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# Bedaquiline for multidrug-resistant tuberculosis and QTc prolongation in California

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ABSTRACT

*Background:* Bedaquiline (BDQ) is recommended for the treatment of multidrug-resistant tuberculosis (MDR TB), however, it has the potential to prolong QTc interval. We assessed the frequency and severity of QTc prolongation in patients receiving BDQ in California.

*Methods:* Based on chart review for patients receiving BDQ as part of MDR TB therapy from January 2013–May 2019, we analyzed QTc values at six pre-specified time points during BDQ therapy (baseline, 2, 4, 8, 12, and 24 weeks), as well as peak QTc, time to peak QTc, and the clinical characteristics of patients who had QTc elevation >500 milliseconds (ms) during therapy.

*Results:* A total of 37 patients were treated with BDQ during the analysis period, with a total of 449 QTc measurements available for analysis. Most patients (89%) received at least one QTc-prolonging drug in addition to BDQ. Median QTc values at all pre-specified time points were <450 ms. Median peak QTc was 455 ms (interquartile range [IQR]: 437–486) and median time to peak was 57 days (IQR: 19–156). Four patients (11%) had a non-transient elevation in QTc to >500 ms, including one patient with profound hypokalemia and one receiving concurrent chemotherapy, but none had cardiac arrhythmia. Less than 10% of patient in our cohort had ECGs performed at all six pre-specified time points.

*Discussion:* BDQ was generally well-tolerated in a cohort of patients treated for MDR TB in California, with 11% of patients experiencing a non-transient QTc elevation >500 ms, and no episodes of arrhythmia. Frequent ECG monitoring during BDQ therapy presents a challenge for TB clinicians, even in well-resourced countries.

## 1. Introduction

Since its approval by the Food and Drug Administration (FDA) in 2012, the drug bedaquiline (BDQ) has contributed to the arsenal of limited options for treating multidrug-resistant tuberculosis (MDR TB). From the beginning, there has been excitement about the drug's potency and concern about its safety. An initial outcome study comparing a regimen containing BDQ to a standard MDR TB regimen found a significantly reduced time to culture conversion and improved cure rate in the BDQ group and an overall incidence of adverse events that was similar in the two groups, but reported ten deaths in BDQ group and two in the control group, without a clear causal pattern [1]. The inclusion of BDQ as a priority drug in newly published MDR TB treatment guidelines [2,3] has heightened the need to understand the safety and tolerability of this drug. Guidance published by the Centers for Disease Control and Prevention (CDC) on the treatment of MDR TB encourages expert consultation with local or state public health departments prior to use of BDQ in MDR TB patients due to the potential for serious adverse events [4], highlighting the public health relevance of the drug's safety.

BDQ is known to increase the length of electrical ventricular systole, corrected for heart rate (QTc). Prolonged QTc is a risk factor for the potentially fatal arrhythmia torsade de pointe (TdP) as well as an independent predictor of sudden cardiac death [5], therefore, the FDA recommends routine electrocardiogram (ECG) monitoring during bedaquiline use and has issued a boxed warning regarding the drug's potential for QTc prolongation. Although the relationship between QTc and TdP is not linear, a scientific statement from American Heart Association regarding QTc-prolonging drugs suggests a QTc interval

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prolongation >500 milliseconds (ms) or increase of >60 ms from pre-drug baseline as thresholds for withdrawal of offending drug, due to risk of arrhythmia [6]. The risk of TdP is correlated with cumulative number of factors in individual patients, including age, female sex, cardiac disease, electrolyte disorders including hypokalemia and hypomagnesemia, genetic predisposition, hepatic and renal dysfunction, and treatment with more the one QTc-prolonging drug [6,7].

Initial cohort data collected by the World Health Organization (WHO) in 2017 indicated that among 511 patients receiving BDQ, 172 (33.7%) had a QTc increase >30–60 ms and 76 (14.8%) had an increase >60 ms [8]. WHO suggests that at a minimum, routine ECG monitoring with use of BDQ should be performed at baseline, and at two, 12, and 24 weeks, with monthly monitoring if a patient receives other QTc prolonging drugs [8], however access to 12-lead ECG equipment and interpretation is an obstacle for many TB control programs. Most previously published data on BDQ comes from an international setting, and there is variability in reported data in terms of frequency of QTc monitoring and presence of other risk factors for QTc-prolongation. Our objective in this analysis was to assess the frequency and severity of QTc prolongation in patients treated with BDQ for MDR TB in a high-resource setting with access to frequent clinical assessment and routine ECG monitoring.

## 2. Methods

California is a state with a high burden of TB in a low-incidence country, with an annual TB rate of 5.3/100,000 [9]. Of the >2000 TB cases diagnosed in the state annually, 1–2% are MDR cases. The California Department of Public Health routinely provides clinical and public health consultation for patients with MDR TB through the California MDR TB Service [10] and collects data on MDR TB cases for both consultation and surveillance purposes. Data collected includes demographic and clinical information, including results of routine ECG monitoring provided by local health departments and treating physicians.

To assess QTc prolongation in the setting of BDQ use, we abstracted data for all MDR TB cases who received consultation from the California MDR TB Service and were treated with BDQ between Jan 1, 2013 and May 1, 2019. This analysis was conducted as part of the California Department of Public Health's mandate to routinely collect and analyze surveillance data for public health purposes. Therefore, this analysis did not require human subjects review, according to CDPH policy and the U. S. Code of Federal Regulations, 45 CFR 46.101. Chart abstraction was performed by a medical doctor for pre-specified data elements, including age, sex, county of residence, BDQ dosages with start and stop dates, additional MDR TB drugs and dosages with start and stop dates, additional drugs not part of MDR regimen with potential to prolong QTc with start and stop dates, pre-existing cardiac disease or hepatic disease, renal dysfunction (including creatinine clearance at time of BDQ start, estimated using Cockcroft-Gault formula), and serum potassium and magnesium values. For each patient, QTc values (automated values using Bazett correction) were abstracted at the following time points: 1) baseline, defined as 12 weeks before to five days after starting BDQ, 2) two weeks after starting BDQ, ± seven days 3) four weeks after starting BDQ, ± seven days, 4) eight weeks after starting BDQ, ± seven days, 5) 12 weeks after starting BDQ, ± seven days, and 6) 24 weeks after starting BDQ, ± seven days. A significant elevation in QTc during BDQ use was defined as either a peak QTc > 500 ms, or an increase of QTc from baseline >60 ms. The medical reviewer reviewed all available ECGs of patients included in the analysis and noted if QTc values >500 were accompanied by repeat ECG within 24 hours (h); if repeat ECG within 24 h recorded a normal QTc, QTc prolongations were designated "single transient values".

## 3. Results

### 3.1. Characteristics of MDR TB patients treated with BDQ

There were 191 MDR TB patients reported in California between Jan 1, 2013 and May 1, 2019, of whom 178 patients (93%) had drug regimen information reported to the California MDR TB Service. Of these 178 patients, a total of 37 MDR TB patients (21%) were treated with BDQ at some point during the analysis period (Table 1). In total they contributed 449 unique QTc measurements to the analysis. Patients on BDQ ranged in age from 15 to 75, with a median age of 38.6 years, and resided in 17 counties throughout California. Sixteen (43%) were female. The majority of patients (89%) received at least one additional drug with the potential to prolong QTc during their BDQ therapy, including groups that received either levofloxacin (40%) or moxifloxacin (27%) during BDQ therapy. No patients had pre-existing cardiac, hepatic, or renal disease. One patient was a person living with HIV (PLHIV) and received concomitant antiretroviral therapy during MDR TB treatment.

All 37 patients (100%) had at least one ECG performed during BDQ therapy for inclusion in QTc analysis. Twenty-two patients (59%) had

**Table 1**
Characteristics of MDR TB patients treated with bedaquiline (total patients = 37).

| | | Number (%) | Mean or Median [IQR] |
|---|---|---|---|
| *Demographic and Clinical factors* | Age in years, median [IQR] | | 38.6 [27.4–51.2] |
| | Female gender | 16 (43) | |
| | Receiving ≥ 1 QTc prolonging drug during BQD therapy[1] | 33 (89) | |
| | LFX | 15 (40) | |
| | MFX | 10 (27) | |
| | MFX, CFZ | 2 (5) | |
| | MFX/LFX | 2 (5) | |
| | MFX, ondansetron, prochlorperazine | 1 (3) | |
| | CFZ | 1 (3) | |
| | MFX/CFZ, fluconazole | 1 (3) | |
| | MFX/LFX, CFZ, ondansetron, cyclophosphamide, doxorubicin | 1 (3) | |
| | Cardiac disease | 0 (0) | |
| | Hepatic disease | 0 (0) | |
| | HIV infection | 1 (3) | |
| | Creatinine clearance (ml/min), median [IQR] | | 96.4 [70.0–123.2] |
| *ECG data availability* | Patients with any ECG data | 37 (100) | |
| | Patients with ECGs at ≥ 3 pre-specified time points[2] | 22 (59) | |
| | Patients with ECGs at 6 pre-specified time points[2] | 3 (8) | |
| *BDQ therapy and QTc* | Received standard loading and maintenance dosing of BDQ | 37 (100) | |
| | Mean duration of BDQ therapy in weeks, [IQR] | | 24.0 [12.0–34.1] |
| | Patients with QTc > 500 msec, any | 7 (19) | |
| | Patients with QTc increase from baseline > 60 msec | 3 (8) | |
| | Patient in whom BDQ stopped due to QTc prolongation | 2 (5) | |

[1]Drugs taken concurrently with bedaquiline (BDQ) therapy: CFZ = clofazimine, LFX = levofloxacin, MFX = moxifloxacin. The "/" symbol denotes both drugs taken during BDQ therapy, but not simultaneously. [2] Pre-specified time points include baseline and 2, 4, 8, 12, and 24 weeks after starting BDQ. IQR = interquartile range; ECG = electrocardiogram; HIV = human immunodeficiency virus; MDR TB = multidrug-resistant tuberculosis; QTc = QT interval, corrected for heart rate

ECGs performed at three or more pre-specified time points, and three (8%) had ECGs performed at all six pre-specified time points, including baseline and two, four, eight, 12, and 24 weeks after BDQ start.

All 37 patients were treated with standard BDQ 400 mg loading dose for 14 days, followed by 200 mg three times weekly, with a mean duration of 24 weeks of BDQ therapy. A total of 7 (19%) had any measured QTc > 500 ms during BDQ therapy or an increase in QTc of >60 ms from baseline, including two patients (5%) in whom BDQ was temporarily interrupted or discontinued because of QTc prolongation. Clinical characteristics of the seven patients with QTc > 500 ms during BDQ therapy are described in Table 2.

### 3.2. QTc trends during BDQ therapy

The median QTc values for patients receiving BDQ therapy at the analysis' pre-specified time points are presented in Fig. 1. Among those with a baseline ECG available, 22 (95.7%) had normal baseline QTc; a single patient receiving BDQ had a baseline QTc of 475 ms. Median QTc at baseline was 428 ms (n = 23, IQR 414–458), with median values at other time points including: week 2, 438 ms (n = 22, IQR 407–461); week 4, 432 ms (n = 20, IQR 403–455); week 8, 426 ms (n = 17, IQR 394–443); week 12, 424 ms (n = 15, IQR 394–447); week 24, 388 ms (n = 10, IQR 376–400). Median peak QTc interval was 455 ms (n = 37, IQR 437–486), median increase in QTc from baseline to peak was 23 ms (n = 23, 12–41), and median time to peak was 57 days (n = 37, 19–156).

To investigate the temporal relationship between QTc and BDQ using all available data, we plotted all QTc values (n = 449) against time since BDQ start in Supplementary Fig. 1. The resulting scatterplot revealed no clear linear or nonlinear trend.

### 3.3. Patients with QTc peak > 500 or BDQ discontinuation

Among the 37 patients with ECG data available for review, 30 patients (81.1%) had no clinically significant elevation in their QTc, defined as either peak QTc > 500 ms, or increase of QTc from pre-drug baseline >60 ms. Seven (18.9%) had an increased QTc > 500 ms at any time during MDR therapy, and three of these seven patients also had an increase of QTc from pre-drug baseline >60 ms; the clinical

**Table 2**
Characteristics of Patients with QTc prolongation ≥500 ms (n = 7).

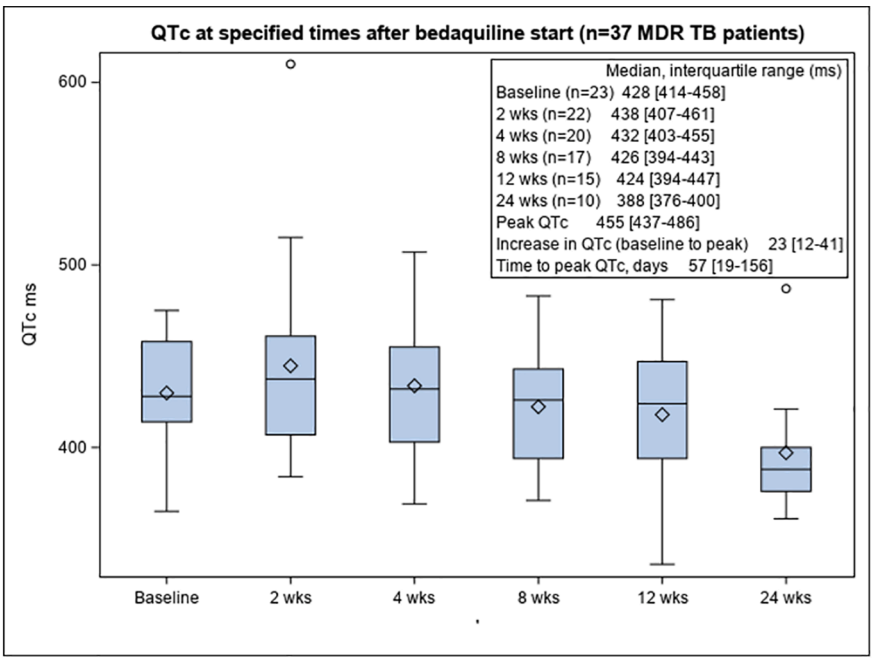
| Pt ID | Sex | Age group (years) | QTc-prolonging drug (s)[1] | Serum electrolytes (mmol/L)[2] | HIV | Cardiac or hepatic disease | CrCl (ml/min) | QTc baseline (ms) | QTc peak (ms) | QTc peak (days) | Non-transient elevation[3] | Clinical scenario and course |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 40–49 | LFX | K 2.2 (Low) Mg 0.8 (Low) | No | No | 78.9 | 420 | 610 | 15 | Yes | Pulmonary, non-cavitary MDR TB; Hypokalemia during QTc elevation, hospitalized, BDQ held 2 weeks & restarted at K > 3; MDR TB cured |
| 2 | M | 30–39 | MFX, CFZ | K 4.6 Mg 1.7 | No | No | 123.2 | 431 | 536 | 156 | No | Pulmonary, cavitary MDR TB & rheumatologic disease on infliximab; transient QTc elevation in clinic, normal QTc next day; no medication changes; MDR TB cured |
| 3 | F | 50–59 | MFX/LFX, CFZ, ondansetron, cyclophosphamide, doxorubicin | – | No | No | 66.5 | – | 546 | 160 | Yes | Pulmonary, non-cavitary MDR TB & cancer on chemo; MFX held and BDQ continued, QTc < 500 in 20 days & BDQ stopped shortly after (completed BDQ course); MDR TB cured |
| 4 | F | 30–39 | MFX | K 4.0 Mg 1.9 | No | No | 94.0 | – | 502 | 26 | Yes | Pulmonary, cavitary MDR TB, no co-morbidities; BDQ stopped and not restarted; MDR TB cured |
| 5 | M | 40–49 | MFX, CFZ | – | No | No | – | 475 | 507 | 29 | Yes | Pulmonary, non-cavitary MDR TB; elevated baseline QTc; BDQ stopped and not restarted; clinical outcome unavailable |
| 6 | F | 30–39 | CFZ | K 4.0 Mg 2.2 | No | No | 100.1 | – | 520 | 98 | No | Pulmonary, non-cavitary MDR TB, no co-morbidities; repeat ECG within minutes had normal QTc; no med changes; clinical outcome unavailable |
| 7 | F | 30–39 | MFX | K 3.6 Mg 2.1 | No | No | 70.0 | 447 | 515 | 14 | No | Pulmonary, non-cavitary, & pleural MDR TB, no-comorbidities; repeat ECG within minutes had normal QTc; BDQ not stopped, MFX → LFX; MDR TB cured |

ECG = electrocardiogram; HIV = human immunodeficiency virus; MDR TB = multidrug-resistant tuberculosis; ms = milliseconds; QTc = QT interval, corrected for heart rate.

[1] Drugs taken concurrently with bedaquiline (BDQ) therapy; CFZ = clofazimine, LFX = levofloxacin, MFX = moxifloxacin.

[2] Measured on day of QTc prolongation or within ±10 days.

[3] Excluded if a repeat ECG within 24 h showed normal QTc.




BDQ = bedaquiline; MDR TB = multidrug-resistant tuberculosis; ms = milliseconds; QTc = QT interval, corrected for heart rate; wks = weeks

**Fig. 1.** QTc are specified times after bedaquiline start (n = 37 MDR TB patients).

characteristics of these patients are summarized in Table 2.

None of the seven patients with a QTc prolongation of any kind during the analysis period were HIV-infected, and none had co-morbid cardiac or hepatic disease or impaired creatinine clearance. After excluding patients with normal repeat QTc measurement within 24 h, only four (11%) patients had a non-transient elevation in QTc. Of these four, all had pulmonary MDR TB, two (50%) were female, and all four were on at least one other MDR TB drug with the potential to prolong QTc (clofazimine, levofloxacin, and/or moxifloxacin). In addition to MDR TB drugs, three (75%) patients with non-transient QTc elevations appeared to have an additional provoking factor: one patient's QTc prolongation occurred in the setting of profound hypokalemia (K 2.2), one patient had co-morbid cancer and was receiving ondansetron, cyclophosphamide, and doxorubicin, in addition to MDR drugs, all of which have been implicated as potentially QTc-prolonging, [11–13] and one patient had an elevated baseline QTc of 475 ms. There were no episodes of torsade de pointe, or other severe cardiac arrhythmias.

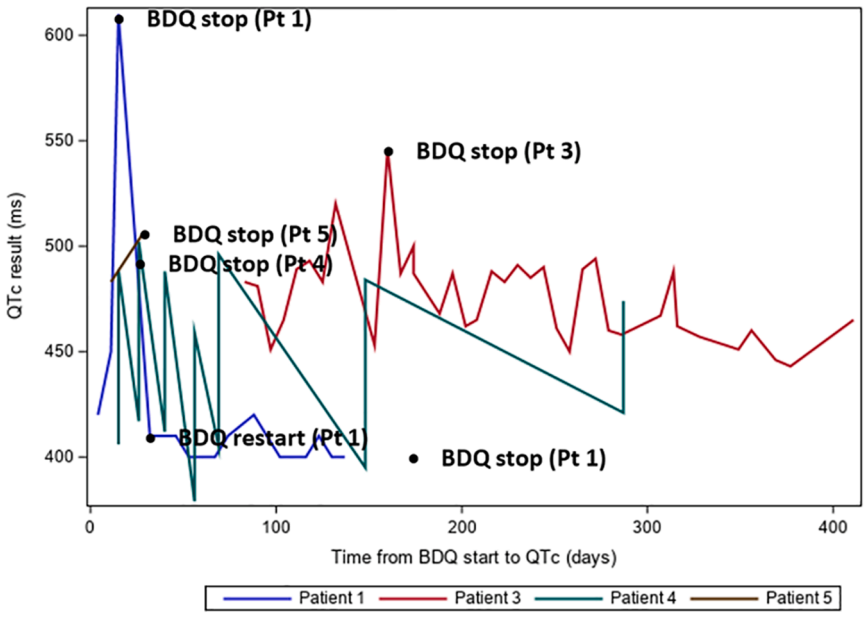
For each of the seven patients with QTc > 500 ms, all available QTc results were plotted against time since BDQ start. Patients with non-transient QTc prolongations (patients 1, 3, 4, and 5) are shown in Fig. 2: three patients had a QTc peak between two and five weeks after starting BDQ therapy; a fourth patient (patient 3, receiving chemotherapy) had a QTc peak after 23 weeks of BDQ therapy, close to the planned end date of BDQ. In patient 1, BDQ was paused for two weeks and restarted, after the patient's hypokalemia had resolved. For patients 4 and 5, BDQ was discontinued and not restarted. Fig. 3 shows QTc results plotted against time since BDQ start for the patients with transient QTc prolongations (patients 2, 6, 7). For this group, QTc peaks occurred both early and late in BDQ therapy.

## 4. Discussion

In a cohort of patients with MDR TB in California, the majority of patients started on BDQ had no elevation in QTc above 500 ms, despite co-administration of other QTc-prolonging drugs. There were no episodes of torsade de pointes. Peak QTc interval in this cohort generally occurred in the first three months of therapy, and most non-transient prolongations of QTc > 500 mc occurred two to five weeks after BDQ start. Approximately one in ten patients had a non-transient elevation in QTc > 500 ms. Descriptive analysis of this small group underscores the additive effect of concurrent QTc-prolonging agents, as well as the clinical importance of checking and correcting serum electrolytes as a potential reversible cause of QTc. Additionally, because QTc prolongation was transient in nearly half of patients, our data also highlight the need to confirm sustained prolongation before permanently discontinuing BDQ or other MDR TB drugs. Our results support the safety and tolerability of BDQ as part of an MDR TB regimen and are particularly relevant in light of revised U.S. and international guidelines which recommend preferential use of BDQ in treating MDR TB [2,3], and BDQ's inclusion in promising investigational MDR TB regimens [14].

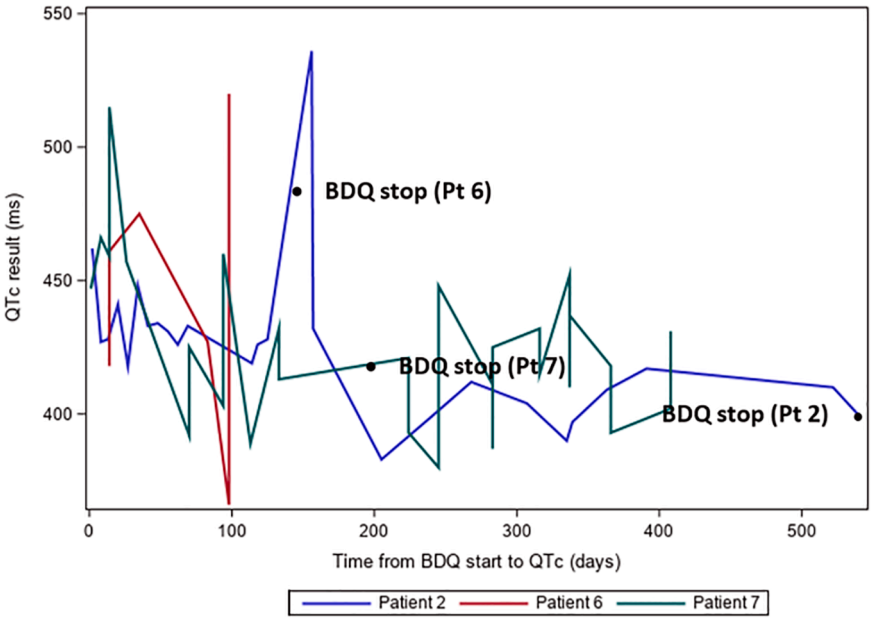
These data contribute to a growing body of literature that suggests that BDQ is generally well-tolerated, and that clinically significant QTc prolongation and cardiac events arising as a result of BDQ are rare. An initial trial of 233 patients to establish the safety and efficacy of BDQ found QTc prolongation > 450 in 27 (11.6%) patients. [15]. A systematic review on the cardiac safety of BDQ published in 2017 notes that among 1303 patients receiving BDQ in clinical trials, case reports or cohort studies, 3.2% had a QTc > 500 ms, and <1% discontinued the drug due to safety or tolerability [16]. In a subsequent study based on surveys distributed to treatment centers in the Tuberculosis Network of European Trials Group, there were a total of 1044 BDQ-treated patients, of which eight cases (0.77% (95% CI 0.04–1.57) had BDQ stopped due to QTc prolongation, and one case (0.10% (95% CI 0.01–0.63) developed an asymptomatic first-degree atrioventricular block associated with QT prolongation [17]. A U.S.-based cohort study of 14 patients published in 2019 reported one patient (7%) with QTc prolongation >500 [18]. Finally, in preliminary data presented at the Conference on Retroviruses and Opportunistic Infections 2019 on 74 MDR TB patient in South Africa and Peru, there were no Grade 3 or 4 QT interval prolongation events, and mean change in QTc-F from baseline was 11.9 (CI 7.4, 16.5) in patients taking BDQ [19].

Despite the overall tolerability, our results highlight the need for clinical and ECG monitoring during BDQ therapy. In our cohort nearly 90% of patients were receiving multiple QTc-prolonging drugs, however less than 10% of patients had ECGs available from the six time points




BDQ = bedaquiline; MDR TB = multidrug-resistant tuberculosis; ms = milliseconds; QTc = QT interval, corrected for heart rate

**Fig. 2.** QTc result versus Time from BDQ start (n = 4 MDR TB patients with QTc > 500 ms, non-transient elevation).




BDQ = bedaquiline; MDR TB = multidrug-resistant tuberculosis; ms = milliseconds; QTc = QT interval, corrected for heart rate

**Fig. 3.** QTc result versus Time from BDQ start (n = 3 MDR TB patients with QTc > 500 ms, transient elevation).

recommended by our MDR TB service highlighting that obtaining frequent ECGs can present a challenge for TB programs, even in well-resourced settings. Although the optimal interval for QTc monitoring is unclear, the BDQ package insert currently suggests a minimum of baseline, two, 12, and 24 week ECGs, with guidance documents suggesting ECG collection monthly or even weekly if a patient is receiving other QTc-prolonging drugs [4,11]. Prior studies report variability in frequency of ECG monitoring and management of QTc prolongation; indeed, 16% of respondents at European Centers reported no ECG monitoring for patients with MDR TB [17]. It is notable that in a phase 2 trial of BDQ that performed ECGs at 2, 4, 8, 12, 16, 20, and 24 weeks, mean maximum change in QTc steadily rose until week 24 of therapy [15]. Although most non-transient QTc elevations in our cohort occurred within 2–5 weeks of BDQ initiation, our analysis suggests that QTc elevations can occur during any point in BDQ therapy, particularly when additional QTc-prolonging medications are used. For this reason, our MDR TB Service continues to suggest that QTc be measured, at a minimum, at baseline, and at two, four, eight, twelve, and twenty-four weeks after starting BDQ therapy, with monthly monitoring recommended if a patient receives other QTc prolonging drugs. Use of consumer mobile ECG devices, which were recently approved by the FDA, may help increase ECG monitoring in places where 12-lead ECGs are

difficult to obtain [20,21].

The primary limitation of this analysis is its observational nature, as well as missing data in our clinical database. It is possible that we had missing information about use of non-prescription medication or drugs of abuse that can prolong the QTc interval. Small numbers preclude our ability to make conclusions about the impact of age or co-morbidities on QTc, and information about the time of day that ECGs were collected was largely unavailable, which limits our understanding of the impact of normal physiological fluctuations in QTc [22,23]. Full ECG tracings, which would enable QT intervals calculated using Fridericia's formula, were not available for all QT measurements, necessitating reporting of QT intervals corrected using Bazett's formula. Finally, our analysis cohort was comprised primarily of persons who were HIV un-infected; while this is representative of our local MDR TB population, it limits our ability to draw conclusions about the significant worldwide population of PLHIV who are co-infected with MDR TB.

With >500,000 cases of MDR TB occurring annually worldwide, the need for effective treatments for drug-resistant TB is acute [24]. As physicians and TB programs treating MDR TB increasingly rely on BDQ as part of an effective treatment regimen, the challenges posed by the need for ECG monitoring must be considered. BDQ inclusion in a global drug safety monitoring system [25] would help consolidate our understanding of this drug's safety and tolerability. Interventions such as mobile ECG devices, as well as careful consideration about ideal interval of monitoring, will be critical as TB programs worldwide work to integrate BDQ into their standard treatment regimens.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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*Author contributions*

S. Katrak and P. Barry planned the analysis. L. True and L. Henry coordinated patient care and supported clinical data collection. R. Shen and S. Katrak performed chart review. P. Lowenthal analyzed data and prepared figures. S. Katrak, R. Shen, P. Barry, and P. Lowenthal performed results interpretation. S. Katrak drafted the manuscript. All authors provided input on writing the manuscript. All authors read and approved the final manuscript.

*Ethics committee approval*

This analysis was conducted as part of the California Department of Public Health's mandate to routinely collect and analyze surveillance data for public health purposes. Therefore, this analysis did not require human subjects review, according to CDPH policy and the U.S. Code of Federal Regulations, 45 CFR 46.101.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2021.100216.

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