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QTc Interval Prolongation in Drug-Resistant Tuberculosis Treated with Bedaquiline and Delamanid Under Programmatic Conditions: A Prospective Cohort Study

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Abstract

This study aimed to analyze the QTc interval during six months of treatment and factors associated with QTc interval prolongation in DR-TB patients receiving regimens containing bedaquiline-delamanid. We conducted a prospective cohort study of drug-resistant tuberculosis (DR-TB) patients who received regimens containing bedaquiline and delamanid between September 2022 and May 2023 at the outpatient department of MDR-TB of the Dr. Soetomo Hospital. Patients were divided into bedaquiline and bedaquiline-delamanid-containing regimen groups, respectively. QTc interval was evaluated before and until the sixth month of treatment using ECG. QTc interval prolongation was categorized as clinically significant if the absolute QTc value was≥ 500 ms or the QTc change was > 60 ms. Sixty-three (63) DR-TB patients enrolled in this cohort, consisting of 51 and 12 patients in the bedaquiline and the bedaquiline-delamanid group, respectively. Grade II and III of QTc interval prolongation was higher in the bedaquiline-delamanid than in the bedaquiline group, 41.7% vs. 8.3%; 15.7% vs. 1.9%, respectively, P-value 0.084. The mean QTc interval was significantly higher from the second week to the sixth month in the bedaquiline-delamanid group compared to the bedaquiline group, P-value < 0.05. However, the mean difference in QTc interval was < 60 ms between the two groups during six months of treatment, with a P-value ≥ 0.05. No patients had serious cardiac events during the study period. Potassium and calcium levels were associated with QTc interval prolongation, P-value < 0.05. We observed modest prolongation of QTc, maximal at the fourth month, and there were no recorded arrhythmias or related deaths. In patients with drug-resistant tuberculosis, this study offers evidence in favor of using these regimens in combination in programmatic treatment.

Key words: Bedaquiline; Delamanid; DR-TB; QTc Interval

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Introduction

Drug-resistant tuberculosis (DR-TB) is characterized by resistance to rifampicin and or isoniazid, with or without resistance to other second-line antituberculosis drugs[1]. According to the WHO Global TB Report 2024, in Indonesia, the estimated proportion of new TB cases with multidrug-resistant (MDR-TB) or rifampicin-resistant (RR-TB) was 2.9% and the estimated proportion of previously treated cases with MDR/RR-TB was 6.0-11.9%[2]. Two novel antitubercular drugs, bedaquiline and delamanid, have been incorporated into DR-TB treatment with high bactericidal and excellent sterilizing activity. WHO categorizes bedaquiline as a group A and delamanid as a group C drug to be included as a part of the individualized treatment regimen for DR-TB If one or more drugs from class A and class B can not be administered to the patients due to adverse effects or contraindication, drugs from class C can be administered. Therefore, patients will receive at least five effective drugs[3].

Studies reported that regimens containing bedaquiline or delamanid demonstrate highly favorable outcomes, including sputum culture conversion and cure rate[4,5]. In addition to effectiveness, drug safety is an important aspect that needs to be considered in patients with DR-TB. Bedaquiline and delamanid have a favorable safety profile but are known to induce QTc interval prolongation, a risk factor for cardiac arrhythmia, especially Torsade de pointes (TdP)[6,7]. DELIBERATE study in South Africa and Peru, suggesting that QTc interval prolongation from bedaquiline-delamanid exerts an additive, rather than synergistic effect[6]. QTc interval prolongation is one of the causes of temporary or permanent discontinuation of bedaquiline-delamanid regimens, potentially prolonging the duration of treatment and hindering cure rates. Therefore, it limits the concomitant use of bedaquiline and delamanid in patients with DR-TB. Several studies in Indonesia have reported the safety profile for the QTc interval when bedaquiline is used with delamanid[8,9]. Nonetheless, the study did not analyze the factors associated with QTc interval prolongation, due to the small sample size and retrospective design. A number of factors are known to contribute to QTc interval prolongation, such as age, gender, and electrolyte levels[10]. The administration of second-line TB drugs, such as levofloxacin and clofazimine, has the adverse effect of prolonging the QTc interval. However, the impact of levofloxacin and clofazimine on QTc interval prolongation when used together with bedaquiline and delamanid in the individualized treatment regimen has not been reported in previous studies in Indonesia. Therefore, evaluation of QTc interval prolongation in DR-TB patients is necessary when receiving both levofloxacin and clofazimine regimens together with bedaquiline and delamanid.

QTc interval prolongation with bedaquiline and delamanid has been confirmed in the programmatic evaluation. However, the QTc interval infrequently exceeded 500 ms, rarely reported arrhythmias, and no Torsade de Pointes (TdP) episodes were documented[11,12]. There is a need for further data on the safety of bedaquiline and delamanid in Indonesia since they were used alongside clofazimine and fluoroquinolone, which also prolong the QTc interval. Further studies, especially prospective or cohort studies, are needed to validate the safety of the combined bedaquiline-delamanid regimen in Indonesia, provide evidence-based support for clinicians not to hesitate to use delamanid, and increase the adoption of the most effective regimen for MDR/XDR-TB in the community. Therefore, this study aimed to analyze the QTc interval during six months of treatment in regimens containing bedaquiline and delamanid and factors associated with

QTc interval prolongation. This study is expected to provide additional scientific evidence in Indonesia regarding the cardiac safety of bedaquiline and delamanid regimens for active pharmacovigilance monitoring.

Method

Patient Selection

This was a prospective cohort study conducted at the MDR TB outpatient clinic of Dr. Soetomo Hospital, involving consecutive patients who initiated bedaquiline- or bedaquiline-delamanid-based treatment from September 2022 to May 2023. Patients were followed prospectively for 6 months to monitor treatment-related outcomes. The study was approved by the Dr. Soetomo Hospital Health Research Ethics Committee (No. 0048/KEPK/VII/2022). Treatment regimens were assigned based on clinical indications, following national DR-TB guidelines. The sample in this study was calculated by referring to the results of the QTc interval prolongation conducted by Dooley et al.,[6] with the following formula:

$$n_1 = n_2 = \frac{2(Z\alpha + Z\beta)^2 S^2}{(x_1 - x_2)^2}$$

Note:

- Zα = standard value of 5% alpha of one-way hypothesis, 1.64
- Zβ = standard value of 20% beta, 0,84
- X1-X2 = mean difference in QTc interval prolongation in Bdq + Dlm and Bdq group
- X1 = mean of QTc interval prolongation Bdq + Dlm group, 20,7 ms
- X2 = mean of QTc interval prolongation in Dlm group, 12,3 ms
- S = standard deviation between the two groups, 8,1 ms
- The number of subjects required is a minimum of 12 subjects per group.

Inclusion and Exclusion Criteria

The inclusion criteria of this study were: patients were treated with bedaquiline and delamanid; age > 18 years old; and an interval QTc < 500 ms at baseline. Patients were excluded from the study if they lacked a baseline ECG at the initiation of bedaquiline and delamanid treatment, had a history of cardiac disease, had concurrent use of macrolide antibiotics or azole antifungals, or did not have at least one follow-up ECG during the 6-month treatment period. Furthermore, patients receiving standardized shorter regimens were excluded, as the study focused only on those treated with individualized longer regimens in which delamanid could be incorporated. In accordance with the national guidelines for DR-TB therapy, the bedaquiline-delamanid regimen is administered for the first six months. All eligible patients were asked to complete written and signed informed consent before enrollment.

Data collection

We collected relevant baseline characteristics, including sex, age, body mass index, history of TB treatment, and comorbidities. In addition, we collected follow-up data for the duration of bedaquiline and delamanid therapy, including all other antitubercular drugs and any interruptions in therapy. Serum electrolyte levels of potassium, calcium, and magnesium were measured before treatment (baseline) and then every month until the sixth month of treatment to identify risk factors of QTc interval prolongation. BMI was calculated using the following formula: BMI = weight (kg)/height (m^2). We used the Fredericia formula to calculate the QTc interval (ms) with QTc = QT/(RR)1/3[13]. QTc interval was estimated from resting 12-lead electrocardiograms for each patient. Twelve-lead ECGs were reviewed by a clinician. Heart rate, QTc interval, and any abnormalities were recorded. The classification of QTc interval prolongation was grade I or mild (450-480 ms), grade II or moderate (481-500 ms),

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grade III or severe (≥ 501 ms), grade IV or life-threatening (≥ 501 ms or > 60 ms from baseline and TdP or severe arrhythmia)[13]. The clinicians at the MDR-TB clinic read and interpret the ECG results. The interpretation is combined with the patient's clinical history and symptoms. To minimize the variability of ECG results, DR-TB patients are asked to have the examination on the same date every month and the examination is performed in a relaxed lying position to avoid muscle noise.

Statistical Analysis

Categorical variables were reported as numbers or percentages. Meanwhile, continuous data were expressed as mean and standard deviation (SD). The data distribution for overall comparisons was evaluated for normality using the Kolmogorov-Smirnov. As continuous data were normally distributed, we compared DR-TB patients for bedaquiline and bedaquiline-delamanid groups using an independent t-test. Categorical or descriptive variables were analyzed using Chi-square or Fisher's exact test, as appropriate. We used Spearman correlation to correlate the levofloxacin dose and the QTc interval. Analysis of variables for inclusion as risk factors for QTc interval prolongation was performed when the QTc interval value reached a peak. Statistical analysis was conducted using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). P-value < 0.05 was considered statistically significant.

Result and Discussion

Patient characteristic

The flowchart of the included patients during the cohort period is shown in Figure 1. The demographic and clinical characteristics of DR-TB patients, including sex, age, BMI, history of TB treatment, comorbidities, type of DR-TB, levels of potassium, calcium, magnesium, and QTc interval at baseline, are shown in Table 1. All of the included patients demonstrate resistance to rifampicin. Sixty-nine DR-TB patients who met the inclusion criteria received bedaquiline or delamanid between September 2022 and May 2023. Of these, 51 and 12 patients were included in the bedaquiline and bedaquiline-delamanid groups for final analysis.

We found that more than 60% of DR-TB patients were male, with an overall mean BMI < 18.5 kg/m^2, and it was classified as underweight between the two groups. Patients previously treated with antitubercular drugs accounted for more than 50% of the two groups. We found only one patient as pre-XDR-TB with fluoroquinolone resistance in the bedaquiline-delamanid group. There were no differences in potassium, calcium, and magnesium levels (P-value ≥ 0.05) at baseline, and all were within normal limits. QTc interval is similar between the two groups (P-value ≥ 0.05). This study did not find patients with a QTc interval of more than 500 ms before treatment between the two groups. This indicates that patients with DR-TB can be given regimens containing bedaquiline or delamanid.

Regimens potentially prolong the QTc interval between the two groups at baseline, as shown in Table 2. All patients received five effective drugs during six months of treatment with regimens containing bedaquiline and delamanid. We found that 11 patients in the bedaquiline-delamanid group could not be administered linezolid due to contraindication (10 patients and one patient demonstrated optic neuritis and anemia before treatment, respectively), which was replaced by delamanid. One patient died in the bedaquiline-delamanid group due to heart failure and it was not related to bedaquiline or delamanid.

According to Table 2, 88% of patients received three regimens consisting of levofloxacin,

bedaquiline, and clofazimine; meanwhile, more than 83% of patients received four regimens consisting of levofloxacin, bedaquiline, clofazimine, and delamanid that potentially prolong the QTc interval in the bedaquiline and bedaquiline-delamanid groups, respectively. Classification of severity of interval QTc prolongation between the two groups is shown in Table 3.

The Mann-Whitney test demonstrated a P-value of 0.084, indicating no difference in the degree of QTc interval prolongation between the two groups, as shown in Table 3. However, grade II and grade III of QTc interval prolongation were higher in the bedaquiline-delamanid group compared to the bedaquiline group. Grade IV or life-threatening QTc interval prolongation was not found in both groups. However, there was a tendency for QTc interval prolongation of grades II and III in the bedaquiline-delamanid group. A large, multi-country cohort demonstrated that the majority of QTc interval prolongation was grade I and II during six months of treatment with bedaquiline and or delamanid[14]. Another study by Dooley et al., indicated that patients with degrees I and II of QTc interval prolongation were more common in the bedaquiline-delamanid group than in the bedaquiline group. However, the study did not report the use of clofazimine. As is known, clofazimine is used in individualized regimens in class B.

The absence of differences in the severity of QTc interval prolongation in this study could be due to several reasons. First, we did not include DR-TB patients who were taking other drugs that could potentially cause QTc interval prolongation, such as azole antifungals or macrolide antibiotics. As reported by Israll et al., DR-TB patients who received bedaquiline and/or delamanid regimens along with azole antifungals experienced QTc interval prolongation than those who did not use the azole[11]. Secondly, the relatively small sample size in the bedaquiline-delamanid group limits the distribution of the severity of QTc interval prolongation among DR-TB patients.

Conversely, a study by Olayanju et al., reported that patients with a QTc interval of 450-500 ms or a QTc difference of> 60 ms were much higher in the bedaquiline-delamanid group compared to the bedaquiline group[15]. It was because 40% of patients received moxifloxacin; meanwhile, in our study, no patient received moxifloxacin in the bedaquiline-delamanid group. Moxifloxacin prolongs the QTc interval mainly through direct molecular block to hERG channels[16]. QTc interval from baseline and during six months of treatment is shown in Table 4.

Based on Table 4, the mean QTc interval from the second week to the sixth month was significantly higher in the bedaquiline-delamanid group than in the bedaquiline group, P-value <0.05. However, the mean QTc interval did not exceed 480 ms, indicating caution against QTc interval prolongation in the bedaquiline-delamanid group. The mean change of QTc from baseline during six months of treatment between the two groups is shown in Table 5.

Based on Table 5, it was found that DR-TB patients in the bedaquiline-delamanid group had a greater mean difference in QTc interval than those in the bedaquiline group. However, the difference in the mean change of QTc interval was < 60 ms from the second week until the sixth month. A P-value of ≥ 0.05 for mean change in QTc from the second week to the sixth month against the baseline QTc, respectively. It indicates no difference in the mean change of QTc interval in patients with DR-TB receiving bedaquiline or bedaquiline-delamanid-based regimens.

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The mean change of QTc interval was greatest in this study in the fourth month, 36.86 ms for the bedaquiline group and 41.50 ms for the bedaquiline-delamanid group. The mean change in QTc interval in this study was higher than Dolley et al.[6] It was because patients using clofazimine were not included in their study. Meanwhile, our study showed that all DR-TB patients received clofazimine. Conversely, a study by Israll et al., demonstrated that the mean change of the QTc interval was higher during six months of bedaquiline therapy[11]. It was more likely because 33.8% of DR-TB patients used azole antifungals together with bedaquiline and delamanid. In contrast, in this study, we did not find patients who used azole antifungals.

The mean change in QTc interval was greatest in the third to the fifth month after administration of bedaquiline or delamanid. Intracellular M2 metabolites were greater from the second to the sixth month than bedaquiline intracellular levels. Cumulation of metabolites with long half-lives (M2, ≈5 months; DM-6705 ≈, 5-13 days) causes the peak QTc effect to be delayed after several weeks[17,18]. The slow formation and elimination of M2 and DM 6705 lead to gradual accumulation in plasma or cardiac tissue; therefore, the QTc prolongation peaks weeks later, not immediately. PK-QTc data showed a linear correlation between metabolite levels (M2 or DM-6705) and QTc, rather than a correlation with the parent drug; for example, DM-6705 correlated significantly with ΔQTc, although it remained <10 ms at Cmax[18]. It was supported by Darmayani et al., who reported that the mean change in QTc interval was greatest in the third month after bedaquiline use[19].A DELIBERATE study demonstrated that mean change in QTc from baseline was 12.3 ms (bedaquiline), 8.6 ms (delamanid), and 20.7 ms (bedaquiline and delamanid). The mean change in QTc of bedaquiline and delamanid was not greater than the sum of the QTc of each drug. This indicates an additive effect, not synergistic[6].

This phenomenon can be explained by the decreased effect of M2 and DM 6705 metabolites on potassium channel receptors in cardiomyocytes. Both metabolites are responsible for prolonging the QTc interval by inhibiting the human ether-a-go-go gene (hERG), which causes the repolarization of the potassium rectifier (Ikr). The interaction between the two metabolites caused a decrease in potency of 28% for metabolite M2 and 33% for metabolite DM 6705. It suggests that the interaction between metabolites M2 and DM 6705 is not greater in increasing the QTc interval but exerts an additive effect. Metabolites M2 and DM 6705 act on hERG receptors by binding and inhibiting potassium channels with different affinities. Therefore, each metabolite decreases the potency of the other metabolite[17].

Correlation analysis determined whether levofloxacin dose contributes to QTc interval prolongation. The correlation between levofloxacin dose and QTc interval (n=60) in the fourth month is shown in Figure 2.

Sixty DR-TB patients in this study received fluoroquinolones (levofloxacin or moxifloxacin) with bedaquiline or delamanid, potentially causing QTc interval prolongation. Spearman correlation demonstrated that the levofloxacin dose did not correlate with the QTc interval (P-value 0.696, r= 0.054). The levofloxacin dose in this study is between 750-1000 mg per day. Several studies reported no correlation between the dose of moxifloxacin or levofloxacin and QTc interval prolongation[20,21]. Furthermore, the plasma concentration of moxifloxacin does not correlate with the QTc interval[20]. This indicates that fluoroquinolones are relatively safe to use with bedaquiline in patients with MDR-TB.

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In addition to levofloxacin and moxifloxacin, clofazimine was also used in this study, and it could potentially cause QTc interval prolongation. Clofazimine can block the IKr current, which is the rapid component of the delayed rectifier potassium current, by inhibiting hERG (human Ether-à-go-go-Related Gene) potassium channels in cardiac tissue. It results in a longer QT interval on the ECG and delayed cardiac repolarization. Clofazimine is at risk of causing QTc interval prolongation by inhibiting the hERG channel[22]. In this study, all patients received clofazimine at 100 mg daily between the two groups. Therefore, further analysis of clofazimine's impact on QTc interval prolongation was impossible in this study.

The study by Ardhianto et al., reported that there was no difference in QTc interval prolongation in patients who received bedaquiline, bedaquiline-levofloxacin, bedaquiline-clofazimine, and bedaquiline-levofloxacin-clofazimine[23]. Conversely, a Taiwanese study in DR-TB patients showed an adjusted hazard ratio of 6.54 for QTcF ≥501 ms in patients taking clofazimine combined with high-dose moxifloxacin. It was because 70% of patients received moxifloxacin that the QTc interval was potentially prolonged[24]. In our study, only one patient received moxifloxacin in the bedaquiline group. Factors associated with QTc interval prolongation in the fourth month are shown in Table 6.

Based on factors associated with QTc interval prolongation, as shown in Table 6, only potassium and calcium levels were associated with QTc interval prolongation. This indicates that potassium and calcium levels play an important role in maintaining hemostasis of cardiomyocyte repolarization. Hypokalemia decreases IKr through increased inactivation of sodium competitive inhibition, eventually leading to prolonged QTc interval. Arrhythmogenicity due to hypokalemia and hypocalcemia is caused by prolonged ventricular repolarization, slow conduction, and abnormal pacemaker activity. The prolongation of repolarization in hypokalemic conditions is due to the inhibition of potassium outflow (IK), paradoxically caused by the decrease in extracellular potassium. A case of hypokalemia functionally mimicking the pharmacological effects of hERG-blocking drugs, resulting in prolonged QTc due to delayed repolarization. This condition is even more dangerous when combined with drugs that also block hERG. Therefore, active monitoring of potassium and calcium levels and rapid correction are key to its mitigation, especially when patients are taking QT-long drugs such as bedaquiline or delamanid. Hypocalcemia causes QTc prolongation through slow inactivation of L-type Ca^{2+} channels, prolonging phase 2 and increasing the potential for early after-depolarization.[24]. A prospective study demonstrated that baseline potassium levels were inversely correlated to the QTc interval. This emphasizes the importance of monitoring electrolytes, especially potassium, before starting bedaquiline therapy. Correction of potassium and calcium levels within the normal limits will shorten the QTc interval[25]. It was similar to the study by Li et al., who reported that when QTc interval prolongation occurred, potassium levels dropped by 10.71%[9]. Therefore, periodic measurements of electrolytes, especially potassium and calcium, are necessary for early detection of QTc interval prolongation.

Conversely, a study by Soedarsono et al., demonstrated that BMI was associated with QTc interval prolongation in a 9-month all-oral regimen[21]. The mean BMI in their study was normal (18.5-22.9 kg/m2); meanwhile, in our study, BMI was classified as underweight (< 18.5 kg/m2) between the two groups. It

was supported by Lodiong et al., who reported that BMI was significantly higher in MDR-TB patients with QTc interval prolongation than those without QTc prolongation26. Increasing BMI is potentially associated with elevated plasma fatty acid concentrations that might have led to prolonged cardiac repolarization and correlation with QTc interval prolongation[27]. Theoretically, BMI will increase as the patient's nutritional status improves during treatment. However, in this study, we did not measure BMI during the six months of treatment.

Our study had limitations. The limited sample size is a major limitation of this study since we retrieved DR-TB patients from one hospital center. Although our study demonstrated that regimens containing bedaquiline and delamanid provide a favorable safety profile for QTc interval prolongation, delamanid cannot be directly used in DR-TB patients. By the individualized treatment regimen, delamanid, a class C drug, will be used if one or more class A or B drugs cannot be used in patients with DR-TB. It limits the use of delamanid in the management of DR-TB patients. In addition, we did not measure plasma concentrations of bedaquiline and delamanid and their metabolites associated with QTc interval prolongation. Therefore, further study with a larger sample size was necessary for the multi-center hospitals to gather more robust data. Hospital pharmacists may recommend dose adjustment, discontinuation of concomitant medications, or implementation of electrolyte correction strategies. Adjustment of QTc interval monitoring frequency is recommended for patients with risk factors, such as combinations with other drugs that could potentially cause QTc interval prolongation, or patients with abnormal electrolyte levels. Pharmacists should record and actively report QTc-related adverse events to the Indonesian Food and Drug Administration.

Conclusion

In conclusion, we found a slight prolongation of the QTc interval in a cohort of patients treated for DR-TB in a programmatic setting in Indonesia with bedaquiline and delamanid. The greatest QTc increase was observed at month four. Neither grade 3 nor grade 4 QTc prolongation was associated with the QTc effects of bedaquiline or delamanid. Potassium and calcium levels were associated with QTc interval prolongation. Periodic electrolyte monitoring is highly recommended to prevent QTc interval prolongation during treatment with such combination regimens. Our research contributes to the growing body of evidence demonstrating the safety of taking these two medications together to treat patients with drug-resistant tuberculosis.

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Conflict of Interest

All authors declare there was no conflict of interest during this study

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Table 1. Baseline characteristics of DR-TB patients

Variables	Bdq (n=51)	Bdq-Dlm (n=12)	P-Value
Sex			
Male	31 (60.7)	8 (66.6)	0.263*
Female	20 (39.3)	4 (33.4)	
Age, mean ± SD (years)	44.7 ± 11.7	49.1 ± 14.3	0.376**
BMI, mean ± SD (kg/m2)	17.22 ± 3.86	16.13 ± 1.94	0.436**
History of TB			
New	21 (41.2)	5 (41.8)	0.975*
Relapse	20 (39.2)	4 (33.3)	
Treatment Failure	8 (15.7)	2 (16.6)	
LTFU	2 (3.9)	1 (8.3)	
Comorbid			0.464*
Without comorbid	25 (49.0)	5 (41.6)	
Diabetes mellitus	25 (49.0)	7 (58.4)	
HIV	1 (2.0)	-	
DR-TB type			0.190*
MDR-TB	51 (100)	11 (91.6)	
Pre-XDR-TB	-	1 (8.4)	
Potassium (mEq/L)	4.81 ± 1.42	4.90 ± 2.11	0.114**
Calcium (mg/dL)	9.22 ± 0.34	9.03 ± 0.44	0.233**
Magnesium (mg/dL)	2.10 ± 0.29	2.07 ± 0.17	0.156**
QTc Interval (ms)	411.74 ± 31.77	422.66 ± 24.41	0.270**

Bdq: bedaquiline; Dlm: delamanid; BMI: body mass index; LTFU: loss to follow-up; MDR-TB: multidrug-resistant TB; pre-XDR-TB: pre extended drug-resistant TB
*:Chi-square
**: independent t-test

Table 2. Regimens potentially prolong the QTc interval between the two groups

Baseline Regimens	Regimens suspected of QTc interval prolongation	Group	
		Bdq (n, %)	Bdq-Dlm (n, %)
Lfx/Bdq/Lzd/Cfz/Cs	Lfx/Bdq/Cfz	45 (88.2)	-
Lfx/Bdq/Lzd/Cfz/E	Lfx/Bdq/Cfz	4 (7.8)	-
Mfx/Bdq/Lzd/Cfz/Cs	Mfx/Bdq/Cfz	1 (1.9)	-
Bdq/Lzd/Cfz/Z/E	Bdq/Cfz	1 (1.9)	-
Lfx/Bdq/Cfz/Cs/Dlm	Lfx/Bdq/Cfz/Dlm	-	10 (83.3)
Bdq/Lzd/Cfz/E/Dlm	Bdq/Cfz/Dlm	-	1 (8.3)
Lfx/Bdq/Cfz/Dlm/Z	Lfx/Bdq/Cfz/Dlm	-	1 (8.3)
Total		**51**	**12**

Bdq: bedaquiline; Cfz: clofazimin; Dlm: delamanid; Lfx: levofloxacin; Mfx: moxifloxacin; E: etambutol; Cs: cycloserine; Z: pirazinamid; Lzd: linezolid

Table 3. Classification of the severity of interval QTc prolongation between the two groups

Group (n, %)	Patients (n, %)					P-Value*
	Without QTc prolongation	Grade I	Grade II	Grade III	Grade IV	
Bdq (n=51)	24 (47.0)	18 (35.3)	8 (15.7)	1 (1.9)	0	0.084
Bdq-Dlm (n=12)	2 (16.6)	4 (33.3)	5 (41.7)	1 (8.3)	0	

*Mann-Whitney; Bdq: bedaquiline; Dlm: delamanid

Table 4. QTc interval during six months of treatment between the two groups

Time	Group		P-value
	Bdq (n=51)	Bdq-Dlm (n=12)	
Baseline	411.74 ± 31.77	422.66 ± 24.41	0.270
Week 2	425.53 ± 23.76	441.25 ± 26.14	0.047
Month 1	432.52 ± 18.58	454.91 ± 22.00	0.001
Month 2	436.07 ± 24.29	459.33 ± 18.83	0.003
Month 3	439.58 ± 22.93	459.16 ± 14.62	0.007
Month 4	448.62 ± 24.48	464.16 ± 15.95	0.041
Month 5	436.41 ± 19.59	457.25 ± 8.25	0.001
Month 6	435.39 ± 19.81	452.25 ± 11.12	0.006

Table 5. QTc interval during six months of treatment between the two groups

Time	Group		P-value
	Bdq (n=51)	Bdq-Dlm (n=12)	
Week 2	13.78 ± 35.40	18.58 ± 42.19	0.685
Month 1	20.78 ± 36.28	32.50 ± 36.43	0.329
Month 2	24.33 ± 37.88	36.66 ± 25.20	0.289
Month 3	27.84 ± 39.66	36.50 ± 20.38	0.468
Month 4	36.88 ± 34.44	41.50 ± 19.49	0.657
Month 5	24.66 ± 34.98	34.58 ± 25.08	0.359
Month 6	23.64 ± 35.52	29.58 ± 22.88	0.584

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Table 6. Factors associated with QTc interval prolongation

Variables	Interval QTc Prolongation (n=39)	No Interval QTc Prolongation (n=24)	P-value
Sex			
Male	30 (76.9)	14 (58.3)	0.101#
Female	9 (23.1)	10 (41.7)	
DM			0.594#
With DM	18 (46.1)	11 (45.8)	
Without DM	21 (53.9)	13 (54.2)	
Age (years), mean ± SD	46.94 ± 11.22	44.45 ± 13.45	0.431^
BMI (kg/m2), mean ± SD	16.44 ± 3.16	17.88 ± 4.10	0.123^
Potassium (mEq/L), mean ± SD	3.77 ± 0.33	3.99 ± 0.25	0.008*^
Calcium (mg/dL), mean ± SD	8.88 ± 0.24	9.01 ± 0.12	0.021*^
Magnesium (mg/dL), mean ± SD	1.99 ± 0.13	2.02 ± 0.14	0.347^

#: Chi-square; ^: Mann-Whitney; *: significant, P-value < 0,05

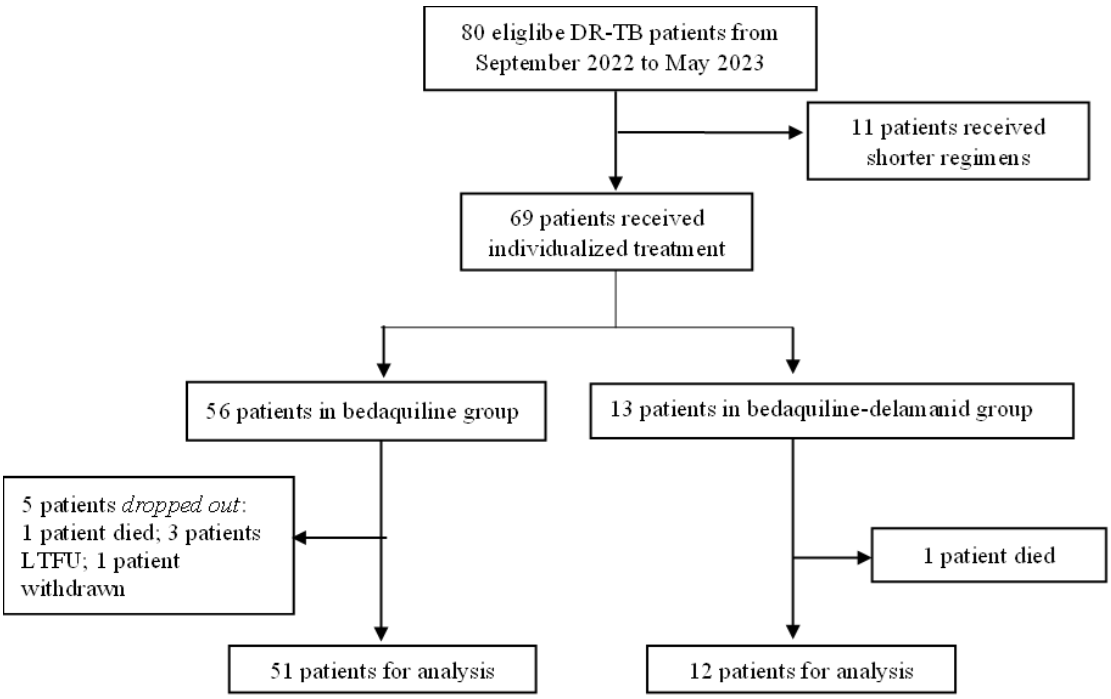

Figure 1. Overview of the study cohort

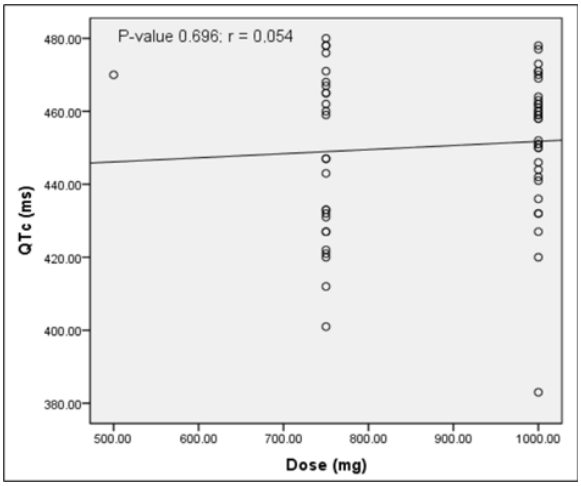

Figure 2. Correlation between levofloxacin dose and QTc interval