*Open Forum Infectious Diseases*

MAJOR ARTICLE

# Increased Moxifloxacin Dosing Among Patients With Multidrug-Resistant Tuberculosis With Low-Level Resistance to Moxifloxacin Did Not Improve Treatment Outcomes in a Tertiary Care Center in Mumbai, India

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***Background.*** *Mycobacterium tuberculosis* (*Mtb*) strains resistant to isoniazid and rifampin (multidrug-resistant tuberculosis [MDR-TB]) are increasingly reported worldwide, requiring renewed focus on the nuances of drug resistance. Patients with low-level moxifloxacin resistance may benefit from higher doses, but limited clinical data on this strategy are available.

***Methods.*** We conducted a 5-year observational cohort study of MDR-TB patients at a tertiary care center in India. Participants with *Mtb* isolates resistant to isoniazid, rifampin, and moxifloxacin (at the 0.5 µg/mL threshold) were analyzed according to receipt of high-dose moxifloxacin (600 mg daily) as part of a susceptibility-guided treatment regimen. Univariable and multivariable Cox proportional hazard models assessed the relationship between high-dose moxifloxacin and unfavorable treatment outcomes.

***Results.*** Of 354 participants with MDR-TB resistant to moxifloxacin, 291 (82.2%) received high-dose moxifloxacin. The majority experienced good treatment outcomes (200 [56.5%]), which was similar between groups (56.7% vs 54.0%, $P = .74$). Unfavorable outcomes were associated with greater extent of radiographic disease, lower initial body mass index, and concurrent treatment with fewer drugs with confirmed phenotypic susceptibility. Treatment with high-dose moxifloxacin was not associated with improved outcomes in either unadjusted (hazard ratio [HR], 1.2 [95% confidence interval {CI}, .6–2.4]) or adjusted (HR, 0.8 [95% CI, .5–1.4]) models but was associated with joint pain (HR, 3.2 [95% CI, 1.2–8.8]).

***Conclusions.*** In a large observational cohort, adding high-dose (600 mg) moxifloxacin to a drug susceptibility test–based treatment regimen for MDR-TB was associated with increased treatment-associated side effects without improving overall outcomes and should be avoided for empiric treatment of moxifloxacin-resistant MDR-TB.

**Keywords.** drug resistance; drug susceptibility testing; India; MDR-TB; moxifloxacin.

Until the coronavirus disease 2019 (COVID-19) pandemic, *Mycobacterium tuberculosis* (*Mtb*) caused more deaths worldwide each year than any other infection [1]. *Mtb* strains resistant to isoniazid and rifampin (multidrug-resistant tuberculosis [MDR-TB]) are increasingly reported, generating new focus on the nuances of drug resistance. The simultaneous expansion of shorter and injectable-sparing MDR-TB treatment regimens highlights the importance of fluoroquinolones such as moxifloxacin for MDR-TB treatment [2]. The World Health Organization (WHO) recently reiterated support for moxifloxacin and recommended updated concentrations for moxifloxacin drug susceptibility testing (DST) [3]. Even before this update, some laboratories assessed moxifloxacin's efficacy at multiple concentrations to identify low-level resistance that could be overcome with higher doses [4]. Similarly, some clinicians prescribe increased doses of moxifloxacin at 600 mg or 800 mg daily instead of standard 400-mg daily doses to patients with low-level moxifloxacin resistance, but clinical data supporting the efficacy of this approach are limited. To assess the impact of high-dose moxifloxacin on patients with low-level resistance, we reviewed treatment outcomes from an observational cohort of patients with MDR-TB in Mumbai, India.

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## METHODS

### Setting

The P. D. Hinduja Hospital and Medical Research Centre (Hinduja Hospital) is a private, tertiary care hospital in Mumbai, India. Each year, the outpatient chest clinic sees approximately 3000 adults with pulmonary disease including both drug-susceptible and drug-resistant tuberculosis (TB), and the laboratory processes >32 000 *Mtb* samples. Phenotypic DST in BACTEC mycobacterial growth indicator tube (MGIT) 960 cultures is performed for amikacin (1 µg/mL), capreomycin (2.5 µg/mL), clofazimine (1 µg/mL), ethambutol (5 µg/mL), ethionamide (5 µg/mL), isoniazid (0.1 µg/mL), kanamycin (2.5 µg/mL), linezolid (1 µg/mL), moxifloxacin (0.5 µg/mL and 2.0 µg/mL; these data predate the WHO recommendation to test 1 µg/mL in 2018 [3]), ofloxacin (2 µg/mL), para-aminosalicylic acid (PAS; 4 µg/mL), pyrazinamide (1 µg/mL at acidic pH), rifampin (1 µg/mL), and streptomycin (1 µg/mL) [5, 6].

### Study Sample and Variables

This ongoing longitudinal observational cohort of MDR-TB patients has been previously described [7, 8]. In brief, all outpatients ≥15 years old with MDR-TB seeking care at the clinic from October 2015 to October 2020 were approached for recruitment by a study clinician. Participants provided informed consent for abstraction of medical records for a noninterventional, observational cohort. Data collected include demographic information, TB symptom history, care-seeking behavior, prior TB treatment, laboratory and imaging studies, and treatment-associated symptoms at each visit. We recorded patients' age at enrollment, sex, initial body mass index (BMI, kg/m$^2$ [2]), site of disease (pulmonary, extrapulmonary, or both), diagnosis in public or private sector, months from symptom onset to MDR-TB treatment, self-reported tobacco use, self-reported household contact with current or prior TB, DST results, and TB regimen prescribed. "Effective drugs" were defined as drugs for which a participant's *Mtb* isolate was phenotypically susceptible in MGIT or drugs without standardized DST methods available but low rates of circulating resistance (cycloserine, bedaquiline, and delamanid). Drugs were prescribed according to contemporaneous national and international guidelines incorporating local resistance, not by study participation [9, 10]. Due to moxifloxacin resistance, no participants received short-course regimens and the decision to include high-dose moxifloxacin was based on the combination of additional drug resistance, disease severity, and comorbidity at the discretion of the treating providers. High-dose moxifloxacin was not provided at 800 mg daily due to concern for higher toxicity. In that context, capreomycin was only prescribed if either amikacin or kanamycin were resistant, and bedaquiline and delamanid were reserved for compassionate use for participants with resistance to standard of care drugs.

Due to the observational nature of this cohort, not every participant had complete records available. At each subsequent clinic visit, participants were asked about common treatment-associated side effects, but frequency and number of return visits varied. Where available, laboratory data were recorded to identify human immunodeficiency virus (HIV) infection, diabetes (defined as glycosylated hemoglobin ≥6.5% or 2 fasting glucose levels ≥125 mg/dL), kidney injury (creatinine >1.1 mg/dL), liver injury (aminotransferases >3 times the upper limit of normal [ULN]), and phenotypic drug resistance. Acid-fast smears and cultures were recorded as positive or negative. All participants were culture positive at enrollment, but repeat cultures were not uniformly available onsite, particularly for extrapulmonary TB. Culture conversion status at 2 and 6 months was defined as first negative culture without subsequent positive culture within 60 and 180 days of treatment initiation, respectively. Chest radiographs (CXRs) were scored by study clinicians according to a published system incorporating percentage of lung involvement and presence or absence of cavities [11]. Loss to follow-up was defined as not seen for ≥1 year and unable to be reached after 3 attempts on 3 different dates. Outcomes were defined as "good" (completed 2 years of treatment or cure, defined as no relapse within 1 year of completion) or "bad" (death, relapse, or loss to follow-up). Transferred participants and those still receiving treatment on 20 October 2020 were censored for analysis at the date of last visit.

### Statistical Analysis

Paper data collection forms were entered in a Microsoft Access database (Office Professional 365, Microsoft Corporation, Redmond, Washington), and analyzed in R (version 3.5.1, R Core Team, Vienna, Austria). All participants had MDR-TB. Participants with additional moxifloxacin resistance at 0.5 µg/mL were selected for this analysis based on the WHO-endorsed MGIT critical concentration when this study began (lowered to 0.25 µg/mL after 2018; Figure 1) [3]. Participants were also characterized by the presence of extensively drug-resistant TB (XDR-TB, defined as MDR-TB also resistant to a fluoroquinolone and either amikacin, kanamycin, or capreomycin). Frequency tables assessed differences in proportion of participants with each baseline characteristic by prescription of high-dose moxifloxacin (600 mg daily). Stratified analysis assessed each side effect or abnormality on laboratory tests, electrocardiograms, or CXRs as a proportion of participants with available data, rather than of total study population. Differences in proportion of categorical variables were evaluated by Fisher exact tests and differences in continuous variables were evaluated by Wilcoxon rank-sum tests. Univariable Cox proportional hazard models were constructed using the survival and survminer R packages to assess contribution of age, sex, site of disease, initial CXR score, presence of cavitary or bilateral lung disease, concurrent resistance to other drugs, and additional drug treatment or lung resection to bad outcomes. Variables with $P < .05$ were

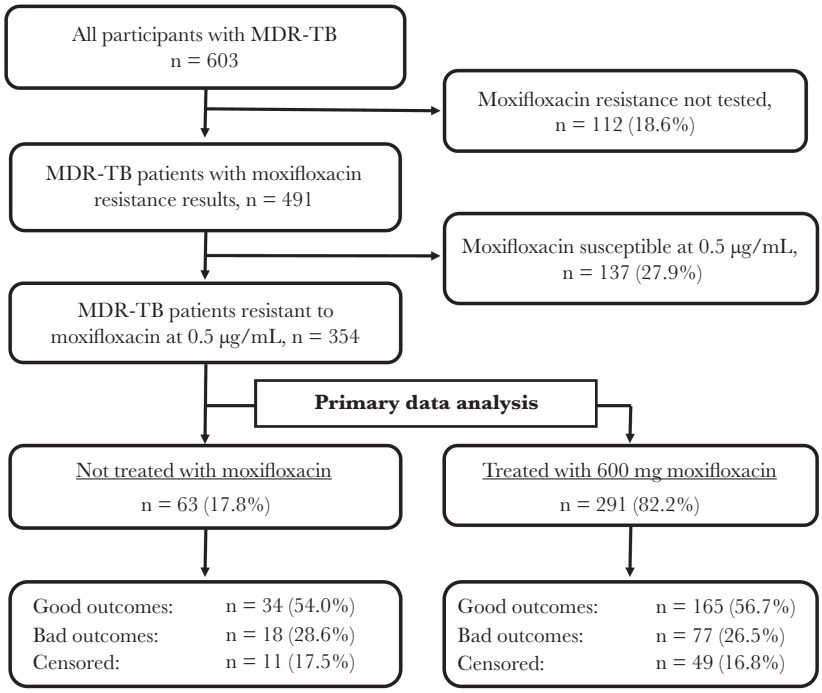


**Figure 1.** Participant inclusion and analytic schema. Study flow indicating the number of participants included at each stage of analysis. The final study population in this analysis is indicated with the header "Primary Data Analysis" and stratified by study group. Abbreviation: MDR-TB, multidrug-resistant tuberculosis.

considered significant. Nested multivariable regression models for treatment outcomes incorporated high-dose moxifloxacin and factors with known clinical relevance (site of disease, smear grade, radiographic findings, treatment delays) as well as potential confounders (age, sex, initial BMI, additional drug resistance, and prior and concurrent treatment). Additional analysis assessed the same factors for their proportional hazard of death, culture conversion at 2 or 6 months, and common moxifloxacin-associated side effects including gastrointestinal symptoms (nausea, vomiting, or anorexia), joint pain, peripheral neuropathy, cognitive changes, aminotransferase elevations, and QTc prolongation (Fridericia corrected Q-T interval >450 msec). In sensitivity analysis, data were reanalyzed after propensity score matching by disease severity using BMI and CXR involvement, additional drug resistance, diabetes, and combinations of those factors using the MatchIt package.

### Patient Consent

All participants provided written informed consent for this study. Participants <18 years old provided assent and their guardians provided written consent. This study was approved by institutional review boards at Hinduja Hospital and the Johns Hopkins University School of Medicine.

## RESULTS

This study enrolled 603 participants with MDR-TB between 20 October 2015 and 20 October 2020. Of these, 491 (81.4%) completed DST for moxifloxacin, and 354 had moxifloxacin-resistant isolates at 0.5 µg/mL (58.7% of all participants, 72.1% of those tested). High-dose moxifloxacin was prescribed as part of an optimized, DST-based treatment regimen for 291 participants (82.2% of those with resistance; Figure 1), and these participants were seen at 1881 total study visits (median, 757 days of follow-up).

Overall, participants prescribed high-dose moxifloxacin were older (median, 27 vs 24 years, $P = .033$), and had higher BMI (median, 19.7 vs 18.1 kg/m$^2$, $P = .021$) and less CXR involvement (median, 10% vs 13%, $P < .001$) than those not prescribed high-dose moxifloxacin (Table 1). There were no significant differences between study groups by diagnosis in the public or private sector, time to effective treatment, known contact with TB, rates of comorbid HIV or diabetes, additional resistance to injectable drugs (XDR-TB), smear or culture positivity, or cavitary lung disease. More participants prescribed high-dose moxifloxacin used tobacco, although this was not significant (19.9% vs 9.5%, $P = .094$). While a history of prior TB was common among all patients (26.3% of participants), no significant differences in prior treatment were identified between study groups. Participants prescribed high-dose moxifloxacin were, however, more likely to also be prescribed linezolid, clofazimine, and capreomycin based on DST profile, and a higher proportion of these patients received ≥4 drugs to which their *Mtb* isolate was confirmed susceptible compared to those who did not receive high-dose moxifloxacin (55% vs 34.9%, $P = .005$). During this study, delamanid was only received

**Table 1. Participant Characteristics According to Moxifloxacin Dose**

| Characteristic | Prescribed Moxifloxacin 600 mg (n = 291) | Not Prescribed Moxifloxacin (n = 63) | All Participants (N = 354) | *P* Value[a] |
|---|---|---|---|---|
| Demographics and social history | | | | |
| Age, y, median (IQR) | 27 (22–34) | 24 (20–29) | 26 (22–34) | .033 |
| Female sex | 171 (58.8) | 45 (71.4) | 216 (61.0) | .065 |
| Tobacco use | 58 (19.9) | 6 (9.5) | 64 (18.1) | .094 |
| Diagnosed in the public sector | 42 (14.4) | 10 (15.9) | 52 (14.7) | .686 |
| Months from symptom onset to MDR-TB treatment, median (IQR) | 4 (2–9) | 3 (2–7.5) | 3.5 (2–8) | .888 |
| Known TB contact | 78 (26.8) | 19 (30.2) | 97 (27.4) | .641 |
| Clinical characteristics | | | | |
| BMI, kg/m$^2$, median (IQR) | 19.7 (16.6–23.0) | 18.1 (15.3–21.4) | 19.4 (16.4–22.9) | .021 |
| Pulmonary TB | 232 (79.7) | 49 (77.8) | 281 (79.4) | .733 |
| HIV positive | 1 (0.3) | 0 (0.0) | 1 (0.3) | 1.000 |
| Diabetes | 34 (11.7) | 5 (7.9) | 39 (11.0) | .510 |
| History of prior TB | 79 (27.1) | 14 (22.2) | 93 (26.3) | .528 |
| Microbiology | | | | |
| XDR-TB | 88 (30.2) | 18 (28.6) | 106 (29.9) | .880 |
| Smear positive | 218 (74.9) | 44 (69.8) | 262 (74.0) | .430 |
| Culture positive | 280 (96.2) | 62 (98.4) | 342 (96.6) | 1.000 |
| Radiographic findings | | | | |
| % of lung involvement on CXR, median (IQR) | 10 (0–30) | 13 (0–30) | 10 (0–30) | <.001 |
| Cavitary lung disease | 157 (54.0) | 34 (54.0) | 191 (54.0) | .426 |
| Additional treatment[b] | | | | |
| Linezolid | 125 (43.0) | 12 (19.0) | 137 (38.7) | <.001 |
| Bedaquiline | 26 (8.9) | 5 (7.9) | 31 (8.8) | 1.000 |
| Clofazimine | 172 (59.1) | 26 (41.3) | 198 (55.9) | .012 |
| Cycloserine | 246 (84.5) | 51 (81.0) | 297 (83.9) | .456 |
| Amikacin | 19 (6.5) | 1 (1.6) | 20 (5.6) | .223 |
| Kanamycin | 103 (35.4) | 22 (34.9) | 125 (35.3) | 1.000 |
| Capreomycin | 49 (16.8) | 4 (6.3) | 53 (15.0) | .033 |
| Pyrazinamide | 22 (7.6) | 2 (3.2) | 24 (6.8) | .276 |
| Ethambutol | 15 (5.2) | 1 (1.6) | 16 (4.5) | .323 |
| Ethionamide | 52 (17.9) | 8 (12.7) | 60 (16.9) | .361 |
| PAS | 153 (52.6) | 25 (39.7) | 178 (50.3) | .071 |
| Delamanid | 7 (2.4) | 0 (0.0) | 7 (2.0) | .361 |
| At least 4 effective drugs available | 160 (55.0) | 22 (34.9) | 182 (51.4) | .005 |
| Treated with lung resection | 23 (7.9) | 7 (11.1) | 30 (8.5) | .453 |
| Treatment-associated side effects | | | | |
| GI upset (nausea, vomiting, anorexia) | 128 (44.0) | 19 (30.2) | 147 (41.5) | .623 |
| Joint pain | 72 (24.7) | 4 (6.3) | 76 (21.5) | .012 |
| Peripheral neuropathy | 97 (33.3) | 8 (12.7) | 105 (29.7) | .023 |
| Cognitive change | 52 (17.9) | 5 (7.9) | 57 (16.1) | .290 |
| Elevated aminotransferases (3× ULN) | 26 (8.9) | 3 (4.8) | 29 (8.2) | .439 |
| QTc over 450 msec | 39 (13.4) | 5 (7.9) | 44 (12.4) | 1.000 |
| Treatment outcomes | | | | |
| Culture converted at 2 months | 75 (25.8) | 19 (30.2) | 94 (26.6) | .533 |
| Culture converted at 6 months | 142 (48.8) | 26 (41.3) | 168 (47.5) | .261 |
| Good treatment outcome | 166 (57) | 34 (54) | 200 (56.5) | .744 |
| Died | 13 (4.5) | 8 (12.7) | 21 (5.9) | .019 |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CXR, chest radiograph; GI, gastrointestinal; HIV, human immunodeficiency virus; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; PAS, para-aminosalicylic acid; TB, tuberculosis; ULN, upper limit of normal; XDR-TB, extensively drug-resistant tuberculosis.

[a] *P* values derived from Fisher exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

[b] Treated based on confirmed phenotypic susceptibility except for bedaquiline, cycloserine, and delamanid.

through compassionate use by participants who also received high-dose moxifloxacin. Joint pain and peripheral neuropathy were more frequent among participants prescribed high-dose moxifloxacin than those who were not (24.7% vs 6.3% and 33.3% vs 12.7%), but aminotransferase elevation and QTc prolongation were uncommon events that did not significantly differ by study group. Fewer participants treated with high-dose moxifloxacin died during follow-up (4.5% vs 12.7%, $P = .019$).

Overall, 95 participants (26.8%) experienced bad treatment outcomes. Univariate regression analysis found increased hazard of bad treatment outcome associated with treatment delay, comorbid diabetes, and extent of radiographic disease, but lower hazard among participants with higher BMI and those treated with linezolid, clofazimine, PAS, or second-line injectable drugs, provided that phenotypic susceptibility was confirmed (Table 2; Figure 2). After adjusting for age, sex, BMI, radiographic involvement, and drug regimen, only extent of lung involvement was associated with increased hazard of bad treatment outcomes, while higher baseline BMI and number of drugs prescribed with confirmed susceptibility were associated with decreased hazard of bad outcomes. High-dose moxifloxacin prescription was not significantly associated with treatment outcomes in either the adjusted or unadjusted models. In a sensitivity analysis, we constructed proportional hazards models after propensity score matching based on additional drug resistance, disease severity, and diabetes. None of these models found significant associations between the high-dose moxifloxacin and improved treatment outcomes

**Table 2. Univariate Hazard of Bad Treatment Outcome**

| Variable | Unadjusted HR (95% CI) | Adjusted HR[a] (95% CI) |
|---|---|---|
| Demographic and clinical characteristics | | |
| Female sex | 0.92 (.61–1.40) | 1.10 (.65–1.86) |
| Age (10-year increments) | 1.10 (.94–1.30) | 1.19 (.98–1.46) |
| Pulmonary TB | 1.80 (.95–3.60) | 1.37 (.53–3.58) |
| Months from symptom to MDR-TB treatment initiation | 1.02 (1.01–1.04)[b] | … |
| Tobacco use | 0.52 (.25–1.10) | … |
| BMI, kg/m$^2$ | 0.92 (.87–.97)[b] | 0.92 (.86–.98)[b] |
| Laboratory features | | |
| Diabetes | 3.70 (1.40–9.90)[b] | … |
| Initial smear grade | 1.00 (.87–1.30) | … |
| Culture converted at 2 months | 0.56 (.22–1.40) | … |
| Culture converted at 6 months | 1.10 (.57–2.10) | … |
| Radiographic findings | | |
| Cavitary lung disease | 1.50 (.87–2.50) | … |
| Lung field involvement (10% increments) | 1.10 (1.00–1.20)[b] | 1.11 (1.02–1.22)[b] |
| Treatment[c] | | |
| Linezolid | 0.49 (.30–.79)[b] | … |
| Bedaquiline | 0.62 (.29–1.40) | … |
| Clofazimine | 0.58 (.38–.87)[b] | … |
| Cycloserine | 0.75 (.46–1.20) | … |
| Amikacin | 0.32 (.079–1.30) | … |
| Kanamycin | 0.63 (.39–1.00) | … |
| Capreomycin | 0.83 (.48–1.40) | … |
| Any DST-confirmed second-line injectable drug (amikacin, kanamycin, or capreomycin) | 0.54 (.36–.82)[b] | … |
| Pyrazinamide | 0.65 (.27–1.60) | … |
| Ethambutol | 0.93 (.34–2.50) | … |
| Ethionamide | 1.40 (.85–2.40) | … |
| PAS | 0.60 (.39–.90)[b] | … |
| Delamanid | 0.57 (.17–1.80) | … |
| No. of effective drugs prescribed | 0.80 (.71–.90)[b] | 0.77 (.67–.87)[b] |
| Took at least 4 effective drugs | 0.45 (.29–.69)[b] | … |
| Treated with lung resection | 0.91 (.49–1.70) | … |
| Prescribed high-dose moxifloxacin | 0.84 (.50–1.40) | 1.24 (.63–2.41) |

Abbreviations: BMI, body mass index; CI, confidence interval; DST, drug susceptibility testing; HR, hazard ratio; MDR-TB, multidrug-resistant tuberculosis; PAS, para-aminosalicylic acid; TB, tuberculosis.

[a]Adjusted for each variable included in the model: female sex, age, pulmonary disease, extent of radiographic involvement, number of effective drugs prescribed, and prescription of high-dose moxifloxacin.

[b]Significant variables at a $P$ value threshold of < .05.

[c]Values indicate associated with treatment when drug is confirmed to be phenotypically susceptible, except for cycloserine, bedaquiline, and delamanid, for which phenotypic drug susceptibility testing was not routinely performed in this study.

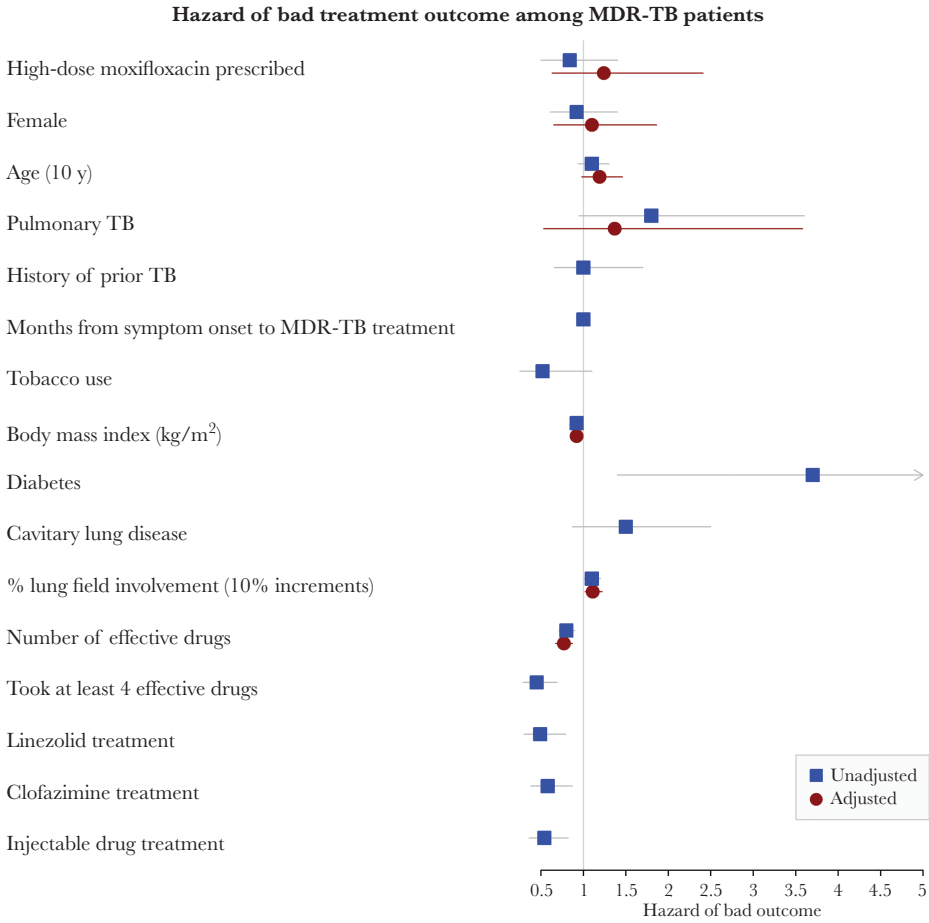


**Figure 2.** Unadjusted and adjusted hazards of bad treatment outcome among study participants with multidrug-resistant tuberculosis. Forest plot indicating the proportional hazards of bad treatment outcomes associated with each variable. Squares indicate unadjusted proportional hazards, and circles indicate proportional hazards adjusted for high-dose moxifloxacin prescription, sex, age, pulmonary disease, extent of disease on chest radiograph, and prescription of additional antituberculosis drugs with confirmed phenotypic susceptibility or no standardized drug susceptibility testing methods available but low rates of circulating resistance (cycloserine, bedaquiline, and delamanid). Abbreviations: MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

($P$ = .174–.929 and $P$ = .119–.996 for unadjusted and adjusted hazards, respectively).

Additional analysis assessed the impact of high-dose moxifloxacin on other outcomes including culture conversion, treatment-associated side effects, and death. High-dose moxifloxacin prescription was not significantly associated with 6-month culture conversion (hazard ratio [HR], 1.10 [95% confidence interval {CI}, .43–2.70]), although number of effective drugs and taking ≥4 effective drugs were both associated with improved culture conversion (HR, 1.20 [95% CI, 1.00–1.40] and 2.20 [95% CI, 1.20–4.10], respectively). Specifically, 6-month culture conversion was associated with prescription of linezolid (HR, 2.10 [95% CI, 1.30–3.60]), clofazimine (HR, 2.10 [95% CI, 1.10–3.90]), and a second-line injectable with confirmed susceptibility (HR, 1.80 [95% CI, 1.00–3.10]). High-dose moxifloxacin was, however, significantly associated with more self-reported joint pain (HR, 3.20 [95% CI, 1.20–8.80]) and peripheral neuropathy (HR, 2.10 [95% CI, 1.00–4.30]), though not with QTc prolongation (HR, 1.10 [95% CI, .43–2.80]), aminotransferase elevation (HR, 1.40 [95% CI, .43–4.80]), gastrointestinal upset (HR, 1.16 [95% CI, .72–1.88]), or cognitive change (HR, 1.84 [95% CI, .73–4.62]). After controlling for additional drugs prescribed, high-dose moxifloxacin use was only associated with increased hazard of joint pain (adjusted HR, 2.89 [95% CI, 1.05–7.94]).

While not associated with bad outcome in either univariate or multivariate analysis, high-dose moxifloxacin prescription was associated with reduced hazard of death (HR, 0.28 [95% CI, .11–.69]), as were higher BMI (HR, 0.82 [95% CI, .72–.94]), number of effective drugs prescribed (HR, 0.75 [95% CI, .58–.97]), and regimens including ≥4 effective drugs (HR, 0.33 [95% CI, .13–.86]). In multivariate analysis, the significant association between high-dose moxifloxacin and death disappeared after adjustment for drug resistance (HR, 0.48 [95% CI, .08–2.77]), concomitant linezolid and capreomycin prescription (HR, 0.33 [95% CI, .1–1.11]), or both additional resistance and prescriptions (HR, 0.73 [95% CI, .12–4.61]).

## DISCUSSION

In this large, single-provider observational cohort in Mumbai's private sector, treatment of participants with MDR-TB and additional low-level moxifloxacin resistance with high-dose moxifloxacin (600 mg daily) was not associated with better treatment outcomes. Although death was more common among participants treated with standard moxifloxacin doses, this association was not significant after controlling for prescription of other TB drugs. Overall, BMI, extent of lung involvement, and prescription of drugs following DST were more statistically reliable predictors of treatment outcomes in this population than the addition of high-dose moxifloxacin. While treatment with high-dose moxifloxacin was not associated with aminotransferase elevation or QTc prolongation, it was associated with increased joint pain.

As reports of drug-resistant TB increase worldwide, it is important to adapt treatment strategies to the best available evidence. During this study period, the WHO updated treatment guidelines for drug-resistant tuberculosis, underscoring the importance of later-generation fluoroquinolones in TB treatment [2, 9, 10]. Unfortunately, optimal regimens for MDR-TB also resistant to fluoroquinolones have not yet been clearly defined. In this context, it is reasonable to prescribe higher moxifloxacin doses (600–800 mg daily) to overcome low-level drug resistance, especially when susceptibility testing is not available or few treatment options remain for highly resistant *Mtb*. In our setting, 600 mg daily was chosen to balance potential benefits of higher dosing with dose-dependent side effects [12]. Pharmacokinetic studies of moxifloxacin suggest an optimal target area under the curve to minimum inhibitory concentration (AUC/MIC) ratio of 100–130 to prevent new resistance and to reduce the transmission of resistant *Mtb* strains during treatment, with an AUC/MIC of 40–102 required for resistance suppression [13–17]. Moxifloxacin doses of 400 mg, 600 mg, and 800 mg daily are associated with AUCs of 33.9 mg hour/L, 60.3 mg hour/L, and 91.4 mg hour/L, respectively, achieving treatment targets for 59%, 86%, and 93% of patients, respectively [15, 18]. This suggests that while susceptible *Mtb* isolates (MIC < 0.5 μg/mL) can be successfully treated with 400 mg daily, higher doses may perform better in patients with MICs of 0.5–2 μg/mL. It also suggests that moxifloxacin 800 mg daily would better treat *Mtb* isolates with MICs ≥1–2 μg/mL, and dose adjustment would not likely succeed for isolates with MICs ≥2 μg/mL. This is reflected in recent WHO guidance to lower moxifloxacin concentrations for MGIT DST from 0.5 μg/mL and 2 μg/mL to 0.25 μg/mL and 1 μg/mL, respectively [3].

The lack of benefit from high-dose moxifloxacin in this cohort highlights the importance of accurate susceptibility testing to guide therapy. Without MIC testing, most clinicians do not know how resistant their patients' isolates will be. In this study, we attempted to address this by selecting participants with low-level resistance, and also assessed the effect of resistance to coadministered drugs. Interestingly, high-dose moxifloxacin had less impact on treatment outcomes than did extent of radiographic disease [14]. Severe disease, often proxied by extent of radiographic involvement and lower BMI, is commonly associated with poor treatment outcomes, which is consistent with our findings. Additionally, diabetes is associated with poor absorption of antituberculosis drugs, including moxifloxacin, which may be reflected in our univariate analysis indicating worse outcomes in patients with poorly controlled blood glucose levels [19]. Finally, we found that death was more common among those who did not receive high-dose moxifloxacin, but this benefit disappeared when we adjusted for other factors, such as extent of resistance and use of other drugs. While they were not all statistically significant, treatment with any effective drug except ethionamide was associated with lower hazard of a bad treatment outcome. This includes injectable drugs, which have recently fallen out of favor due to poor associations with treatment outcomes in global individual patient data meta-analyses [20]. One potential difference in our setting is that these prescriptions were only provided if the drug was confirmed to be susceptible, which has been shown to improve expected outcomes associated with injectable drugs for tuberculosis [21]. Neither additional injectable resistance (XDR-TB) nor the presence of high-level moxifloxacin resistance (>2 μg/mL in MGIT) changed our findings that high-dose moxifloxacin did not improve treatment outcomes ($P = .866$ and $P = .481$, respectively). Overall, the lack of association between high-dose moxifloxacin and improved outcomes in >350 participants suggests that increasing moxifloxacin dose to 600 mg daily in this setting has minimal benefit, and underscores the importance of DST-derived therapy for MDR-TB.

This single center, nonrandomized study had several limitations. Recruitment from a referral center with a young, female-predominant, and largely HIV-negative population with significant additional drug resistance may limit generalizability to other populations and other countries. During the years that most participants were treated, bedaquiline was not yet standard of care for MDR-TB, so the lack of benefit in this study may not be generalizable to newer drug regimens that also include high-dose moxifloxacin. Similarly, delamanid was available to study participants under compassionate use and was therefore infrequently prescribed, limiting generalizability of results to the use of high-dose moxifloxacin in combination with delamanid- or pretomanid-based regimens. Much of the treatment benefit in this cohort depended on the use of drugs with confirmed phenotypic drug susceptibility. Unfortunately, DST cannot be performed at many clinics around the world. This further limits generalizability of our results, particularly to sites with lower prevalence of moxifloxacin resistance

than Mumbai. This study did not include direct observation of treatment, assess drug levels among study participants, or directly measure MICs of cultured isolates. It is possible that participants at this referral center had isolates with higher moxifloxacin MICs than normal, which would limit the efficacy of high-dose treatment. A previous study of quinolone-resistant isolates at our site found moxifloxacin MICs <2 μg/mL in only a third of isolates, while the remainder were more resistant [4]. The same study found that many samples had genotypic mutations indicating amino acid changes at position 94 in gyrA, associated with moxifloxacin resistance that may not be overcome by higher doses. Improved knowledge of MICs or MICs inferred from genotypes may improve dosing in future studies. Additionally, our use of a composite "bad" outcome may have blunted the benefits of high-dose moxifloxacin among study participants. To test the assumption that loss to follow-up was a bad outcome (presumably leading to later death or disease progression), we contacted the families of 116 study participants who were not seen for ≥1 year. Of 40 participants for whom vital status could be determined, 30 had died (75% of those with successful communication, 25.9% of all attempted contacts), suggesting that the composite endpoint was reasonable. We also found that high-dose moxifloxacin was associated with increased frequency and hazard of neuropathy, but this finding was not significant after adjusting for other MDR-TB drugs prescribed, most notably linezolid. A larger study would be required to directly assess each combination of drugs in a personalized regimen with sufficient statistical power. Finally, these results may not be generalizable to settings prescribing moxifloxacin at doses of 800 mg daily, which were avoided at this clinic due to concerns for treatment-associated side effects [12].

As we work to establish more effective and personalized treatment regimens for patients with MDR-TB, it will be important to incorporate pharmacokinetic considerations into drug dosing strategies. While low-level moxifloxacin resistance may be overcome by increasing moxifloxacin doses, we did not find improved outcomes with 600 mg daily after controlling for resistance profiles and the coadministration of other effective drugs. High-dose moxifloxacin may be helpful if MICs and therapeutic drug monitoring can be performed, but in this study, 600 mg daily increased treatment-associated side effects without improving overall outcomes and should be avoided for empiric treatment of moxifloxacin-resistant MDR-TB.

## Notes

***Author contributions.*** J. A. T. and A. G. contributed to study design, data analysis, and manuscript preparation. Z. F. U., J. B. M., L. M. P., T. F. A., and C. R. contributed to study design, data collection, data analysis, and manuscript preparation. P. R. A., I. G., S. S., M. K., N. S., N. K., and S. V. Y. B. S. contributed to data collection and manuscript preparation. A. J. B. contributed to manuscript preparation. A. N. G. and N. G. contributed to data analysis and manuscript preparation.

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## References

1. World Health Organization. Global Tuberculosis Report 2018. Geneva, Switzerland: WHO; **2018**.
2. World Health Organization. Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampin-Resistant Tuberculosis (MDR/RR-TB). Geneva, Switzerland: WHO; **2018**.
3. World Health Organization. Technical Report on Critical Concentrations for Drug Susceptibility Testing of Medicines Used in the Treatment of Drug-Resistant Tuberculosis. Geneva, Switzerland: WHO; **2018**.
4. Kambli P, Ajbani K, Sadani M, et al. Correlating minimum inhibitory concentrations of ofloxacin and moxifloxacin with gyrA mutations using the genotype MTBDRsl assay. Tuberculosis **2015**; 95:137–41.
5. Rodrigues C, Jani J, Shenai S, et al. Drug susceptibility testing of *Mycobacterium tuberculosis* against second-line drugs using the Bactec MGIT 960 system. Int J Tuberc Lung Dis **2008**; 12:1449–55.
6. Pfyffer GE, Palicova F, Rusch-Gerdes S. Testing of susceptibility of *Mycobacterium tuberculosis* to pyrazinamide with the nonradiometric BACTEC MGIT 960 system. J Clin Microbiol **2002**; 40:1670–4.
7. Udwadia ZF, Tornheim JA, Ganatra S, et al. Few eligible for the newly recommended short course MDR-TB regimen at a large Mumbai private clinic. BMC Infect Dis **2019**; 19:94.
8. Tornheim JA, Intini E, Gupta A, Udwadia ZF. Clinical features associated with linezolid resistance among multidrug resistant tuberculosis patients at a tertiary care hospital in Mumbai, India. J Clin Tuberc Other Mycobact Dis **2020**; 20:100175.
9. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis—2011 Update. Geneva, Switzerland: WHO; **2011**.
10. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis—2016 Update. Geneva, Switzerland: WHO; **2016**.
11. Ralph AP, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest X-ray severity in adult smear-positive pulmonary tuberculosis. Thorax **2010**; 65:863–9.
12. Ganatra SR, Udwadia ZF, Mullerpattan JB, et al. High dose moxifloxacin for drug resistant tuberculosis; is 600 mg the optimal dose in high resistance settings? In: C15. TB Game Changers: Diagnostics, HIV, Drug-Resistance, and Treatment. San Francisco, CA: American Thoracic Society 2016 International Conference, 13–18 May **2016**. Available at: https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A4570
13. Al-Shaer MH, Alghamdi WA, Alsultan A, et al. Fluoroquinolones in drug-resistant tuberculosis: culture conversion and pharmacokinetic/pharmacodynamic target attainment to guide dose selection. Antimicrob Agents Chemother **2019**; 63:e00279-19.
14. Gumbo T, Louie A, Deziel MR, et al. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. J Infect Dis **2004**; 190:1642–51.

15. Heinrichs MT, Drusano GL, Brown DL, et al. Dose optimization of moxifloxacin and linezolid against tuberculosis using mathematical modeling and simulation. Int J Antimicrob Agents **2019**; 53:275–83.
16. Pranger AD, Kosterink JG, van Altena R, et al. Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with tuberculosis. Ther Drug Monit **2011**; 33:350–4.
17. Nuermberger E, Grosset J. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. Eur J Clin Microbiol Infect Dis **2004**; 23:243–55.
18. Stass H, Kubitza D, Schühly U. Pharmacokinetics, safety and tolerability of moxifloxacin, a novel 8-methoxyfluoroquinolone, after repeated oral administration. Clin Pharmacokinet **2001**; 40(Suppl 1):1–9.
19. Dekkers BGJ, Akkerman OW, Alffenaar JWC. Role of therapeutic drug monitoring in treatment optimization in tuberculosis and diabetes mellitus comorbidity. Antimicrob Agents Chemother **2019**; 63: e02074-18.
20. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet **2018**; 392:821–34.
21. Cegielski JP, Chan PC, Lan Z, et al. Aminoglycosides and capreomycin in the treatment of multidrug-resistant tuberculosis: individual patient data meta-analysis of 12 030 patients from 25 countries, 2009-2016. Clin Infect Dis **2020**; 73:e3929–36.