Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Treatment Outcomes for Drug-Resistant Tuberculosis Patients on Bedaquiline-Based Regimens in a Mostly Rural South Africa

Ivy Rukasha[1,2], Kabelo Gabriel Kaapu[1], Sarah M Fortune[3], Molebogeng Ruth Lekalakala-Mokaba[1,2]

[1]Department of Pathology, University of Limpopo, Polokwane, South Africa; [2]Department of Microbiology, National Health Laboratory Service, Polokwane, South Africa; [3]Department of Microbiology, Harvard TH Chan School of Public Health, Boston, MA, USA

Correspondence: Ivy Rukasha, University of Limpopo Turfloop Campus, Private Bag X1106 Sovenga, Limpopo, 0727, South Africa, Email ivy.rukasha@ul.ac.za

Background: Tuberculosis (TB) has maintained its position as a leading global health crisis. The situation of DR-TB is exacerbated by the emergence of drug resistance, particularly rifampicin resistant TB (RR-TB), multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB). Bedaquiline (BDQ) has now become part of all standard drug-resistant regimens globally. However, emerging BDQ resistance is a growing worry, especially in areas with high rates of TB and HIV. This study aimed to compare BDQ-based regimens to non-BDQ-based treatments over a four-year period (2016–2019) to retrospectively examine the treatment outcomes of DR-TB patients in Limpopo Province, South Africa.

Methodology: Using patient data from the Limpopo Province Electronic Drug-resistant TB Register (EDR) Web, a retrospective study was carried out. The study comprised 1,665 DR-TB patients; 880 (52.8%) of them were given BDQ-based regimens, whereas 785 (47.2%) were given non-BDQ regimens. Treatment success, death, loss to follow-up, and six-month sputum culture conversion were important outcomes. Kaplan–Meier survival analysis was used to assess the data for mortality, chi-square tests were used for categorical comparisons, and logistic regression models were used to find treatment success predictors.

Results: The results of the analysis showed that the BDQ cohort had far better treatment success rates 560/785 (71%) than the non-BDQ cohort 549/880 (62%). Patients receiving BDQ had a reduced overall death rate and quicker sputum culture conversion at six months 608/785 (77.5%) vs 597/880 (67.8%). Kaplan–Meier curve survival analysis revealed a statistically significant survival benefit. Age, HIV status, and BDQ use were found to be significant determinants of treatment effectiveness using logistic regression.

Conclusion: In South Africa's mostly rural areas, BDQ-containing regimens proved to be more effective in enhancing treatment outcomes and lowering mortality rates for DR-TB patients. But to keep TB treatment regimens successful, comprehensive drug susceptibility testing and ongoing surveillance are required considering the growing concern over BDQ resistance.

Keywords: Bedaquiline, treatment outcomes, drug-resistant tuberculosis, Limpopo

Introduction

The World Health Organization (WHO) has long declared drug-resistant TB (DR-TB) as a major public health crisis and a threat to health security that requires urgent management.[1] Drug resistance is an obstacle to TB care and prevention around the world, making it difficult to treat, often resulting in unfavorable outcomes for patients.[1–4] According to the World Health Organization's Global Tuberculosis Report 2024, an estimated 10.8 million people worldwide fell ill with TB in 2023. Among these, approximately 400,000 individuals developed multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB). This indicates that about 3.7% of all TB cases were classified as MDR/RR-TB.[5,6] WHO has reported MDR-TB to occur in 3–4% of new TB cases, and 18–21% of previously treated cases.[1] The burden of pre-extensive DR-TB (pre-XDR-TB), defined as MDR-TB with resistance to fluoroquinolones, and extensive drug resistant TB (XDR-TB), defined as pre-XDR-TB with resistance to either BDQ and/or linezolid, has also been reported to be increasing.[5,7] BDQ has emerged as a critical component in addressing these forms of DR-TB due to its efficacy against both MDR-TB and

Received: 22 October 2024
Accepted: 25 January 2025
Published: 12 April 2025

more advanced forms such as pre-XDR-TB and XDR-TB. Its inclusion in treatment regimens has been significantly improved outcomes in patients with limited therapeutic options.[8,9]

BDQ is a life-saving drug introduced in South Africa (SA) on compassionate grounds that was scaled up in March 2013.[10] The drug BDQ has now become part of all standard DR-TB regimens globally.[11–14] As a diarylquinoline compound, BDQ specifically inhibits mycobacterial ATP synthase, providing a novel mechanism of action against *Mycobacterium tuberculosis*.[15] However, resistance to BDQ can arise through mutations in Rv0678, a gene encoding a transcriptional regulator that modulates the efflux pump system. These mutations reduce the drug's intracellular concentration, thereby compromising its efficacy. The dual role of ATP synthase as the primary drug target and Rv0678 as a critical determinant of resistance highlights the complexity of BDQ's mechanism of action and its susceptibility to resistance mechanisms.[16] The WHO guidelines recommend phenotypic drug susceptibility testing (pDST) for BDQ before patients start a BDQ-containing regimen to monitor resistance emergence; however, such recommendations are neither practiced nor enforced due to the poor laboratory resources and lack of experienced personnel.[11,17,18] The lack of programmatic implementation of drug susceptibility testing (DST) for BDQ due to poor infrastructure and lack of expertise and resources has led to the use of the drug without proper susceptibility results.[11] While BDQ is primarily used in MDR-TB cases, it is particularly vital in treating pre-XDR-TB and XDR-TB, where other drugs fail due to resistance. Its ability to target resistant strains underscores its significance in combating DR-TB globally and in resource-limited settings like South Africa.

The effectiveness of BDQ in treating MDR-TB, pre-XDR-TB, and XDR-TB has made it an essential drug in TB management, but the emergence of BDQ resistance in these categories threatens its role in current regimens. Programmatic BDQ resistance has been documented globally, and rates vary greatly between nations and regions. They range from approximately 1.0% in France to 1.3% in Russia, 2.3% in China, 2.3% in multinational populations, and 2.2–2.9% in China.[19] A global review of BDQ resistance reported a pooled frequency of 2.2% phenotypic resistance and 4.4% genotypic resistance in patients treated with BDQ-based regimens.[20] A 5-year BDQ resistance surveillance study (2015–2019) of 5036 MDR-TB isolates from BDQ-treatment-naïve patients across 11 countries revealed significant differences in BDQ-resistance rates between countries, with South Africa reported to have a rate of 3.4%.[21,22]

Further studies focused on South Africa reported baseline resistance of 3.6% among patients without previous exposure to BDQ as compared to 21.1% among those with previous exposure.[23] Moreover, South Africa has a national study of a sample of 3005 patients receiving BDQ treatment and has revealed that 199 (7%) had phenotypic resistance.[16,24] These findings suggest that South Africa BDQ resistance rates are comparable to or already exceeds international rates, underscoring the growing threat of BDQ resistance to TB control efforts.

In alignment with national guidelines for use of BDQ treatment for the implementation of BDQ, Limpopo Province, the fifth largest province in South Africa, scaled up the use of BDQ following national guidelines with the optimism of achieving a better treatment outcome.[10] Limpopo Province plays a key role in the region's healthcare landscape, serving as a gateway to the rest of Africa and the first point of contact for migrants north of Africa, who intend to seek treatment. Research on the profile and management of TB treatment outcomes and related factors in Limpopo is scarce. Previous studies conducted in the Limpopo province have used small sample sizes, resulting in limited and under-representative results for nearly 6 million people in the province.[23,25]

This study is the first large-scale comparison of BDQ- and non-BDQ-containing regimens in Limpopo Province, offering valuable insights into treatment outcomes in a mostly rural, resource-limited setting. The findings will inform systemic inefficiencies, influence decision-making, and enhance future DR-TB management.

Methodology

Study Site

The study was carried out in Limpopo Province, the fifth most populated province in South Africa. The province is bordered by 3 countries—Mozambique, Zimbabwe, and Botswana—and has five district municipalities, namely, Capricorn, Waterberg, Mopani, Sekhukhune, and Vhembe. The population of Limpopo province contributes an estimated 10% of the population of South Africa, which is more than 60 million. Limpopo has been greatly affected by TB, with a noticeable

increase in TB cases over the past years.[26,27] Limpopo also serves as a gateway for migrants from African countries seeking employment, education, and advanced medical services.[28,29] The province still experiences new cases of TB with extensive drug resistance, and some of these cases further complicate the development of extensive forms of DR-TB.[27]

Study Population

All patients who were diagnosed with DR-TB in Limpopo Province, South Africa, between January 2016 and December 2019 were included. In this study, all patients diagnosed with XDR-TB, MDR-TB, pre-XDR-TB, or RR-TB within the period under review were targeted in this study. The sample consisted of 1,665 patients. Of these, 880 represented 52.8% who received treatment with regimens including BDQ, while 785 represented 47.2% receiving treatment without the inclusion of BDQ.

These patients were then divided into three subgroups according to the resistance profile of the drug: MDR/RR-TB, pre-XDR-TB, and XDR-TB. A significant number of patients in this cohort were also co-infected with HIV and were further stratified as those receiving ART and those not receiving ART. Patients with incomplete treatment outcome data and those who did not meet the exclusion criteria were excluded from the study.

Data Collection

Data for this study were obtained retrospectively from the Limpopo Province Electronic Drug-resistant TB Register (EDR) Web. The register is an electronic system utilized for routine monitoring and reporting of TB cases across health facilities in the province. Records extracted were for patients initiated on DR-TB treatment between 1st January 2016 and 31st December 2019.

These included demographic data for the patients: age, sex, and HIV status; clinical data on drug resistance profile, history of TB treatment, and other comorbid conditions; and treatment outcomes. Outcomes were defined in accord with WHO guidelines and included treatment success, defined as cure or treatment completion, failure, death, and loss to follow-up. Other microbiological data included sputum smear and culture results and specifically six-month culture conversion rates.

All data were anonymised, and ethical clearance was obtained from the University of Limpopo's Turfloop Research Ethics Committee (TREC/564/2022), with patient consent waived because it is retrospective.

Definition of Treatment Outcomes

We used WHO standard definitions to measure the following treatment outcomes: cure, completion of treatment, success of treatment (the sum of cure and completion of treatment), loss to follow-up, and death.[30] We computed culture conversion at 6 months as 2 consecutive cultures taken >30 days apart that were negative before or at the end of the sixth month of treatment. Favorable outcomes were defined as treatment success, while unfavorable outcomes were defined as treatment failure, death, or loss to follow-up. The 'treatment failure' refers to patients whose primary smear/culture was positive and remained positive or became positive again five months or later in the treatment. 'Died' refers to a patient who died while on treatment.

'Default' refers to patients whose treatment was interrupted for two or more consecutive months through the treatment period.

'Cured' means that a patient had a positive primary smear/culture before treatment initiation and two consecutive negative smears/cultures 30 days before finishing treatment.

"Completed treatment" means that the patient had a positive baseline smear or culture but was not smear/culture negative in the last month of treatment or at least thirty days prior to completion of the treatment.

'Loss to follow-up' refers to patients who did not initiate treatment or initiated the treatment but did not continue with it throughout.

Sputum Culture Conversion

The microbiological outcome was based on patient sputum smear and culture results. Positive sputum cultures were considered non-conversion, and sputum culture conversion was based on two consecutive negative cultures obtained at 30-day intervals. The median time to the primary outcome was estimated by the Kaplan–Meier method.

Ethical Approval

Ethical approval was granted from the Turfloop Research Ethics Committee of the University of Limpopo (TREC/564/2022:PG), and the study was authorized by the Limpopo Department of Health. The ethics committee granted a waiver for individual patient consent, since the accumulated data was identified using research identity numbers instead of using the participant's identity at the provincial level. The study complies with the declaration of Helsinki.

Data Analysis

Data analysis was performed using the Statistical Package for Social Sciences version 27. The following demographic and clinical characteristics of the study population were summarized with the aid of descriptive statistics: age, gender, HIV status, drug resistance profiles, and previous treatment exposure. Continuous variables are summarized by mean and IQR; categorical variables are expressed as frequency and percentage.

The primary outcomes of interest were treatment success, deaths, and six-month sputum culture conversion. Categorical variable associations, including BDQ exposure and treatment outcomes, were tested for using Chi-square tests. The level of significance was set at $p \leq 0.05$. The Kaplan-Meier survival analysis was applied, comparing mortality rates between patients on BDQ-containing and non-BDQ containing regimens.

Multivariate logistic regression models were developed to identify the independent predictors of treatment success. The covariates assessed included BDQ use, gender, HIV status, drug resistance profile, and prior exposure to second-line TB drugs. Associations between covariates and the outcomes were measured by adjusted odds ratios, OR at 95% CI.

Inclusion and Exclusion Criteria

The study included patients diagnosed with DR-TB in Limpopo Province, South Africa, between January 1, 2016, and December 31, 2019. Eligible participants were those diagnosed with RR-TB, MDR-TB, pre-XDR-TB, or XDR-TB during this period. Both patients treated with regimens containing BDQ and those without BDQ were considered, provided they had complete demographic, clinical, and treatment outcome data. Treatment outcomes were defined in accordance with WHO guidelines, including cure, treatment completion, success, failure, loss to follow-up, and death. Patients were excluded if their records lacked the necessary demographic, clinical, or treatment outcome data, if they were diagnosed outside the specified timeframe, or if their TB type did not fall under the classifications of RR-TB, MDR-TB, pre-XDR-TB, or XDR-TB. Additionally, patients whose treatment outcomes were not categorized according to WHO definitions were excluded from the study.

Results

Demographic and Clinical Characteristics

We thus analyzed 1,665 patient records; 880 patients, constituting 52.8%, received BDQ-containing regimens, while 785 patients, or 47.2%, were on non-BDQ-containing regimens. The median age of patients in the BDQ cohort was 40 years (IQR 31–48), and the median age for those in the non-BDQ cohort was 31 years (IQR 30–48). Males constituted 947/1665 (56.9%) of the total study population, with both cohorts showing a similar gender distribution. There was a high prevalence of HIV co-infection, where 1115/1668 (67%) of the tested patients were positive for HIV. Of these, 954/1115 (85.5%) were on ART. (Table 1).

Six-Month Sputum Culture Conversion

At six months, sputum conversion rates among those receiving BDQ were 609/785 (77.5%) versus 597/880 (67.8%) in the non-BDQ cohort. Large improvements in culture conversion were seen for both the pre-XDR-TB and XDR-TB patients with BDQ treatment. In contrast, in the non-BDQ cohort, a higher percentage of patients remained sputum-positive after six months of treatment (Figure 1). Patients who achieved sputum culture conversion within six months demonstrated significantly better long-term treatment outcomes, including higher rates of treatment success and lower mortality, compared to those with delayed conversion.

Table 1 Demographics and Clinical Characteristics of the Patients (n=1665)

Demographic and Clinical Characteristics		On BDQ n= 785 n (%)	Not on BDQ n= 880 n (%)	P value	Total N= 1665 n (%)
Age	0–14	4 (0.5)	37 (4.2)	**<0.001**	41 (2.5)
	15–34	282 (35.9)	293 (33.3)		575 (34.5)
	35–54	392 (49.9)	426 (48.4)		818 (49.1)
	55–74	101 (12.9)	109 (12.4)		210 (12.6)
	>74	6 (0.8)	15 (1.7)		21(1.3)
Sex	Male	453 (57.7)	494 (56.1)	0.518	947 (56.9)
	Female	332 (42.3)	386 (43.9)		718 (43.1)
Previous exposure to second-line drugs*	Yes	305 (38.9)	342 (38.8)	**0.022**	647 (38.8)
	No	442 (61.1)	508 (61.2)		950 (57.2)
Resistance profile	MDR/RR-TB	668 (87.8)	768 (96.4)	**<0.001**	1436 (92.0)
	Pre-XDR-TB	79 (10.3)	25 (3.1)		104 (6.8)
	XDR-TB	14 (1.9)	3 (0.5)		17 (1.2)
Patient Category	New	443 (63.0)	508 (60.2)		951 (61.5))
	Relapse	152 (21.6)	169 (20.1)		321 (20.8)
	Treatment failure	52 (7.4)	94 (11.2)		146 (9.4)
	TALFU	56 (8.0)	72 (8.5)		128 (8.3)
HIV	Positive	524 (66.7)	591 (67.1)	**0.008**	1115 (67.0)
	On ART	468 (89.3)	486 (82.2)	**0.012**	954 (85.5)
Treatment year	2016	54 (6.9)	425 (48.4)	**0.005**	479 (28.8)
	2017	151 (19.2)	259 (29.4)		410 (24.6)
	2018	311 (39.6)	129 (14.6)		440 (26.4)
	2019	269 (34.3)	67 (7.6)		336 (20.2)
Baseline sputum smear	Positive	531 (67.6)	561 (63.8)	**0.022**	1092 (64.4)
	Negative	254 (32.4)	319 (36.2)		603 (65.6)
Six months culture conversion	Converted to negative	608 (77.5)	597 (67.8)	**0.005**	1205 (72.4)
Six months sputum smear	Positive	38 (4.8)	70 (8.0%)	**<0.001**	108 (6.5)

Notes: *Thirty-eight patients on the BDQ and 30 patients not on the BDQ had no drug history records; 65 were not specified for the patient category, and the P-value was determined using the chi-square test. The bolded values indicate statistical significance.
Abbreviation: TALFU -treatment after loss to follow-up, ART - antiretroviral therapy.

Treatment Outcomes

The proportion of patients with successful treatment outcomes was higher in patients on BDQ-containing regimens, 560/785 (71%), compared to that in the non-BDQ-containing regimens, (549/880) 62% ($p < 0.05$). Among the patients with MDR/RR-TB, the cure rate for those treated with BDQ was 476/668 (71%), while those on non-BDQ regimens had a cure rate of 473/768 (62%). This success was even more pronounced in pre-XDR-TB patients, where 60/79 (76%) of BDQ-treated patients achieved success versus only 1/25 (4%) in the non-BDQ cohort. For XDR-TB patients, the success rate was 9/14 (64%) in the BDQ cohort and 1/3 (33%) in the non-BDQ cohort (Figure 2).

Mortality and Survival

Overall, the mortality rate was 156/785 (20%) among the patients on BDQ-containing regimens versus 381/880 43.3% among the non-BDQ containing regimen ($p < 0.05$). In the subgroup of pre-XDR-TB patients, mortality was strikingly high among non-BDQ cohort patients, in whom 17/25 (68%) of patients died, while the mortality rate in the BDQ cohort was 17/79 (22%) (Figure 2). According to Kaplan–Meier survival analysis, the survival benefit for BDQ-treated patients was statistically significant, as shown by the separation of survival curves over time (Figure 3). The analysis showed that BDQ-based regimens were associated with a significantly higher treatment success rate (71% vs 62%, $p < 0.005$) and reduced mortality. Cox proportional hazards regression revealed that patients on BDQ-containing regimens had a 35% lower risk of mortality compared to those on non-BDQ regimens (HR = 0.65, 95% CI: 0.53–0.87, $p = 0.01$).

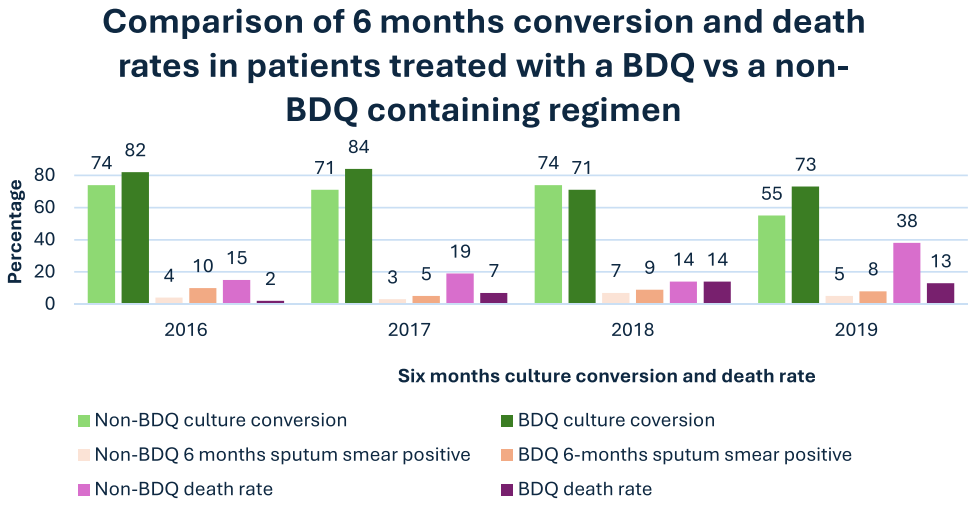

Figure 1 Comparison of the 6-months sputum smear conversion and death rate between BDQ-exposed patients and non-BDQ-exposed patients.

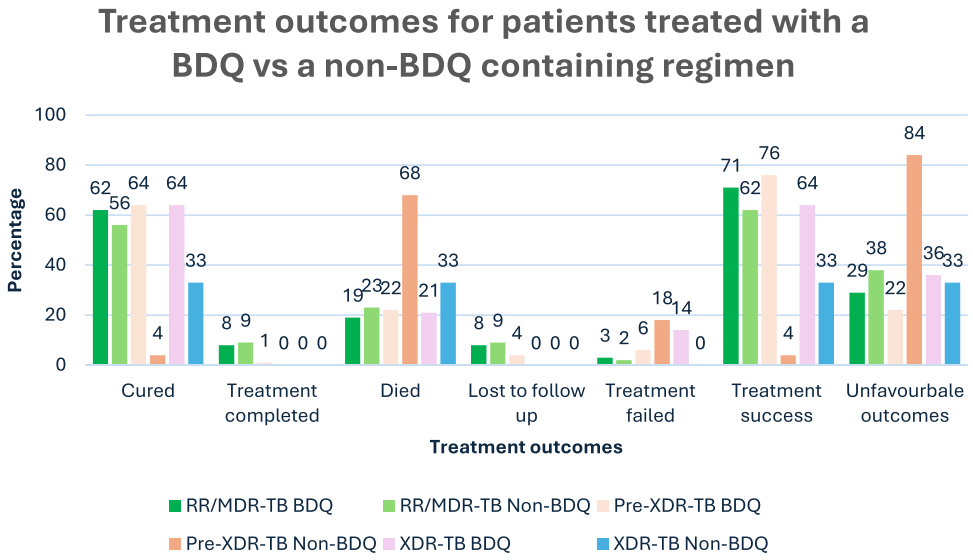

Figure 2 Treatment outcomes observed for DR-TB patients treated with a BDQ containing regimen vs those treated with a non-BDQ containing regimen (n=1665). Treatment success is a combination of cured and treatment completion.

Multivariate Logistic Regression Analysis

In multivariate logistic regression analysis, BDQ use was strongly associated with successful treatment outcome: odds ratio 1.5 (95% CI 1.2–2.0, $p < 0.01$). Other factors independently and significantly associated with successful treatment included gender—female gender was associated with higher odds of successful treatment: odds ratio 1.2 (95% CI 1.0–1.5), $p < 0.05$—and resistance profile, with pre-XDR-TB patients having lower odds of successful treatment: odds ratio 0.6 (95% CI 0.4–0.8, $p < 0.01$). HIV status did not significantly affect treatment success per se, $p = 0.22$, though definitely the overall outcome was better in patients on ART (Table 2).

Key Implications of the Statistical results

BDQ is positively associated with sputum smear conversion and treatment success and significantly reduces mortality, underscoring its critical role in improving outcomes. HIV-positive individuals have reduced odds of treatment success, highlighting the need for tailored interventions. Age: Older age is associated with higher mortality, suggesting age-specific management strategies may be needed.

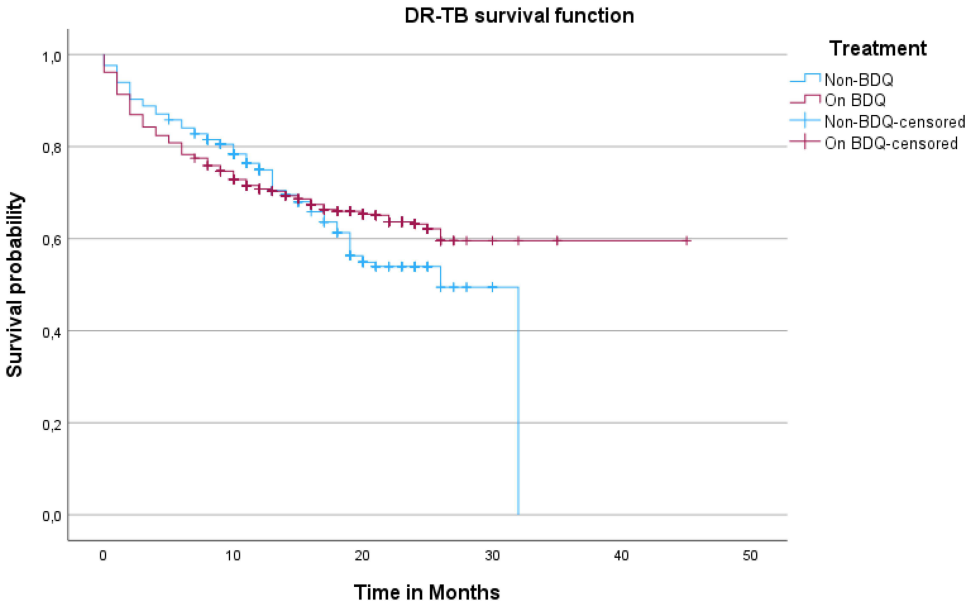

Figure 3 Kaplan–Meier survival curve for deaths defined per WHO treatment outcome for DR-TB infected patients in Limpopo province.

Discussion

These findings indicate the enormous advantages of BDQ in treatment outcomes for DR-TB patients in Limpopo Province. BDQ-containing regimens were associated with higher treatment success rates, faster sputum culture conversion, and lower mortality than non-BDQ regimens. These findings are in tandem with international studies that have shown that BDQ improves MDR/XDR-TB treatment outcomes.[31,32]

The larger proportion of successful treatments among BDQ-treated patients is consistent with other reports emanating from other regions, including South Africa, where BDQ has been reported to bring about improved outcomes, especially in MDR-TB and pre-XDR-TB.[14,31,33,34] Of particular importance is the marked survival advantage of the patients in the BDQ cohort, considering that deaths among those suffering from resistant forms of TB still pose a big challenge. Our study confirms that BDQ offers a survival benefit, especially among the high-risk patient subgroup with advanced drug resistance.

This is even more important, given that the mortality rates in BDQ-treated patients were markedly lower, especially among the pre-XDR-TB patients. In this subgroup, the mortality rate was alarmingly high, amounting to 68% for patients on non-BDQ containing regimen; by contrast, this reduced to 22% in cases where BDQ was included in the regimen, showing thereby

Table 2 Multivariate Logistic Regression Analyses for Key Outcomes in the Studies of BDQ Treatment for MDR/RR-TB, Pre-XDR and XDR-TB

Covariate	Sputum Smear Conversion at 6 Months		Treatment Success		Mortality	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Gender (males)	1.26 (0.72 to 1.22)	0.086	1.231 (1.00 to 1.50)	0.344	0.80 (0.67 to 0.89)	**<0.001**
Age (years)	1.21 (1.01 to 1.69)	0.234	0.96 (0.80 to 1.11)	0.521	1.06 (1.01 to 1.09)	**0.012**
HIV positive	0.99 (0.78 to 1.27)	0.139	0.68 (0.39 to 0.98)	**0.021**	0.91 (0.67 to 3.19)	0.653
Resistance profile*	0.57 (0.43 to 0.76)	0.101	1.13 (0.26 to 2.19)	0.062	1.23 (0.99 to 2.82)	0.142
Previous drug history	0.92 (0.67 to 1.27)	0.944	0.89 (0.65 to 1.23)	0.226	1.23 (1.17 to 2.88)	0.765
Bedaquiline use	1.05 (1.01 to 1.09)	**0.005**	0.39 (0.25 to 0.43)	**<0.001**	0.60 (0.53 to 0.88)	**0.009**

Notes: *Resistance profiles used were MDR/RR-TB pre-XDR-TB and XDR-TB. The bolded values indicate statistical significance.

https://doi.org/10.2147/IDR.S502302

that this drug does have the potential to alter the course of events in difficult TB cases. These findings emphasize the benefit of adding BDQ to existing standard therapies to achieve increased survival in pre-XDR-TB and XDR-TB patients.

Mycobacterial load reduction, evidenced by sputum culture conversion, is one of the most important indicators of response to treatment in TB. Patients receiving BDQ had faster and higher rates of sputum culture conversion at six months, significantly outperforming those in the non-BDQ cohort. Similarly, high rates of conversion were reported by the WHO meta-analysis.[35] Faster culture conversion is associated with reduced transmission risk and better long-term outcomes,[36] suggesting that the benefits of BDQ accrue not only to the individual patients but also have important implications for public health in controlling the spread of TB. The faster sputum culture conversion observed among patients treated with BDQ (77.5% vs 67.8%) not only underscores the drug's efficacy in achieving microbiological clearance but also correlates with improved long-term outcomes, including higher treatment success rates and reduced mortality. These findings suggest that early culture conversion may serve as a key prognostic indicator and a marker of effective TB treatment.

Although the current study has demonstrated the effectiveness of BDQ, its resistance is an emerging concern. In fact, several studies have documented resistance rates in some settings ranging between 2.2% and 7%, one of which was from South Africa and estimated the baseline resistance among BDQ-naïve patients to be at 3.4%.[16,22,23,37] Resistance rates rose dramatically in previously exposed patients.[22,37,38] Another evidence highlights critical findings: 8% of BDQ-naïve patients showed primary resistance, while 47% of those assessed acquired resistance or were reinfected with resistant strains. Mutations in genes such as *Rv0678* and *pepQ* were significantly associated with BDQ resistance, whereas variants in *Rv0676c* and *Rv1979c* were not. The detection of low-level variants via targeted deep sequencing, undetectable by whole-genome sequencing, underscores the complexity of resistance emergence. Factors like baseline fluoroquinolone resistance, prior clofazimine exposure, and regimens containing fewer than five effective drugs were associated with increased likelihood of BDQ resistance acquisition.[11] The present study emphasizes the need for robust DST and resistance monitoring since the long-term efficacy of BDQ might be threatened by unrestricted development of resistance. The rapid scaling up of BDQ use, without parallel development of diagnostic tools to detect resistance, has thus far undermined the effectiveness of this critical TB drug.

In this study, success in treatment was not particularly different among categories based on HIV status; however, generally ART had a much better outcome. Given the high burden of HIV infection in South Africa,[39,40] ART given together with the DR-TB regimen will be of essence to improve survival among co-infected patients. Nevertheless, further studies about BDQ are needed, specifically regarding its interactions with ART and how these interactions affect TB treatment outcomes, to identify any possible interactions of drugs.

Our study found that gender was independently associated with successful treatment outcomes, with female gender being linked to higher odds of treatment success (odds ratio 1.2, 95% CI 1.0–1.5, $p < 0.05$). This aligns with existing literature that suggests females may generally exhibit better adherence to treatment regimens, possibly due to greater health-seeking behavior or a more proactive approach to healthcare.[41–43] Additionally, female patients may experience fewer interruptions to treatment due to societal or behavioral factors, including a higher level of engagement with healthcare services. Our findings support the need for gender-sensitive strategies in TB management, ensuring that both male and female patients receive tailored care that accounts for these differences. Further research is needed to explore the underlying factors contributing to gender-based treatment success, which could inform more effective, personalized approaches in TB control programs.

The limitations to this study are several. First, it is a retrospective analysis and hence may suffer from all the biases related to incomplete or missing data in the EDR Web. Some of the patients had incomplete treatment records; this might have influenced the accuracy in reporting the treatment outcomes. Second, this study did not include a longer-term follow-up beyond the treatment completion period; therefore, relapse rates and long-term treatment durability were not assessable. Third, because there is no elaboration on the comorbidities of the patients, such as diabetes or other immunosuppressive diseases, interpretation of the treatment outcomes may be compromised. Further, although HIV status was captured, viral load and CD4 count information was not available; thus, full assessment of the implications of HIV co-infection on TB treatment outcomes was limited.

Another limitation of this study is the lack of information concerning adverse drug reactions, which is crucial in the evaluation of BDQ's safety profile. Considering that BDQ has the potential of prolonging the QT interval, their frequency and

severity would have been of value in this case. Finally, this was a study conducted among patients in the Limpopo Province alone, and although the findings have relevance for other similar mostly rural resource-poor settings, the results cannot be generalized beyond such regions with different characteristics in their healthcare infrastructure or TB burden profile.

The study is the first large-scale evaluation of BDQ-containing regimens in a mostly rural South African study with a dual high burden of HIV and DR-TB. Furthermore, the study used data routinely collected from patients with DR-TB. Thus, presenting the real-world benefit of a BDQ-based regimen in the treatment of DR-TB in a mostly rural province. The data were also obtained from all the five districts of Limpopo, all of which have unique characteristics allowing data generalization to larger communities with similar characteristics. Given the ongoing global change in resistance patterns, regular monitoring of drug susceptibility during treatment through prospective long-term follow-up studies is crucial for investigating the factors associated with development resistance, especially in patients who have not previously been exposed to the drug.

The study's focus on mostly rural, resource-limited settings fills an important knowledge gap, assessing the effectiveness of BDQ use in resource constrained environments where there is shortage of healthcare resources.

Conclusion

Our retrospective cohort analysis of routinely reported data in the context of a high DR-TB burden setting revealed that BDQ-based treatment regimens were associated with improved outcomes and a significant reduction in mortality in patients with DR-TB compared to the standard regimen. While these findings underscore the potential of BDQ in enhancing treatment success, the study's retrospective design and potential biases must be acknowledged. The lack of longer-term follow-up, absence of detailed patient comorbidity data, and limitations in assessing adverse drug reactions, such as QT interval prolongation, further limits the generalizability of our results. Additionally, as this study was conducted in the Limpopo Province of South Africa, its findings may primarily apply to mostly rural, resource-constrained settings. Monitoring of drug resistance remains imperative for guiding BDQ use, particularly in areas with limited DST resources. The development of reliable and rapid BDQ DST must be prioritized to categorize and care for patients with baseline BDQ resistance. Routine DST should be implemented alongside the scale-up of new regimens, despite the ongoing challenges in achieving rapid DST for BDQ.

Author Contributions

All authors played an important role in the work presented, whether through the conception, study design, execution, data collection, analysis and interpretation, or across these areas. They contributed to drafting, revising, or critically reviewing the article, approved the final version for publication, agreed on the journal for submission, and took responsibility for all aspects of the work.

Funding

No funding support is associated with this study.

Disclosure

Dr Sarah Fortune reports personal fees from Oxford Nanopore, outside the submitted work. The authors have no competing interests.

References

1. World Health Organization. Global tuberculosis report. 2023. Available from: https://www.who.int/publications/i/item/9789240083851. Accessed February 19, 2024.
2. Varshney K, Anaele B, Molaei M, Frasso R, Maio V. Risk factors for poor outcomes among patients with extensively drug-resistant tuberculosis (XDR-TB): a scoping review. *Infect Drug Resist*. 2021;14:5429–5448. doi:10.2147/IDR.S339972
3. Safaev K, Parpieva N, Liverko I, et al. Trends, characteristics and treatment outcomes of patients with drug-resistant tuberculosis in Uzbekistan: 2013-2018. *Int J Environ Res Public Health*. 2021;18(9):4663. doi:10.3390/IJERPH18094663
4. Sharma N, Khanna A, Chandra S, et al. Trends & treatment outcomes of multidrug-resistant tuberculosis in Delhi, India (2009-2014): a retrospective record-based study. *Indian J Med Res*. 2020;151(6):598–603. doi:10.4103/IJMR.IJMR_1048_18
5. Dheda K, Mirzayev F, Cirillo DM, et al. Multidrug-resistant tuberculosis. *Nat Rev Dis Primers*. 2024;10(1). doi:10.1038/s41572-024-00504-2

6. World Health Organization. 2024 global tuberculosis report. World Health Organization. 2024. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024. Accessed April 02, 2025.
7. Bu Q, Qiang R, Fang L, Peng X, Zhang H, Cheng H. Global trends in the incidence rates of MDR and XDR tuberculosis: findings from the global burden of disease study 2019. *Front Pharmacol*. 2023;14:1156249. doi:10.3389/FPHAR.2023.1156249/BIBTEX
8. Olayanju O, Limberis J, Esmail A, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. *Europ Resp J*. 2018;51(5):1800544. doi:10.1183/13993003.00544-2018
9. Ndjeka N, Schnippel K, Master I, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. *Europ Resp J*. 2018;52(6):1–9. doi:10.1183/13993003.01528-2018
10. National Department of Health South Africa. Introduction of new drugs and drug regimens for the management of drug-resistant tuberculosis in. 2015. Available from: https://www.nicd.ac.za/assets/files/IntroductionofnewdrugsanddrugregimensforthemanagementofdrugresistantTBinSA-2015.pdf. Accessed April 02, 2025
11. Derendinger B, Dippenaar A, de Vos M, et al. Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study. *Lancet Microbe*. 2023;4(12):e972–e982. doi:10.1016/S2666-5247(23)00172-6
12. Ndjeka N, Campbell JR, Meintjes G, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. *Lancet Infect Dis*. 2022;22(7):1042–1051. doi:10.1016/S1473-3099(21)00811-2
13. Singh B, Singh C. Bedaquiline in drug-resistant tuberculosis: a mini-review. *Curr mol Pharmacol*. 2023;16(3):243–253. doi:10.2174/1874467215666220421130707
14. Pai H, Ndjeka N, Mbuagbaw L, et al. Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: a retrospective cohort analysis. *BMC Infect Dis*. 2022;22(1):1–15. doi:10.1186/s12879-022-07861-x
15. Worley MV, Estrada SJ. Bedaquiline: a novel antitubercular agent for the treatment of multidrug-resistant tuberculosis. *Pharmacotherap J Human Pharmacol Drug Therapy*. 2014;34(11):1187–1197. doi:10.1002/PHAR.1482
16. Omar SV, Ismail F, Ndjeka N, Kaniga K, Ismail NA. Bedaquiline-Resistant tuberculosis associated with Rv0678 mutations. *N Engl J Med*. 2022;386(1):93–94. doi:10.1056/NEJMC2103049
17. Dlamini MT, Lessells R, Iketleng T, de Oliveira T. Whole genome sequencing for drug-resistant tuberculosis management in South Africa: what gaps would this address and what are the challenges to implementation? *J Clin Tuberc Other Mycobact Dis*. 2019;16:100115. doi:10.1016/j.jctube.2019.100115
18. Kaniga K, Aono A, Borroni E, et al. Validation of bedaquiline phenotypic drug susceptibility testing methods and breakpoints: a multilaboratory, multicountry study. *J Clin Microbiol*. 2020;58(4). doi:10.1128/JCM.01677-19
19. Tong E, Zhou Y, Liu Z, et al. Bedaquiline resistance and molecular characterization of rifampicin-resistant mycobacterium tuberculosis isolates in Zhejiang, China. *Infect Drug Resist*. 2023;16:6951–6963. doi:10.2147/IDR.S429003
20. Vu DH, Anthony RM, Bañuls AL, Vu DH, Alffenaar JWC, Alffenaar J-WC. Bedaquiline resistance: its emergence, mechanism, and prevention. *Clin Infect Dis*. 2018;66(10):1625–1630. doi:10.1093/CID/CIX992
21. Kaniga K, Hasan R, Jou R, et al. Bedaquiline drug resistance emergence assessment in multidrug-resistant tuberculosis (MDR-TB): a 5-year prospective in vitro surveillance study of bedaquiline and other second-line drug susceptibility testing in MDR-TB isolates. *J Clin Microbiol*. 2022;60(1). doi:10.1128/JCM.02919-20
22. Timm J, Bateson A, Solanki P, et al. Baseline and acquired resistance to bedaquiline, linezolid and pretomanid, and impact on treatment outcomes in four tuberculosis clinical trials containing pretomanid. *PLOS Global Public Health*. 2023;3(10). doi:10.1371/journal.pgph.0002283
23. 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(4):496–506. doi:10.1016/S1473-3099(21)00470-9
24. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893–902. doi:10.1056/NEJMOA1901814
25. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med*. 2018;6(9):699–706. doi:10.1016/S2213-2600(18)30235-2
26. Tshitangano TG, Ramaliba TM, Akinsola HA, Thendele M. Tuberculosis risk factors in Lephalale local municipality of Limpopo province, South Africa. *South African Family Practice*. 2017;59(5):38. doi:10.4102/SAFP.V59I5.4557
27. Massyn N, Day C, Ndlovu N, Padayachee T. District health barometer 2019/2020. Health Systems Trust. 2020. Available from: https://www.hst.org.za/publications/Pages/DHB2019-20.aspx. Accessed July 9, 2023.
28. Kudakwashe V. Migrants in South Africa have access to healthcare: why it's kicking up a storm - wits university. University of the Witswatersrand. 2022. Available from: https://www.wits.ac.za/news/latest-news/opinion/2022/2022-08/migrants-in-south-africa-have-access-to-healthcare-why-its-kicking-up-a-storm.html. Accessed August 27, 2024.
29. Ginsburg C, Collinson MA, Gómez-Olivé FX, et al. Internal migration and health in South Africa: determinants of healthcare utilisation in a young adult cohort. *BMC Public Health*. 2021;21(1). doi:10.1186/s12889-021-10590-6
30. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014. 403. Published online.
31. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9153 patients. *PLoS Med*. 2012;9(8). doi:10.1371/JOURNAL.PMED.1001300
32. Cegielski JP, Kurbatova E, Van Der Walt M, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. *Clin Infect Dis*. 2016;62(4):418–430. doi:10.1093/CID/CIV910
33. Zhao Y, Fox T, Manning K, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis*. 2019;68(9):1522–1529. doi:10.1093/CID/CIY727
34. El Hamdouni M, Bourkadi JE, Benamor J, Hassar M, Cherrah Y, Ahid S. Treatment outcomes of drug resistant tuberculosis patients in Morocco: multi-centric prospective study. *BMC Infect Dis*. 2019;19(1):1–7. doi:10.1186/S12879-019-3931-5/TABLES/4

35. World Health Orgnaization. Report of the guideline development group meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: a review of available evidence. Geneva, Switzerland. World Health Organization. 2016 Published online 2017. https://iris.who.int/handle/10665/254712.
36. Lu P, Liu Q, Martinez L, et al. Time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis: a prospective cohort study from urban China. *Europ Resp J*. 2017;49(3):1601558. doi:10.1183/13993003.01558-2016
37. Ismail NA, Omar SV, Joseph L, et al. Defining Bedaquiline susceptibility, resistance, cross-resistance and associated genetic determinants: a retrospective cohort study. *EBioMedicine*. 2018;28:136–142. doi:10.1016/J.EBIOM.2018.01.005
38. 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(2). doi:10.1093/jacamr/dlac029
39. Kubjane M, Osman M, Boulle A, Johnson LF. The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: a mathematical modeling analysis. *Inter J Infect Dis*. 2022;122:811–819. doi:10.1016/j.ijid.2022.07.047
40. Wondmeneh TG, Mekonnen AT. The incidence rate of tuberculosis and its associated factors among HIV-positive persons in Sub-Saharan Africa: a systematic review and meta-analysis. *BMC Infect Dis*. 2023;23(1). doi:10.1186/s12879-023-08533-0
41. Murphy ME, Wills GH, Murthy S, et al. Gender differences in tuberculosis treatment outcomes: a post hoc analysis of the REMoxTB study. *BMC Med*. 2018;16(1):1–11. doi:10.1186/s12916-018-1169-5
42. Feng JY, Huang SF, Ting WY, et al. Gender differences in treatment outcomes of tuberculosis patients in Taiwan: a prospective observational study. *Clin Microbiol Infect*. 2012;18(9):E331–E337. doi:10.1111/j.1469-0691.2012.03931.x
43. Baluku JB, Mukasa D, Bongomin F, et al. Gender differences among patients with drug resistant tuberculosis and HIV co-infection in Uganda: a countrywide retrospective cohort study. *BMC Infect Dis*. 2021;21(1):1–11. doi:10.1186/s12879-021-06801-5