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Comparative Analysis of Treatment Outcomes in Drug-Resistant Tuberculosis Patients with and Without Bedaquiline in Pakistan: A Retrospective Cohort Study

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Abstract
Background: Multidrug-resistant tuberculosis (MDR-TB) poses a significant threat to global TB control, with new drugs such as bedaquiline being introduced to improve treatment outcomes. This study aimed to compare the treatment outcomes of drug-resistant TB (DR-TB) patients treated with and without bedaquiline.
Methods: We conducted a retrospective cohort analysis of 450 patients registered in Pakistan's rifampicin-resistant tuberculosis case registry (ENRS) between January 1, 2015, and December 31, 2022. Of these, 32 patients received bedaquiline, while 418 did not. Key demographic and clinical characteristics were compared between groups. Kaplan-Meier survival analysis was performed to assess survival probabilities. The primary outcomes were treatment success, failure, loss to follow-up (LTFU), and mortality.
Results: No significant difference in overall treatment success was observed between patients treated with bedaquiline (81.3%) and those without bedaquiline (78.9%) (p=0.75). Both groups had a high cure rate, with 75.0% of bedaquiline-treated patients and 74.6% of non-bedaquiline patients achieving a cure (p=0.85). However, no treatment failures were recorded in the bedaquiline group, compared to a 4.8% failure rate in the non-bedaquiline group. Kaplan-Meier survival analysis revealed similar survival probabilities between MDR-TB and rifampicin-resistant TB patients, irrespective of bedaquiline use. Urban residence was significantly associated with bedaquiline use (p=0.007), suggesting better access to newer treatments in urban areas.
Conclusion: Although bedaquiline did not significantly alter overall treatment outcomes in this cohort, its use appears to prevent treatment failure, particularly in complex DR-TB cases. Sociodemographic factors, such as urban residence, are critical in determining bedaquiline access. Equitable access to advanced TB therapies and optimizing bedaquiline use in combination regimens remain essential for improving MDR-TB treatment outcomes. Further research is needed to explore the long-term impact of bedaquiline in diverse populations.

Keywords: Multidrug-resistant tuberculosis, Bedaquiline, Treatment outcomes, Retrospective cohort, Pakistan, Drug-resistant tuberculosis, Kaplan-Meier, Tuberculosis

Introduction

The ongoing prevalence of multidrug-resistant tuberculosis (MDR-TB) threatens TB control efforts. MDR-TB is characterized as a tuberculosis strain exhibiting resistance to at least isoniazid and rifampicin (Dheda et al., 2024). In 2017, approximately 600,000 new cases of multidrug-resistant or rifampicin-resistant tuberculosis were expected to have occurred worldwide (Tiberi et al., 2021). Detection rates have more than doubled in countries such as China, India, and Russia in recent years, with about 20% of Mycobacterium tuberculosis isolates worldwide now exhibiting resistance to at least one first- or second-line anti-TB medication (Farhat et al., 2024). Approximately 10% of global multidrug-resistant tuberculosis (MDR-TB) strains are believed to be extensively drug-resistant tuberculosis (XDR-TB), characterized by added resistance to a fluoroquinolone and a second-line injectable medication (Nehru et al., 2024). These strains may undermine worldwide TB management due to their association with elevated mortality and morbidity, posing a significant threat to healthcare personnel and incurring unsustainable treatment costs in nations with high TB incidence (Paleckyte et al., 2021). In 2016, around 7.1% of patient samples examined in South Africa were rifampicin-resistant or multidrug-resistant tuberculosis (MDR-TB), with about 8% classified as extensively drug-resistant tuberculosis (XDR-TB) (Salaam-Dreyer, 2021). It was projected that MDR-/XDR-TB

would account for over 80% of tuberculosis treatment expenditures in South Africa during 2017/2018, notwithstanding the prevalence of MDR-TB (Diriba et al., 2023).

Novel pharmaceuticals, including bedaquiline and delamanid, have been formulated for the management of MDR/RR-TB, with their efficacy established by randomized controlled trials and cohort studies (Ahmed et al., 2024). Consequently, the 2019 WHO guidelines advocated for the utilization of these novel medications in the treatment of individuals with MDR/RR-TB (Mirzayev et al., 2021). The updated guidelines advocate for bedaquiline as an essential medication in the usual combination therapy for rifampin-resistant tuberculosis (Shaw et al., 2024). Consequently, the population of patients qualified for bedaquiline-containing regimens will markedly rise (Shim et al., 2023). Promising findings from research on bedaquiline's application in all-oral, shorter-course regimens for treating rifampin-resistant tuberculosis will likely lead to increased utilization of bedaquiline by tuberculosis control programs (Han et al., 2021). The increased utilization of bedaquiline necessitates not only comprehensive pharmacovigilance to track side effects but also the establishment of the capacity to swiftly detect the onset of resistance in patients undergoing treatment (Berry et al., 2022).

Bedaquiline is a diarylquinoline that obstructs mycobacterial ATP synthase activity (Courbon et al., 2023). As of June 2017, a minimum of 89 nations reported the utilization of bedaquiline for the treatment of rifampicin-resistant TB (E. Chesov et al., 2021). Results from the clinical trial indicated an increase in the percentage of patients with multidrug-resistant tuberculosis who achieved a negative sputum culture at 8 weeks, rising from 9% to 48%, following the addition of bedaquiline to a standard multidrug-resistant tuberculosis regimen, without a significant rise in the incidence or severity of adverse drug reactions (Dooley et al., 2021). However, interim WHO recommendations advise the use of bedaquiline in cases of rifampicin-resistant tuberculosis just where there is resistance to second-line drugs, the patient is ineligible for routine treatment for rifampicin-resistant tuberculosis, or when no alternative treatment alternatives are available (Organization, 2022). Due to the documented heightened mortality risk, regulatory approvals in the USA incorporated a black box warning, stipulating that bedaquiline should only be utilized when an effective treatment plan is not feasible (Willmer, 2023).

Methods

Setting and standard of care

Establishing and upholding a standard of care Per the WHO 2022 treatment guidelines, a standard long-course regimen was the recommended treatment for newly diagnosed cases of multidrug-resistant or rifampicin-resistant tuberculosis in South Africa, unless an individualized regimen was warranted due to documented resistance or drug intolerance (Gao et al., 2024). The treatment for standard multidrug-resistant and rifampicin-resistant tuberculosis comprises two phases (Bereda, 2022): the intensive phase, which lasts six months and includes five medications (kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide); and the continuation phase, which lasts twelve to eighteen months and involves four medications (moxifloxacin, ethionamide, terizidone, and pyrazinamide) (Bereda, 2022; Daley, 2022). Personalized therapy protocols may incorporate high-dose isoniazid, para-aminosalicylic acid, clofazimine, or capreomycin for patients with pre-extensively drug-resistant or extensively drug-resistant tuberculosis. Linezolid's availability was constrained due to its cost and potential toxicity (Graciaa et al., 2023).

Data Source

Pakistan National Tuberculosis Programme has utilized the electronic nominal recording and reporting system (ENRS) to monitor treatment outcomes and patients with drug-resistant tuberculosis. As a conclusive treatment outcome, fatalities occurring during drug-resistant tuberculosis treatment, irrespective of the reason, are documented within ENRS. Standard WHO definitions are employed to disclose additional ENRS final treatment outcomes. We also used data from TB registers, which accurately monitor over 80% of all fatalities in the country.

Study Design and Participants

We performed a retrospective cohort analysis utilizing data from patients registered in the Pakistan rifampicin-resistant tuberculosis case registry (ENRS). Patients who began treatment before January 1, 2015, or after December 31, 2022, as well as those older than 17 years, were not included in our study. The start date for our time-to-event analysis was the date when drug-resistant tuberculosis treatment was started. The date of the final treatment outcome was utilized when accessible.

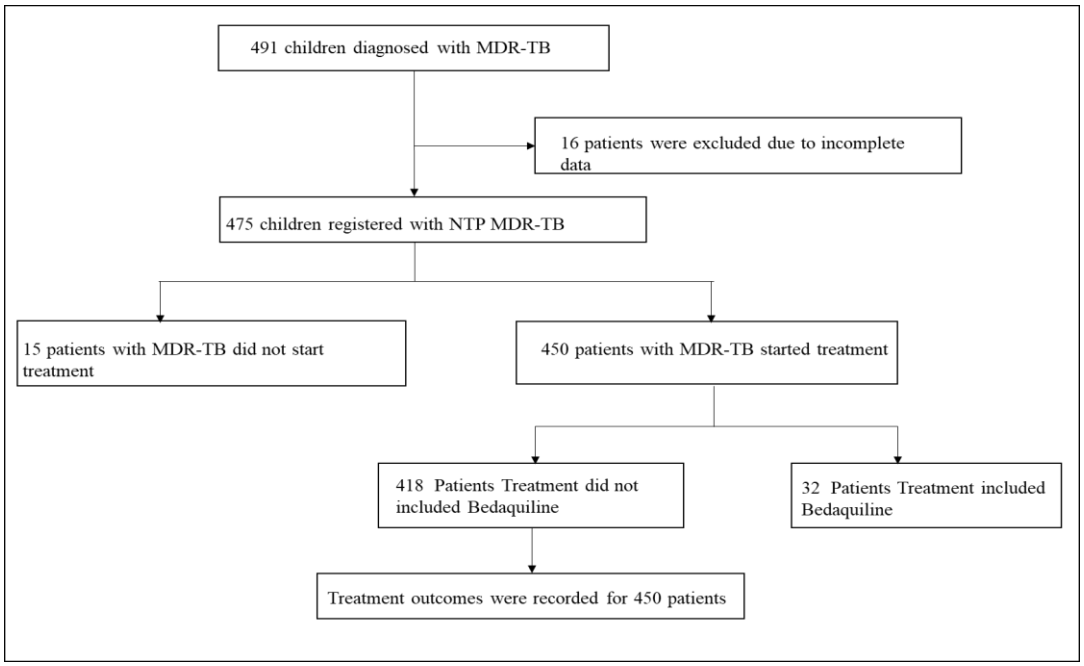

Figure 1: Study Flow chart

Results

Characteristics of the participants

In this cohort of 450 patients, comprising 418 who did not receive Bedaquiline and 32 who did, key demographic and clinical characteristics were analyzed. The majority of patients in both groups were female (52.2% and 46.9%, respectively), and there was no statistically significant difference in gender distribution (p=0.56). Age distribution showed that most patients were between 5–14 years old (64.1% without Bedaquiline, 71.9% with Bedaquiline), with no significant differences across age groups (p=0.51).

Weight status revealed that 84.4% of patients on Bedaquiline were underweight compared to 76.3% in the no Bedaquiline group (p=0.29). Residence significantly differed between groups, with 93.7% of patients on Bedaquiline residing in urban areas compared to 71.8% in the no-Bedaquiline group (p=0.007). Case registration showed a higher proportion of new cases in the Bedaquiline group (62.5% vs. 31.6%, p<0.001).

Regarding the type of drug-resistant tuberculosis (DR-TB), MDR-TB was predominant in both groups (75.4% without Bedaquiline, 71.9% with Bedaquiline, p=0.66). Lung cavitation was also similar between groups, with 69.4% and 68.8% of patients having bilateral cavitation (p=0.94). However, comorbidity rates differed significantly, with only 21.9% of patients on Bedaquiline reporting comorbidities, compared to 62.7% in the no Bedaquiline group (p<0.001).

Table 1. Characteristics of Participants in the study

Characteristics	No Bedaquiline (n=418)	Bedaquiline (n= 32)	Total (n= 450)	p-value
Gender				
Male	200(47.8)	17(53.1)	217(48.2)	0.56
Female	218(52.2)	15(46.9)	233(51.8)	
Age				
0-4 months	19(4.5)	2(6.3)	21(4.7)	0.51
5-14 years	268(64.1)	23(71.9)	291(64.7)	
15-24 years	131(31.3)	7(21.9)	138(30.7)	
Weight				
Underweight	319(76.3)	27(84.4)	346(76.9)	0.29
Normal weight	99(23.7)	5(15.6)	104(23.1)	
Residence				
Urban	300(71.8)	30(93.7)	330(73.3)	**0.007**
Rural	118(28.2)	2(6.3)	120(26.7)	
Case Registration				
New Case	132(31.6)	20(62.5)	152(33.8)	**<0.001**
Retreated Case	286(68.4)	12(37.5)	298(66.2)	
Type of DR-TB				
MDR-TB	315(75.4)	23(71.9)	338(75.1)	0.66
MDR Rifampicin resistance	103(24.6)	9(28.1)	112(24.9)	
Lungs Cavitation				

Unilateral cavitation	128(30.6)	10(30.6)	138(30.6)	0.94
Bilateral cavitation	290(69.4)	22(68.8)	312(69.3)	
Comorbidity				
Yes	262(62.7)	7(21.9)	269(59.8)	**<0.001**
No	156(37.3)	25(78.1)	181(40.2)	

Treatment Outcomes

In this analysis of 450 patients with drug-resistant tuberculosis (DR-TB), including 418 patients not treated with Bedaquiline and 32 who received Bedaquiline, treatment outcomes were largely comparable between the two groups. The cure rate was high in both groups, with 75.0% of Bedaquiline-treated patients and 74.6% of those not treated with Bedaquiline being cured (p=0.85). Treatment completion was slightly higher in the Bedaquiline group (6.3% vs. 4.3%), while loss to follow-up (LTFU) and mortality rates were similar across both groups (LTFU: 6.3% vs. 5.5%; died: 6.3% vs. 5.3%). No treatment failures were observed in the Bedaquiline group, compared to a 4.8% failure rate in the non-Bedaquiline group.

When categorized by treatment success, 81.3% of patients on Bedaquiline achieved successful outcomes, compared to 78.9% in the non-Bedaquiline group (p=0.75). Unsuccessful outcomes, including treatment failure, death, and loss of follow-up, were reported in 18.8% of Bedaquiline patients and 21.1% of non-Bedaquiline patients. Overall, the results suggest that Bedaquiline use does not significantly alter the likelihood of treatment success or failure in this cohort.

Table 2 Treatment outcomes of the participants

Characteristics	No Bedaquiline (n=418)	Bedaquiline (n= 32)	Total (n= 450)	p-value
Type of DR TB				
MDR	315(75.4)	23(71.9)	338(75.1)	0.66
MTB Rif. Res	103(24.6)	9(28.1)	112(24.9)	
Treatment outcomes				
Cured	312(74.6)	24(75.0)	336(74.7)	0.85
Treatment completed	18(4.3)	2(6.3)	20(4.4)	
LTFU	23(5.5)	2(6.3)	25(5.6)	
Failed	20(4.8)	0	20(4.4)	
Died	22(5.3)	2(6.3)	24(5.3)	
Not evaluated	6(1.4)	0	6(1.3)	
Shifted to LTR	17(4.1)	2(6.3)	19(4.2)	
Treatment category				
Successful	330(78.9)	26(81.3)	356(79.1)	0.75
Unsuccessful	88(21.1)	6(18.8)	94(20.9)	

Survival Analysis

The Kaplan-Meier survival curve illustrates the cumulative survival function for two types of drug-resistant tuberculosis (DR-TB) patients: those with multidrug-resistant tuberculosis (MDR-TB) and those with rifampicin-resistant tuberculosis (MTB Rif Res). The survival probability decreases over time for both groups, with a similar overall trend in survival. Both the MDR and MTB Rif Res groups demonstrate stepwise declines in survival probability, with censored observations marked at key time points. By the fifth time point, both groups have reached a cumulative survival rate below 0.4, indicating significant mortality or treatment failure by this stage. There is no substantial difference between the survival outcomes of MDR-TB and MTB Rif Res patients, as the curves for both groups remain close throughout the follow-up period.

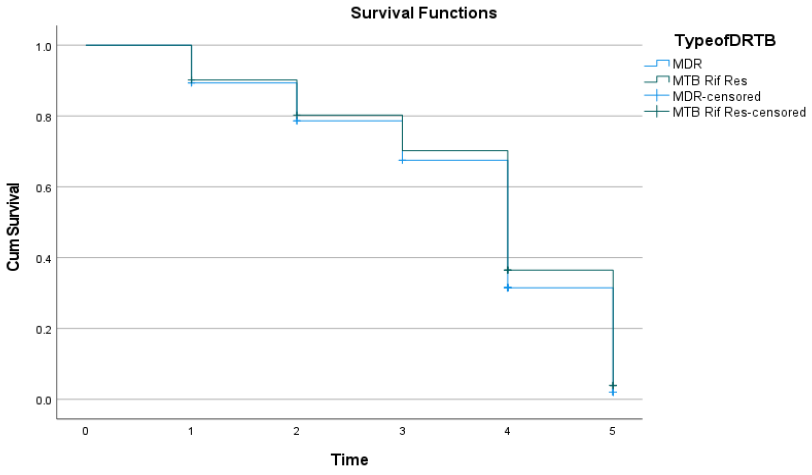

Figure 2: Kaplan-Meier survival curve, by regimen inclusive of bedaquiline

Mortality in MDR-TB Patients

The Kaplan-Meier survival curve demonstrates the cumulative survival functions for two patient groups based on mortality: those who survived and those who died during the follow-up period. The survival probability gradually decreases over time, with distinct drops observed at several time points. By the fifth time point, survival rates have declined significantly, with less than 20% cumulative survival for those in the mortality group. Censored data points are marked, indicating observations where follow-up was incomplete.

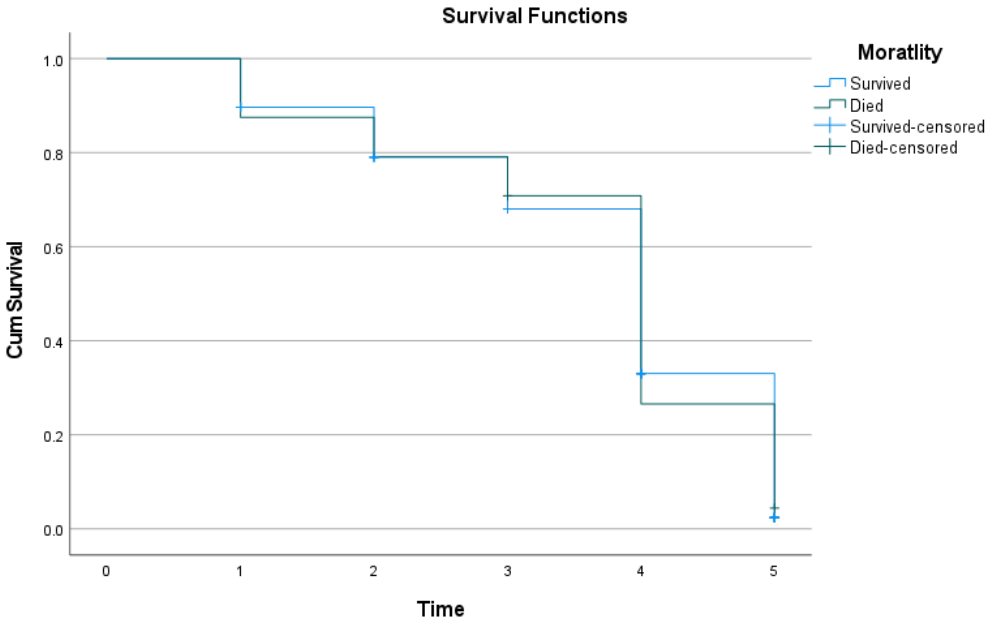

Figure 3 Kaplan-Meier Survival Curve for Mortality in MDR-TB Patients

Discussion

In this retrospective cohort study analyzing 450 patients with drug-resistant tuberculosis (DR-TB), we compared the outcomes of individuals treated with and without bedaquiline, a novel anti-tuberculosis drug approved for managing multidrug-resistant TB (MDR-TB) (Deshkar & Shirure, 2022). Our analysis showed no significant difference in the overall success rates between the two groups, suggesting that while bedaquiline is a valuable addition to DR-TB treatment regimens, it may not drastically alter treatment outcomes within this cohort. These results are in line with the study conducted in high-burden countries where there is no significant effect of bedaquiline on treatment outcomes (D. Chesov et al., 2021). In contrast to this finding a meta-analysis proved that bedaquline-containing regimens improve treatment success rate by 30% (Jihwaprani et al., 2024).

The demographic distribution of patients in our study is consistent with global MDR-TB data, which often shows a higher burden among younger populations and females. Although a slightly higher proportion of patients on bedaquiline were female (46.9%) compared to those not receiving the drug (52.2%), this difference was not statistically significant. Women in low- and middle-income countries often face limited access to healthcare due to cultural, financial, and logistical constraints (Sangy et al., 2023). Gender-based discrimination in some societies further delays their access to timely and appropriate medical care, which can result in incomplete TB treatment, increasing the likelihood of developing MDR-TB (Naidoo et al., 2024). Additionally, societal norms that prioritize the healthcare needs of men may cause women to seek medical attention later, raising the risk of treatment failure and drug resistance (Campesi et al., 2021). Age, similarly, did not significantly differ between the groups, with the majority of patients being in the 5–14-year age range (71.9% in the bedaquiline group and 64.1% in the non-bedaquiline group).

Of particular note is the weight status of patients: 84.4% of those treated with bedaquiline were underweight, as compared to 76.3% in the non-bedaquiline group. Although this difference did not reach statistical significance, the high prevalence of underweight status highlights the malnutrition commonly associated with TB and its potential role in modulating treatment outcomes. In contrast to our findings, several studies proved that malnutrition is both a risk factor for developing TB and a complication that can arise from the disease itself. This bidirectional relationship creates a cycle that can adversely affect the efficacy of TB treatment and contribute to poor clinical outcomes, including increased mortality and treatment failure (Tobing et al., 2021; VanValkenburg et al., 2022).

Residence, however, emerged as a significant factor, with the vast majority (93.7%) of bedaquiline patients residing in urban areas, compared to 71.8% in the non-bedaquiline group ($p=0.007$). This finding may reflect the concentration of advanced healthcare facilities in urban regions, where access to newer treatments like bedaquiline is more feasible. Urban residence may also be indicative of better healthcare infrastructure, which could influence treatment adherence and outcomes. Moreover, the study conducted in China also proved the same (Liu et al., 2023). The higher rate of new case registration in the bedaquiline group (62.5% vs. 31.6%, $p<0.001$) further suggests that bedaquiline use may be prioritized for newly diagnosed cases or those deemed more challenging to treat with standard regimens. These findings are in line with the study conducted by Hewison and colleagues (Hewison et al., 2022)

Our study found comparable treatment success rates between patients who received bedaquiline (81.3%) and those who did not (78.9%), with no statistically significant difference in outcomes (p=0.75). This is consistent with findings from prior studies (Afifi et al., 2024; Ndjeka et al., 2022) that demonstrate the effectiveness of bedaquiline in achieving cure or treatment completion without substantially altering the overall treatment trajectory in certain populations. The comparable loss to follow-up and mortality rates between the two groups, though not significantly different, suggest that while bedaquiline is a promising addition to DR-TB treatment regimens, other factors—such as the social and healthcare context—may play a more pivotal role in influencing outcomes.

Interestingly, no treatment failures were recorded in the bedaquiline group, in contrast to a 4.8% failure rate in the non-bedaquiline group. This finding aligns with clinical trials that have demonstrated the efficacy of bedaquiline in improving sputum culture conversion (Fu et al., 2021), which could contribute to preventing treatment failure. However, this study's relatively small sample size of bedaquiline recipients (n=32) limits the generalizability of these findings, and further research is necessary to confirm this trend in larger cohorts.

The Kaplan-Meier survival analysis, which did not reveal a significant difference between survival outcomes of MDR-TB and MTB Rif Res patients, also underscores the challenge of managing drug-resistant TB. The same results are proven in the study conducted in East China and South Africa which showed that despite treatment with or without bedaquiline, the survival probability for both groups declined similarly over time, suggesting that while the drug is an important part of the therapeutic armamentarium, other factors such as patient comorbidities, adherence to treatment, and healthcare access are critical in determining long-term survival (Saimen, 2021; Zhang et al., 2022).

Although bedaquiline did not significantly improve overall treatment outcomes in this cohort, its incorporation into MDR-TB regimens remains crucial, particularly in challenging cases with extensive drug resistance or intolerance to other medications (Dookie et al., 2022; Oelofse et al., 2021). The lack of significant differences in treatment outcomes may reflect the rigorous selection criteria for bedaquiline use, as recommended by the World Health Organization (WHO), limiting its use to the most severe or complex cases of DR-TB (Organization, 2021). The absence of treatment failures in the bedaquiline group could indicate that the drug is particularly effective in stabilizing otherwise intractable cases.

The increasing utilization of bedaquiline, especially in all-oral, shorter-course regimens, has significant implications for national TB programs, particularly in low- and middle-income countries like Pakistan, where healthcare infrastructure and access to novel drugs may be limited (Enane & Christenson, 2021). The urban bias observed in our cohort raises concerns about equitable access to advanced TB therapies, necessitating targeted interventions to ensure that rural populations can benefit from these newer treatments.

Additionally, our data are drawn from a single country, Pakistan, and may not be generalizable to other settings, particularly those with different healthcare systems and TB burdens. Further research is needed to explore the long-term impact of bedaquiline on mortality and morbidity in larger and more diverse populations.

Moving forward, robust pharmacovigilance systems are essential to monitor for adverse events and resistance emergence in patients treated with bedaquiline. Given its novel mechanism of action and association with increased survival in some studies, bedaquiline should continue to be evaluated in different cohorts, with particular attention to optimizing its use in combination with other anti-TB drugs.

Conclusion

While bedaquiline is a vital addition to the DR-TB treatment arsenal, our findings suggest that it does not significantly alter treatment success rates in this cohort. Sociodemographic factors, such as urban residence and case registration status, seem to play more prominent roles in determining access to bedaquiline and, potentially, treatment outcomes. Ensuring equitable access to advanced DR-TB therapies like bedaquiline and continuing to refine treatment protocols based on patient characteristics will be critical in improving TB control efforts, particularly in countries with high burdens of MDR- and XDR-TB.

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