical challenge in the fight against tuberculosis (TB), particularly multidrug-resistant (MDR) strains. The emergence of resistance to BDQ, a key drug in treating MDR-TB, poses significant threats to TB treatment effectiveness.

Methods. The National Institute of Tuberculosis and Respiratory Diseases in Delhi and the Médecins Sans Frontières clinic in Mumbai provide BDQ, delamanid, and carbapenem-based regimens for patients with suspected or confirmed treatment failure. BDQ phenotypic drug-susceptibility testing (DST) was performed for all BDQ-exposed patients. Treatment regimens were individualized based on exposure history, comorbidities, drug interactions, prior adverse drug reactions, and DST results.

Results. Of 117 BDQ-exposed patients from December 2020–December 2022, 42 (36%) exhibited a BDQ-resistant strain. Median (IQR) age was 24 (22–32) years, with 63 (54%) females and 94% with pulmonary TB. Patients with a BDQ-resistant strain were older (median age: 27 vs 23 years; $P = .04$), more likely to have lung cavities (risk ratio [RR]: 1.8; 95%-CI: 1.1–3.1; $P = .02$), and be resistant to clofazimine (RR: 2.3; 95%-CI: 1.5–3.6; $P = .001$). Overall, 102 patients initiated treatment. Patients with BDQ-resistance had higher risk of unfavorable outcomes compared with BDQ-susceptible patients (RR:2.1; 95%-CI: 1.5–2.8; $P < .001$). Overall, 87% (33/38) of patients with BDQ-resistance experienced unfavorable treatment outcomes: 15 (40%) died, 15 (40%) had treatment failure, and 3 (8%) were lost-to-follow-up.

Conclusions. The study highlights a concerning rate of BDQ-resistance among previously treated patients, resulting in poor treatment outcomes. To prevent treatment failure, we recommend implementing BDQ-DST, developing affordable and accurate rapid tests for BDQ-resistance, and intensifying research and development efforts for newer TB drugs.

Keywords. drug resistance; operational research; India; drug-susceptibility testing.

According to the Global Tuberculosis (TB) Report 2023, there were 410 000 new cases of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) worldwide in 2022 [1]. India has the largest share globally, accounting for 27% of the world's burden of TB and MDR/RR-TB [1]. Extensively drug-resistant TB (XDR-TB) is TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to rifampicin, isoniazid and, at least 1 fluoroquinolone (FQ) (levofloxacin or moxifloxacin) and at least 1 other "group A" drug (bedaquiline [BDQ] or linezolid).

Bedaquiline has been designated as a group A drug by the World Health Organization (WHO) for the management of multidrug-resistant TB (MDR-TB) and XDR-TB. India brought BDQ into use in 2016 under the Conditional Access Program following strict enrollment criteria and close monitoring [2].

The Indian National TB Elimination Program (NTEP) included the shorter oral BDQ-containing MDR/RR-TB regimen in the 2021 national guidelines for the management of drug-resistant TB (DR-TB) [3].

With increased use of BDQ across the country there is concern regarding development of resistance. Resistance to BDQ was first described in 2015 and is a growing problem [4–7].

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A systematic review published in 2022, which included 13 studies on BDQ resistance including data from India, found that the median proportion of participants with baseline phenotypic BDQ resistance was 2.8% (interquartile range [IQR]: 1.9%–3.3%) and the median frequency of acquired BDQ resistance during treatment was 2.2% (IQR: 1.1%–4.6%) [8].

In a study in programmatic contexts in South Africa from 2015 to 2019, 3.8% (95% CI: 2.9%–4.6%) of patients exhibited resistance to BDQ. The BDQ-resistant patients showed poorer treatment outcomes (odds ratio [OR]: .5; 95% CI: .3–1) [9].

The study aims to describe BDQ resistance in a cohort of patients with DR-TB who have been exposed to BDQ and with suspected or confirmed treatment failure. It describes potential risk factors for BDQ resistance and the treatment outcomes of these patients treated with individualized regimens.

METHODS

Study Design

This was a multicentric retrospective cohort study using programmatic data.

Study Setting and Study Population

This study used data from 2 sites treating patients with DR-TB with extensive resistance patterns who require newer drugs and have limited treatment options: the National Institute of Tuberculosis and Respiratory Diseases (NITRD) in New Delhi and the Médecins sans Frontières (MSF) clinic in Mumbai, India.

The patients with DR-TB in the study population encompass TB patients with MDR/RR-TB, pre-XDR TB, and XDR-TB who had been treated with BDQ-based regimens for a minimum of 1 month and had experienced treatment failure and were therefore referred to either NITRD or MSF clinics between December 2020 and December 2022.

Description of Activities in NITRD and MSF Clinics

The patients with DR-TB referred to the NITRD and MSF clinic were evaluated by a multidisciplinary team. A detailed medical history and relevant microbiological, radiological, and laboratory investigations were performed as per the Indian NTEP guidelines in a national accredited laboratory [3].

Drug-susceptibility testing was performed at the supranational reference laboratory of India using the Mycobacteria Growth Indicator Tube (MGIT; BD, Franklin Lakes, NJ, USA) in modified Middlebrook 7H9 broth medium for BDQ, second-line injectable agents (kanamycin, amikacin, capreomycin), ethionamide, para-aminosalicylic acid, clofazimine (CFZ), linezolid, and FQs [10]. In addition, HAIN genotype line probe assays were performed to elicit the mutations for injectable agents (kanamycin, amikacin, capreomycin) and FQs [11].

After enrolling eligible patients with treatment failure, new treatment regimens were individualized using BDQ, delamanid (DLM) and carbapenem, and other appropriate drugs to form an optimized background regimen. This was based on drug-exposure history, comorbidities, interactions with concomitant medications, previous history of adverse drug reactions (ADRs), and DST.

The patients were followed up every 2 weeks for the first 2 visits and then monthly at the NITRD or MSF clinic to check treatment response, ADRs, laboratory abnormalities, and nutritional status and to receive psychosocial support. Systematic monitoring of patients' progress was carried out and recorded in an electronic database.

Operational Definitions

Culture conversion, culture reversion, and treatment outcomes were defined according to the WHO 2021 Definitions and Reporting Framework for Tuberculosis [12]. Accordingly, treatment completion and cured is considered as "treatment success." Treatment failure, death, and loss to follow-up were considered as "unfavourable treatment outcomes."

We defined culture conversion as 2 consecutive negative cultures taken at least 30 days apart following an initial positive culture. We defined time to initial culture conversion as the time in months from the date of start of DR-TB treatment to the date of specimen collection for the first of 2 consecutive negative sputum culture results, irrespective of whether there was a subsequent sputum culture positive result. We defined culture reversion to positive when at least 2 subsequent positive sputum cultures were recorded after initial culture conversion.

Data Management and Statistical Analysis

Patient data from both MSF and NITRD clinics were entered from patients' treatment files into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) by trained data entry operators.

Patients' demographic and treatment characteristics were summarized using frequencies and percentages for categorical variables and medians and IQRs for continuous variables. All statistical differences were tested in univariable analyses using chi-square, Fisher's exact, or Wilcoxon rank-sum tests, as appropriate. Risk factors with $P < .05$ in univariate analysis or clinically important variables were further analyzed in a multivariable logistic regression model.

All estimates were reported with their respective 95% CIs. *P* values below the threshold of .05 were considered statistically significant. All analyses were performed using R software (version 4.3.2; The R Foundation, Vienna, Austria).

Ethics

The study fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for a posteriori analysis of routinely collected clinical data and thus did not require MSF ERB full review. The study received ethics approval from the

Institutional Review Board of the NITRD, Delhi (NITRD/EC/2022/1947).

RESULTS

During the study period, 121 patients with confirmed TB with previous exposure to BDQ and suspected or confirmed treatment failure underwent DST for BDQ. Four patients refused treatment and hence were excluded from the analysis (Figure 1).

Of the remaining 117 patients, the baseline demographic and clinical characteristics of patients stratified by BDQ-resistance status are shown in Table 1. Forty-two (36%) patients had strains of BDQ resistance; the median (IQR) age was 24 (22, 32) years and 63 (54%) were females. The majority (96%; n = 112) had pulmonary TB. All patients were human immunodeficiency virus (HIV) seronegative.

In the univariate analysis the patients with strains of BDQ resistance were older (median age: 27 vs 23 years; $P = .04$), in contrast to patients who were susceptible to BDQ. A greater proportion of BDQ-resistant patients had lung cavities (OR = 2.5; 95% CI: 1.2–5.6; $P = .02$) and were resistant to CFZ (OR = 4.9; 95% CI: 2.0–12.0; $P = .001$) (Table 1).

In the multivariable logistic regression analysis, the presence of lung cavities and resistance to CFZ were significantly associated with higher odds of BDQ resistance (Table 1). Figure 2 shows the patients' baseline resistance pattern to BDQ, FQs, linezolid, and CFZ.

Of the 117 patients, 7 (6.0%) patients died before initiating treatment and 8 (6.8%) were transferred to another health facility to continue treatment (Figure 1). The treatment regimen and treatment outcome of the remaining 102 patients stratified by BDQ-resistance status are shown in Table 2. Among these 102 patients, 38 patients were BDQ resistant and, among them, 87% (33/38) experienced unfavorable treatment outcomes compared to 42% (27/64) in the BDQ-susceptible cohort (risk ratio [RR] = 2.1; 95% CI: 1.5–2.8; $P < .001$).

Risk factors for unfavorable treatment outcomes are shown in Table 3. On univariate analysis, older age ($P = .016$) and involvement of both lungs ($P = .035$) were associated with a higher risk of unfavorable treatment outcomes. However, none of the variables retained statistical significance ($P < .05$) in a multivariable logistic regression model that incorporated age, lung involvement, and CFZ resistance (Table 3).

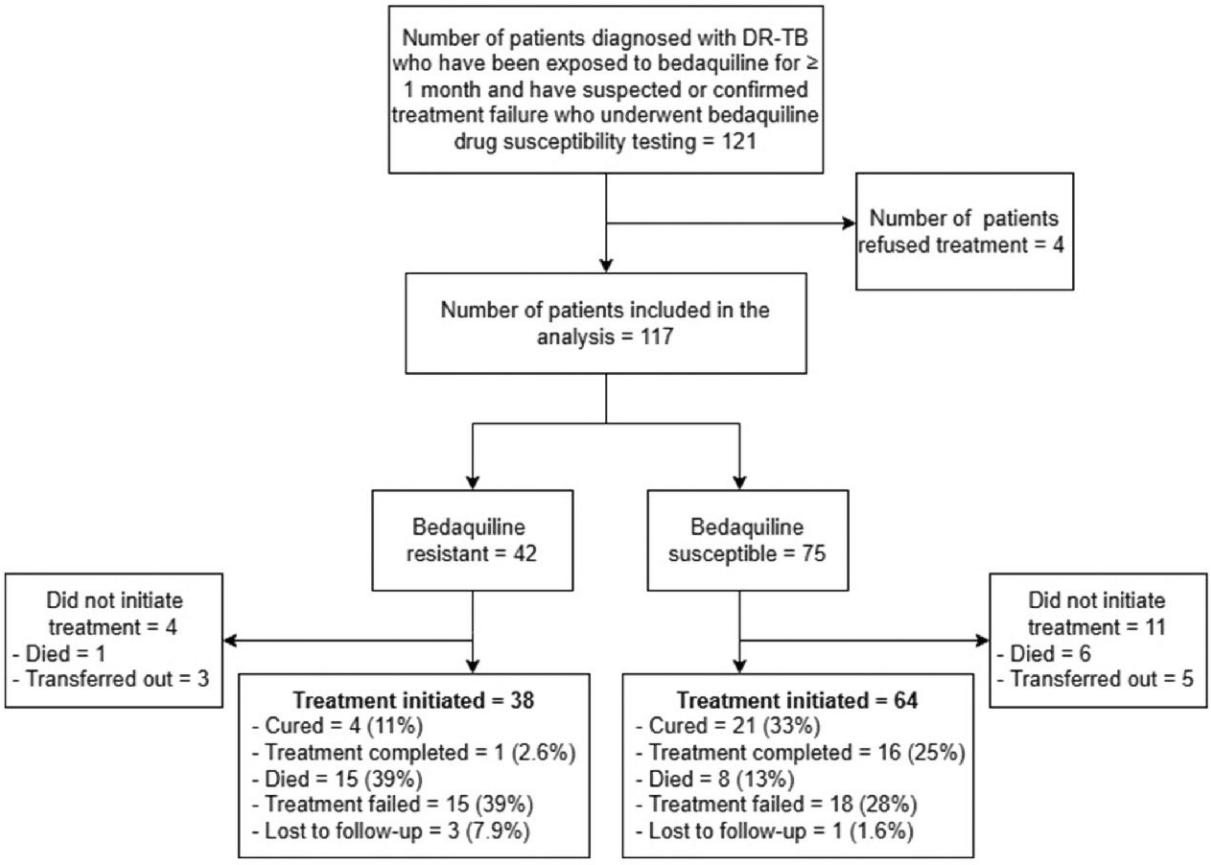

Figure 1. Flow chart. Abbreviation: DR-TB, drug-resistant tuberculosis.

Table 1. Baseline Patient Characteristics Stratified According to Their Bedaquiline Resistance Profile

Characteristics	Overall (n = 117)	Bedaquiline Resistant (n = 42)	Bedaquiline Susceptible (n = 75)	P^a	aOR (95% CI)	P^a
Age group				.8		
<20 y	21 (18%)	7 (17%)	14 (19%)		…	
20 to <40 y	85 (73%)	30 (71%)	55 (73%)		…	
40 to <60 y	11 (9.4%)	5 (12%)	6 (8.0%)		…	
Median (IQR) age, y	24 (22, 32)	27 (22, 37)	23 (21, 29)	.043	1.1 (1.0, 1.1)	.1
Gender				.077		
Female	63 (54%)	18 (43%)	45 (60%)		Reference	
Male	53 (45%)	23 (55%)	30 (40%)		1.8 (.7, 4.5)	.2
Transgender female	1 (0.9%)	1 (2.4%)	0 (0%)		…	>.9
Site of tuberculosis				.3		
Pulmonary	112 (96%)	42 (100%)	70 (93%)		…	
Extrapulmonary	3 (2.6%)	0 (0%)	3 (4.0%)		…	
Disseminated	2 (1.7%)	0 (0%)	2 (2.7%)		…	
Lung involvement[b]				.6		
Unilateral	25 (22%)	8 (19%)	17 (24%)		…	
Bilateral	89 (78%)	34 (81%)	55 (76%)		…	
Lung cavity				.02		
No	56 (48%)	14 (33%)	42 (56%)		Reference	
Yes	61 (52%)	28 (67%)	33 (44%)		2.8 (1.1, 7.5)	.032
Diabetes				>.9		
No	107 (91%)	39 (93%)	68 (91%)		…	
Yes	10 (8.5%)	3 (7.1%)	7 (9.3%)		…	
Nutritional status				.2		
BMI ≥16 kg/m^2	57 (49%)	24 (57%)	33 (44%)		Reference	
BMI <16 kg/m^2	60 (51%)	18 (43%)	42 (56%)		.5 (.2, 1.3)	.2
Resistance profile						
Clofazimine-resistant	28 (25%)	18 (44%)	10 (14%)	<.001	5.5 (2.1, 15.7)	<.001
Missing data[c]	6	1	5		…	
Linezolid-resistant	33 (30%)	15 (37%)	18 (26%)	.2	1.1 (.4, 3.0)	.9
Missing data[c]	6	1	5		…	
Fluoroquinolone-resistant	100 (90%)	38 (93%)	62 (89%)	.7	…	
Missing data[c]	6	1	5		…	

Data are presented as n (%) or median (IQR).

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; IQR, interquartile range.

[a]Fisher's exact test; Wilcoxon rank-sum test; Pearson's chi-square test.

[b]Lung involvement does not include extrapulmonary (3 patients).

[c]Missing data means the drug-resistance profiles of some patients were not available.

Twenty-four (67%) of the 38 BDQ-resistant patients and 43 (69%) of the 64 BDQ-sensitive patients culture-converted in a median of 75 days (IQR: 60–135 days) and 90 days (IQR: 60–150 days), respectively, following baseline positive culture results, as shown in Table 4. However, 10 of 24 (41.7%) BDQ-resistant patients who achieved culture conversion experienced culture reversion in a median of 240 days (IQR: 120–128 days). Of the remaining 14 (58.3%) patients who remained culture-converted, 2 were found to have failed treatment based on the clinical and radiological results, 2 were lost to follow-up, and 5 died despite being continuously culture-negative.

DISCUSSION

The emergence of DR-TB poses a significant challenge to global TB control efforts. In this study, we investigated the prevalence of BDQ resistance among patients with TB with previous exposure to BDQ who had experienced treatment failure, and its impact on subsequent treatment outcomes. Our findings also provide evidence on important clinical factors associated with BDQ resistance and its implications for TB management.

In a study from South Africa during a surveillance period spanning from 2015 to 2019 within programmatic contexts, the prevalence of BDQ resistance was 11.1% (1/9; 95% CI: .3%–48.3%) in patients previously exposed to BDQ [9]. Our study indicates a concerning prevalence of BDQ resistance at 36% (42/117) in people previously exposed to BDQ.

Our study results concurred with the observations of Ismail et al [9] that resistance to CFZ was significantly associated with BDQ resistance. The correlation between CFZ and BDQ resistance was observed to be lower, probably due to the small sample size and lack of mutation elicitation in absence of whole-genome

sequencing [13]. This indicates that BDQ resistance was associated with prior exposure to either BDQ or CFZ [9]. We have seen no such significant difference in BDQ resistance among the patients harboring FQ resistance and FQ-sensitive strains, and the reason for the difference is not quite clear.

Our study revealed a significantly higher risk of unfavorable treatment outcomes among BDQ-resistant patients compared with BDQ-susceptible patients (RR = 2.1; 95% CI: 1.5– 2.8; $P < .001$). Similarly, Ismail et al's study reported a 1.5 times higher incidence of unfavorable outcomes in the BDQ-resistant group compared with the BDQ-susceptible group [9].

Mortality was higher in BDQ-resistant cases at 40% compared to 13% in BDQ-sensitive cases. This mortality rate demonstrates the impact of BDQ resistance on the success of the regimen for patients with DR-TB.

In our study, older age, the presence of cavities, and concomitant resistance to CFZ were identified as significant risk factors for BDQ resistance on univariate analysis. Lung cavities are known to harbor bacilli due to parenchymal destruction, leading to poor drug penetration and possible exposure to a suboptimal concentration of BDQ during treatment, leading to resistance. Multivariable analyses of these factors, however, were found to be non–statistically significant, probably due to the small sample size and resistance to CFZ and BDQ only elicited by phenotypic DST (pDST) [14–16].

Treating individuals with BDQ resistance is challenging as effective drugs are limited; in our cohort, intravenous carbapenems were required by 87% of patients. These drugs pose a significant financial and logistical challenge to national programs in resource-constrained countries. Most patients would not be able to afford these drugs if not covered by national programs.

In the BDQ-resistant cohort, time to culture conversion was unexpectantly shorter than that of the BDQ-susceptible cohort, although the numbers for comparison are small. Although a considerable proportion of BDQ-resistant patients achieved culture conversion during treatment, a significant proportion of those patients experienced subsequent culture reversion. This underscores the challenges in achieving treatment success in patients with strains of BDQ resistance and highlights the need for close monitoring and follow-up to prevent relapse and treatment failure.

The use of pDST for anti-TB drugs, including BDQ, is recommended to detect resistance early, reduce the risk of developing further resistance, and to ensure patients are on the most effective regimens [17]. Although BDQ has been recommended for programmatic use in India since 2016, access to BDQ pDST is still limited. According to the latest definition of XDR-TB

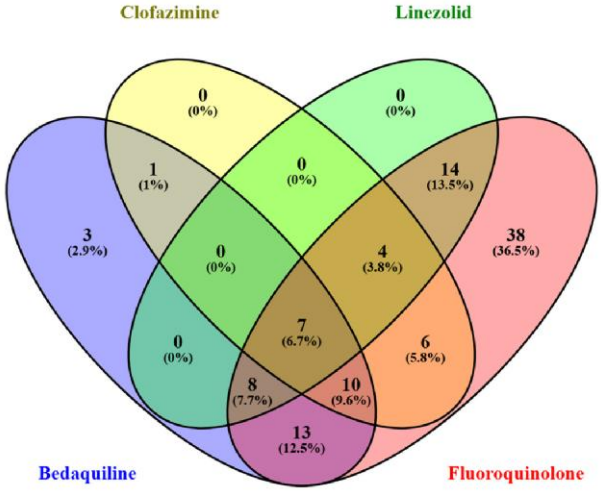

Figure 2. Clofazimine-, linezolid-, and fluoroquinolone-resistance profile of patients (N = 115).

Table 2. Treatment Outcome Among Patients Who Initiated Treatment Stratified by Bedaquiline-Resistance Profile

	Overall (n = 102)	Bedaquiline Resistant (n = 38)	Bedaquiline Susceptible (n = 64)	P^a
Characteristic				
Treatment included bedaquiline	76 (75%)	28 (74%)	48 (75%)	.9
Treatment included delamanid	101 (99%)	38 (100%)	63 (98%)	>.9
Treatment included carbapenems	84 (82%)	33 (87%)	51 (80%)	.4
Treatment included linezolid	75 (74%)	27 (71%)	48 (75%)	.7
Treatment success	42 (41%)	5 (13%)	37 (58%)	<.001
Completed treatment	17 (17%)	1 (2.6%)	16 (25%)	
Cured	25 (25%)	4 (11%)	21 (33%)	
Unfavorable treatment outcomes	60 (59%)	33 (87%)	27 (42%)	<.001
Died	23 (23%)	15 (40%)	8 (13%)	
Treatment failure	33 (32%)	15 (40%)	18 (28%)	
Lost to follow-up	4 (3.9%)	3 (7.9%)	1 (1.6%)	

Data are presented as n (%).

[a]Pearson's chi-square test; Fisher's exact test.

Table 3. Risk Factors for Unfavorable Treatment Outcome Among Patients Resistant to Bedaquiline

Characteristics	Overall (n = 38)	Treatment Success (n = 5)	Unfavorable Outcome (n = 33)	P[a]	aOR (95% CI)	P[a]
Age				.3		
<20 y	7 (18%)	2 (40%)	5 (15%)		…	
20 to <40 y	27 (71%)	3 (60%)	24 (73%)		…	
40 to <60 y	4 (11%)	0 (0%)	4 (12%)		…	
Median (IQR) age, y	28 (22, 37)	20 (17, 23)	31 (24, 37)	.016	1.2 (1.0, 1.7)	.12
Sex				>.9		
Female	14 (37%)	2 (40%)	12 (36%)		…	
Male	23 (61%)	3 (60%)	20 (61%)		…	
Transgender female	1 (2.6%)	0 (0%)	1 (3.0%)		…	
Lung involvement				.035		
Unilateral	7 (18%)	3 (60%)	4 (12%)		Reference	
Bilateral	31 (82%)	2 (40%)	29 (88%)		3.9 (.3, 50.2)	.3
Lung cavity				.14		
No	12 (32%)	3 (60%)	9 (27%)		…	
Yes	26 (68%)	2 (40%)	24 (73%)		…	
Diabetes				>.9		
No	36 (95%)	5 (100%)	31 (94%)		…	
Yes	2 (5.3%)	0 (0%)	2 (6.1%)		…	
Nutritional status				>.9		
BMI ≥16 kg/m^2	21 (55%)	3 (60%)	18 (55%)		…	
BMI <16 kg/m^2	17 (45%)	2 (40%)	15 (45%)		…	
Resistance profile at baseline						
Clofazimine-resistant	17 (46%)	4 (80%)	13 (41%)	.2	0.2 (0.01, 2.9)	.3
Missing	1	0	1		…	
Linezolid-resistant	12 (32%)	3 (60%)	9 (28%)	.3	…	
Missing	1	0	1		…	
Fluoroquinolone-resistant	34 (92%)	5 (100%)	29 (91%)	>.9	…	
Missing	1	0	1		…	

Data are presented as n (%) or median (IQR).

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; IQR, interquartile range.

[a]Fisher's exact test; Wilcoxon rank-sum test.

Table 4. Time to Culture Conversion According to Bedaquiline-Resistance Profile

Characteristic	Overall (n = 102)	Bedaquiline Resistant (n = 38)	Bedaquiline Susceptible (n = 64)
Culture conversion			
Yes	67 (68%)	24 (67%)	43 (69%)
No	31 (32%)	12 (33%)	19 (31%)
Missing data[a]	4	2	2
Median no. of days to culture conversion	90 (60, 50)	75 (60, 135)	90 (60, 150)
Culture reversion	16 (24%)	10 (42%)	6 (14%)
Median no. of days to culture reversion	315 (195, 420)	240 (120, 128)	435 (300, 323)

Data are presented as n (%) and median (IQR).

Abbreviation: IQR, interquartile range.

[a]Missing data means that after baseline culture no further culture report is available.

[18], without BDQ DST we are underestimating the burden of XDR-TB. Bedaquiline DST should be widely scaled-up at treatment initiation and especially for retreatment patients with a history of BDQ exposure. The results of these tests can take weeks to months in programmatic settings and there is an urgent need for rapid cartridge-based molecular tests for BDQ resistance to be developed or to further evaluate DST methods, such as thin-layer-agar–based DST, which are quicker than traditional alternatives [19, 20]. As the laboratory capacity of the country improves, we recommend baseline BDQ DST for all patients with TB with BDQ-containing regimens. Drug-susceptibility testing for linezolid and CFZ is already part of the NTEP diagnostic algorithm in India, and DLM whenever feasible. In India, laboratory capacity is being scaled-up to include DST for other newer drugs including BDQ, DLM, and pretomanid. Next-generation sequencing can evaluate drug resistance in a single test, and the WHO has found it practical and cost-effective; however, it is not yet widely available [21]. Well-supported, person-centered models of care are necessary to address patient needs from care-seeking all the way to effective cure. Finally, addressing the financial shortage for TB programs and research is crucial to meeting the demands. India has been using BDQ since 2016; hence, the observation of high

resistance among BDQ-treated patients is of concern as the country rolls out the newer BPaLM (bedaquiline [B], pretomanid [Pa], linezolid [L], and moxifloxacin [M]) regimen India is aiming to implement BDQ DST at baseline for all patients started on the BPaLM regimen. The main limitation of this study is that it concerns a highly selected cohort, and its findings might be highly contextual with very limited generalizability. However, we believe that the resistance patterns emerging in epidemic hotspots such as Mumbai's and Delhi's urban slums, where the majority of patients in this study lived, might indicate what could occur in similar contexts. The small study sample size and the retrospective study design limit its power to produce robust estimates. Despite these limitations, the lack of knowledge on BDQ resistance, especially in patients failing BDQ-based regimens, make the results an important contribution to the growing evidence base.

Conclusions

In conclusion, our study highlights the high occurrence of BDQ resistance among patients with TB with previous exposure to the drug and its impact on treatment outcomes. The presence of lung cavities and concomitant CFZ resistance was independently associated with BDQ resistance in the multivariable analysis. These findings highlight the importance of monitoring for drug resistance and the need for tailored treatment strategies to optimize outcomes in this high-risk patient population.

Notes

Financial support. This work was based on routinely collected programmatic data at both clinics and did not require additional data to be conducted. The authors of the work are salaried staff by the 2 centers and were not paid additionally for this work.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. World Health Organization. Global Tuberculosis Report 2023. **2023**. Available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023. Accessed 15 December 2023.
2. Revised National Tuberculosis Control Programme (RNTCP). Guidelines for use of bedaquiline in RNTCP through conditional access under Programmatic Management of Drug Resistant Tuberculosis in India. **2016**. Available at: https://www.tbcindia.gov.in/WriteReadData/l892s/8649978567selection.pdf. Accessed 2 July 2024.
3. National TB Elimination Programme. Guidelines for Programmatic Management of Drug Resistant Tuberculosis in India—March 2021. **2021**. Available at: https://tbcindia.gov.in/WriteReadData/l892s/8368587497Guidelines%20for%20PMDT%20in%20India.pdf. Accessed 2 July 2024.
4. Xu J, Wang B, Hu M, et al. Primary clofazimine and bedaquiline resistance among isolates from patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother **2017**; 61:e00239-17.
5. Satapathy P, Itumalla R, Neyazi A, et al. Emerging bedaquiline resistance: a threat to the global fight against drug-resistant tuberculosis. J Biosaf Biosecur **2024**; 6: 13–15.
6. Nguyen TVA, Anthony RM, Bañuls A-L, Nguyen TVA, Vu DH, Alffenaar J-WC. Bedaquiline resistance: its emergence, mechanism, and prevention. Clin Infect Dis **2018**; 66:1625–1630.
7. Chesov E, Chesov D, Maurer FP, et al. Emergence of bedaquiline resistance in a high tuberculosis burden country. Eur Respir J **2022**; 59:2100621.
8. Mallick JS, Nair P, Abbew ET, Van Deun A, Decroo T. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. JAC Antimicrob Resist **2022**; 4:dlac029.
9. Ismail NA, Omar SV, Moultrie H, et al. Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study. Lancet Infect Dis **2022**; 22:496–506.
10. Siddiqi SH, Rüsch-Gerdes S. MGIT™ procedure manual: for BACTEC™ MGIT 960™ TB system (also applicable for manual MGIT). *Mycobacteria Growth Indicator Tube (MGIT) culture and drug susceptibility demonstration projects*. **2006**. Available at: https://www.finddx.org/wp-content/uploads/2023/02/20061101_rep_mgit_manual_FV_EN.pdf. Accessed 25 February 2025.
11. World Health Organization. Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. 2018. Available at: https://www.who.int/publications/i/item/9789241514842. Accessed 3 July 2024.
12. World Health Organization. Definitions and reporting framework for tuberculosis—2013 revision: updated December 2014 and January 2020. **2013**. Available at: https://www.who.int/publications/i/item/9789241505345. Accessed 1 March 2024.
13. Shang Y, Chen S, Shi W, et al. Bedaquiline resistance pattern in clofazimine-resistant clinical isolates of tuberculosis patients. J Glob Antimicrob Resist **2023**; 33:294–300.
14. Irwin SM, Prideaux B, Lyon ER, et al. Bedaquiline and pyrazinamide treatment responses are affected by pulmonary lesion heterogeneity in Mycobacterium tuberculosis infected C3HeB/FeJ mice. ACS Infect Dis **2016**; 2:251–67.
15. Ong CWM, Elkington PT, Friedland JS. Tuberculosis, pulmonary cavitation, and matrix metalloproteinases. Am J Respir Crit Care Med **2014**; 190:9–18.
16. Urbanowski ME, Ordonez AA, Ruiz-Bedoya CA, Jain SK, Bishai WR. Cavitary tuberculosis: the gateway of disease transmission. Lancet Infect Dis **2020**; 20: e117–28.
17. Mishra GP, Mulani J. Implications of bedaquiline-resistant tuberculosis. Lancet Infect Dis **2022**; 22:166.
18. Viney K, Linh NN, Gegia M, et al. New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization. Eur Respir J **2021**; 57:2100361.
19. Branigan D, Denkinger CM, Furin J, et al. Diagnostics to support the scaling up of shorter, safer tuberculosis regimens. Lancet Microbe **2023**; 4:e758–60.
20. Ardizzoni E, Ariza E, Mulengwa D, et al. Thin-layer-agar-based direct phenotypic drug susceptibility testing on sputum in Eswatini rapidly detects mycobacterium tuberculosis growth and rifampicin resistance otherwise missed by WHO-endorsed diagnostic tests. Antimicrob Agents Chemother **2021**; 65:e02263-20.
21. World Health Organization. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis. **2023**. Available at: https://iris.who.int/bitstream/handle/10665/371687/9789240076372-eng.pdf?sequence=1. Accessed 13 May 2024.