Increased Moxifloxacin Dosing among MDR-TB Patients with Low-Level Resistance to Moxifloxacin did not Improve Treatment Outcomes in a Tertiary Care Center in Mumbai, India

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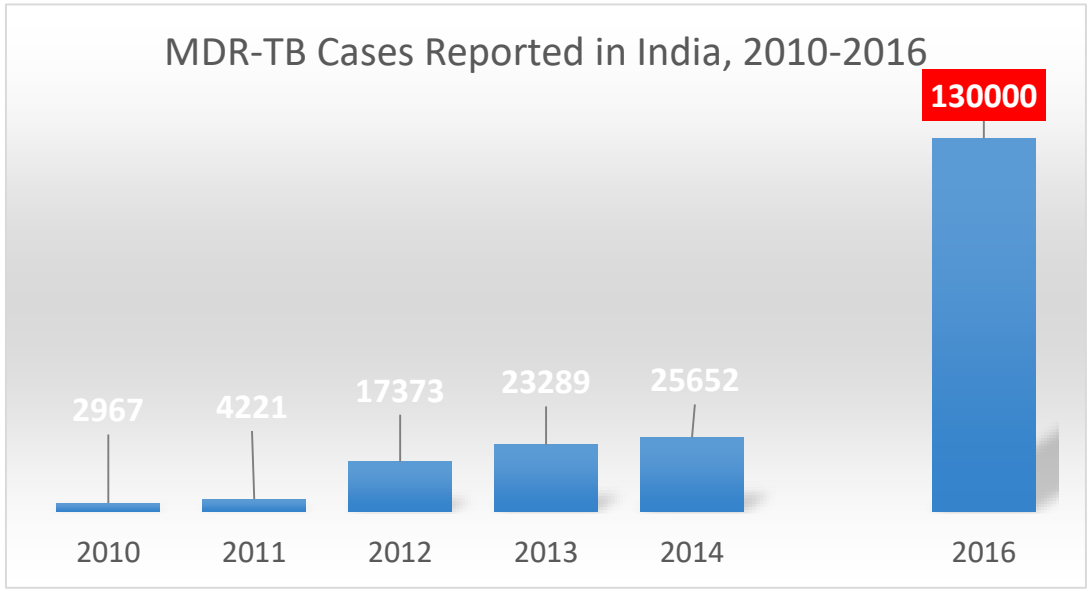
Disclosures

- Nothing to Disclose

Background

- Tuberculosis is the #1 infectious disease killer worldwide
  - 26.8% of global cases in India[1]
  - Rates of MDR-TB are increasing in India[2]
  - Mumbai disproportionately affected

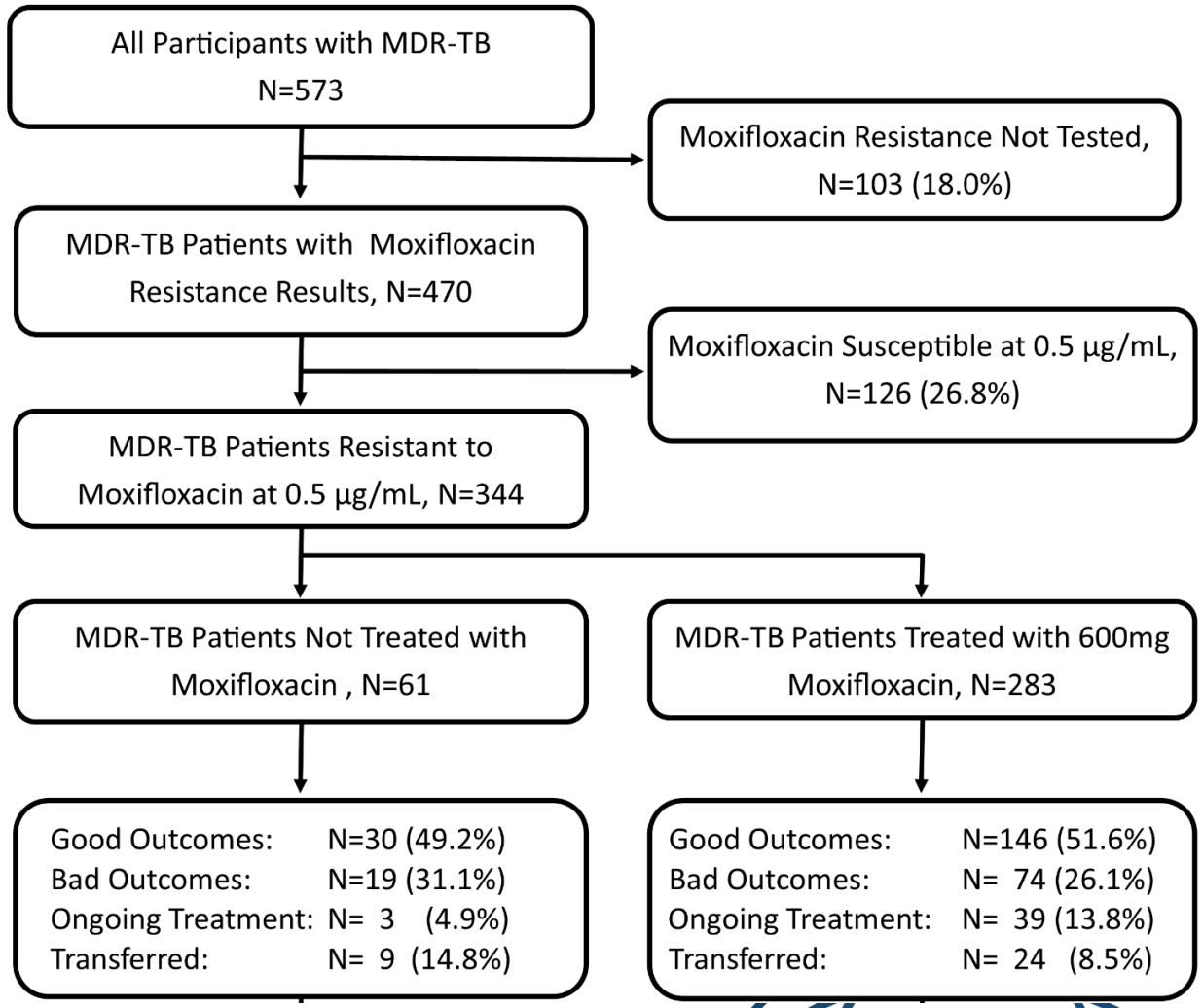


- Outcomes relate directly to drug resistance:
  - Susceptible TB: 88% good outcome
  - MDR-TB: 46% good outcome
  - XDR-TB: 12% good outcome[3]

[1]WHO Global Tuberculosis Report 2017 [2]Revised National TB Control Program Annual Reports 2011–2017
[3]Pietersen E, et al. Lancet 2014

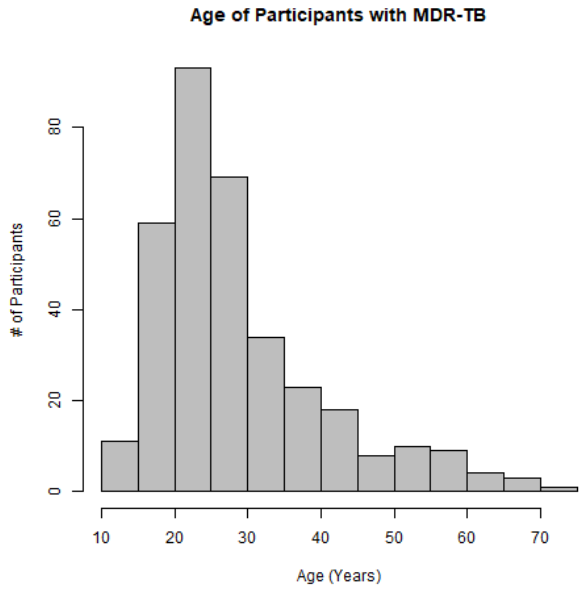
Prospective Observational Cohort of MDR-TB

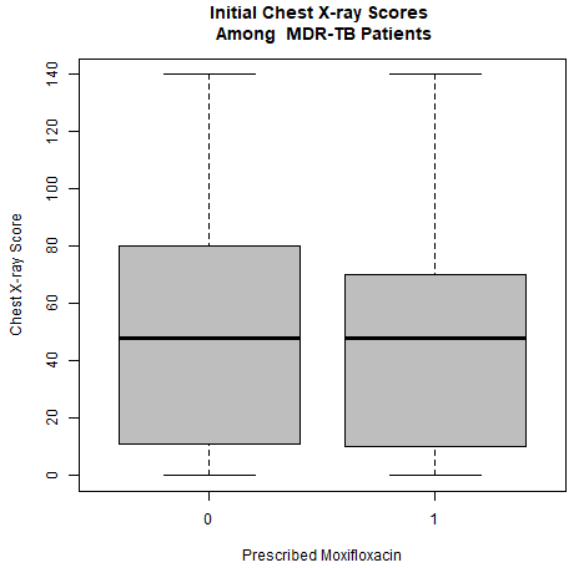
- **Study Site**: P. D. Hinduja National Hospital and Medical Research Centre in Mumbai, India
  - Extensive clinical experience with complex resistance, bedaquiline, and delamanid
  - CAP & NABL accredited BSL 2+ lab (>32,000 samples/ yr)
  - Diagnostic test and pharmacokinetic assessments
- **Participants**: MDR-TB patients treated at the study site
- **Outcome**: Improved rates of "good" (cure/completion) vs. "bad" (death, default, relapse, loss to follow-up) outcome associated with moxifloxacin 600mg
- **Data Analyzed**:
  - Participant visit data from October 2015-October 2019
  - 573 total cohort participants
  - 344 (60%) moxifloxacin R at 0.5ug/mL
  - 283 (82.2%) prescribed 600mg daily
  - 1650 patient visits



Participant Characteristics

	Prescribed Moxifloxacin (N=283)	Not Prescribed Moxifloxacin (N=61)	p-value
Age, Median (IQR)	26 (22-34)	24 (20-29.8)	0.066
Female, N (%)	168 (59.4)	43 (70.5)	0.113
Pulmonary TB Only, N (%)	227 (80.2)	47 (77.0)	0.600
Known TB Contact, N (%)	79 (27.9)	18 (29.5)	0.875
History of Prior TB, N (%)	76 (26.9)	13 (21.3)	0.423
BMI at Diagnosis, Median (IQR)	19.7 (16.5-22.9)	18.7 (15.4-21.8)	0.065
HIV Positive,* N (% of those tested)	1 (0.5)	0 (0.0)	1.000
Diabetic,* N (% of those tested)	33 (35.5)	5 (31.3)	1.000
Smear Positive, N (%)	212 (74.9)	43 (70.5)	0.520
X-Ray Score at Diagnosis	48 (10-70)	48 (11.5-80)	0.659
Good Treatment Outcome	146 (51.6)	30 (49.2)	0.510
Culture Negative at 2 Months*	44 (52.4)	4 (50.0)	1.000
Culture Negative at 6 Months*	60 (40.0)	5 (38.5)	1.000
GI Upset (Nausea, Vomiting, Anorexia)*	119 (47.0)	18 (43.9)	0.739
Joint Pain*	67 (26.5)	4 (9.8)	0.019
Peripheral Neuropathy*	82 (32.4)	8 (19.5)	0.104
Elevated Transaminases (3x ULN)*	25 (10.3)	3 (6.4)	0.590
QTc Over 450msec*	34 (40.0)	4 (33.3)	0.760

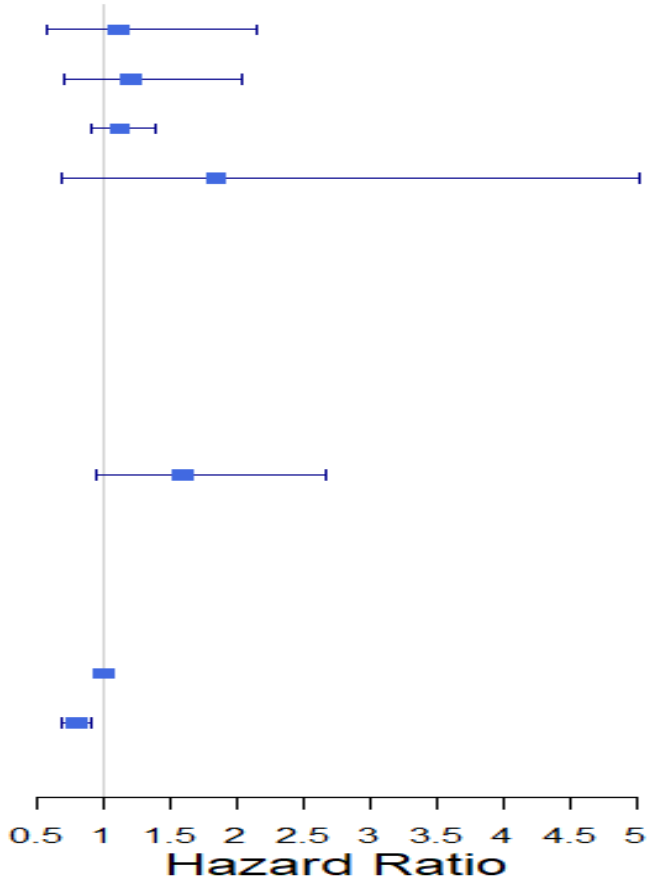




- No significant difference in demographics, treatment, or outcomes
  - More frequent self-reported joint pain with moxifloxacin

Hazard of Bad Outcome from MDR-TB

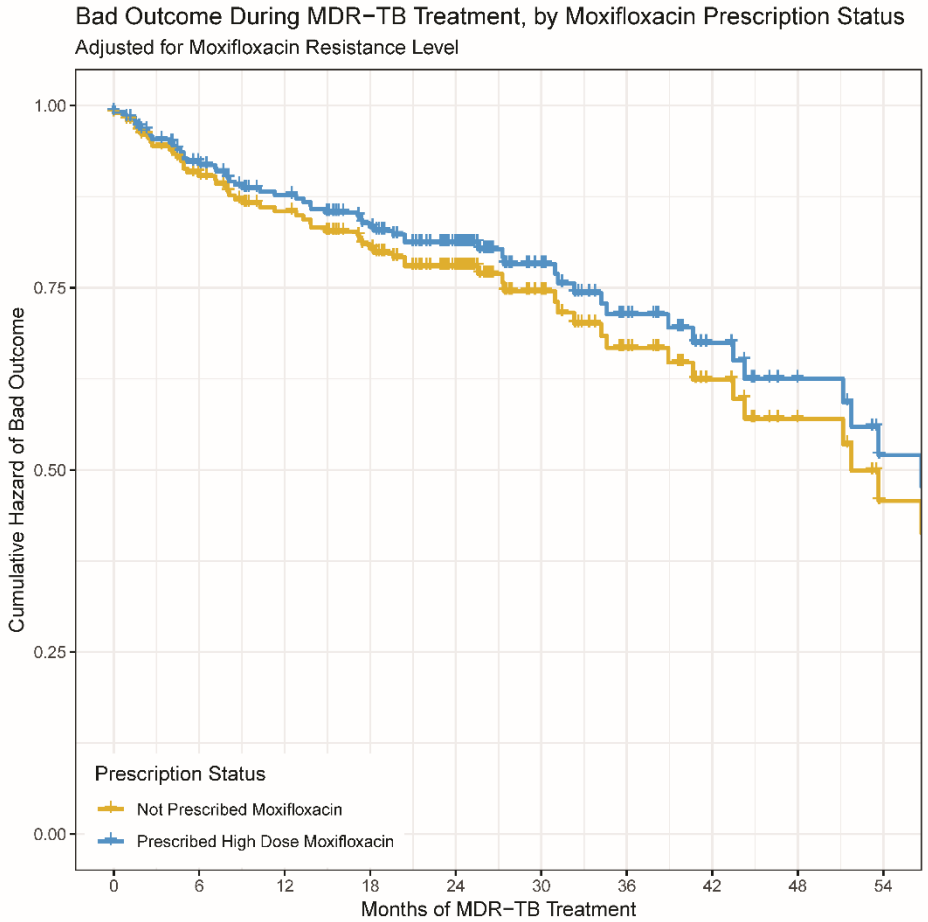
Variable	Adjusted Hazard Ratio (95% Confidence Interval)	p-value
Prescribed High Dose Moxifloxacin During Study	1.11 (0.77-1.57-1.30)	0.32764
Female	1.20 (0.79-1.64-1.50)	0.9594
Age (10-year increments)	1.12 (0.99-1.38-1.30)	0.60081
Pulmonary TB Only	1.84 (1.68-3.09-3.70)	0.05231
Known TB Contact	1.10 (0.72-1.70)	0.620
History of Prior TB	0.97 (0.60-1.60)	0.910
Alcohol Use	2.70 (0.67-11.00)	0.160
Tobacco Use	0.59 (0.27-1.30)	0.180
Stopped Work Due to TB	1.30 (0.80-2.10)	0.300
Underweight (BMI<18.5)	1.59 (1.96-2.66-2.50)	**0.04278**
Diabetes	3.00 (1.10-8.30)	**0.030**
% Lung Field Opacity on Chest X-Ray (10% increments)	1.00 (0.92-1.08*-1.20)	0.96458
% Cavitary Lung Disease on Chest X-Ray (10% increments)	1.80 (1.00-3.10)	**0.042**
Number of Effective Drugs Prescribed	0.80 (0.69-0.97-0.92)	**0.00001**
Took At Least 4 Effective Drugs	0.49 (0.32-0.76)	**0.001**



- Underweight and # of effective drugs were associated with good outcome
- Moxifloxacin 600mg daily was not significantly associated with outcomes

Conclusions

- In a large single site prospective observational cohort with complex drug resistance and individualized treatment:
  - Moxifloxacin resistance at 0.5ug/mL is common
  - Moxifloxacin 600mg daily did not improve treatment outcomes compared no moxifloxacin
    - This was true independent of specific drugs and additional resistance data
    - Also not associated with culture conversion at 2M, culture conversion at 6M, or time to culture conversion
    - It was associated with joint pain (OR 3.3 (1.2-11.4)
  - # of effective drugs associated with improved outcomes in adjusted and unadjusted analysis
  - Results for moxifloxacin 600mg daily may not be generalizable to moxifloxacin 800mg daily



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Hazard of Bad Outcome from MDR-TB

Variable	Unadjusted Hazard Ratio (95% Confidence Interval)	p-value	Adjusted Hazard Ratio (95% Confidence Interval)	p-value
Prescribed High Dose Moxifloxacin During Study	0.77 (0.47-1.30)	0.320	1.11 (0.57-2.15)	0.764
Female	0.99 (0.64-1.50)	0.950	1.20 (0.71-2.04)	0.494
Age (10-year increments)	1.00 (0.88-1.30)	0.600	1.12 0.91-1.38)	0.281
Pulmonary TB Only	1.90 (0.99-3.70)	0.055	1.84 (0.68-5.01)	0.231
Known TB Contact	1.10 (0.72-1.70)	0.620		
History of Prior TB	0.97 (0.60-1.60)	0.910		
Alcohol Use	2.70 (0.67-11.00)	0.160		
Tobacco Use	0.59 (0.27-1.30)	0.180		
Stopped Work Due to TB	1.30 (0.80-2.10)	0.300		
Underweight (BMI<18.5)	1.60 (1.00-2.50)	**0.042**	1.59 (0.95-2.66)	0.078
Diabetes	3.00 (1.10-8.30)	**0.030**		
% Lung Field Opacity on Chest X-Ray (10% increments)	1.10 (1.00-1.20)	0.064	1.00 (0.92-1.08)*	0.958
Cavitary Lung Disease	1.80 (1.00-3.10)	**0.042**		
Number of Effective Drugs Prescribed	0.81 (0.72-0.92)	**0.001**	0.80 (0.69-0.91)	**0.001**
Took At Least 4 Effective Drugs	0.49 (0.32-0.76)	**0.001**		

- Underweight and # of effective drugs were the strongest predictors of treatment outcomes
- Moxifloxacin 600mg daily was not significantly associated with outcomes

Role of Additional Treatment

Hazard of Bad Treatment Outcome Associated with Concomitant Treatment, by Drug

	Hazard Ratio (95% Confidence Interval)	p-value
Linezolid	0.56 (0.35-0.90)	**0.018**
Bedaquiline	0.45 (0.18-1.10)	0.091
Clofazimine	0.66 (0.44-1.00)	0.056
Cycloserine	0.44 (0.29-0.67)	**<0.001**
Ethambutol	0.90 (0.33-2.50)	0.850
Pyrazinamide	0.52 (0.19-1.40)	0.200
Ethionamide	1.60 (0.97-2.70)	0.068
Injectable (Amikacin, Kanamycin, or Capreomycin)	0.56 (0.37-0.86)	**0.008**
PAS During Study	0.65 (0.43-1.00)	**0.048**
Delamanid During Study	0.36 (0.09-1.50)	0.160
Summarized by Number of Concurrent Drugs		
Number of Effective Drugs Prescribed	0.81 (0.72-0.92)	**0.001**
Took At Least 4 Effective Drugs	0.49 (0.32-0.76)	**0.001**

- Confirmed benefit of additional treatments, across WHO drug groups
  - Linezolid, cycloserine, injectable, drugs, and PAS demonstrated protection (P<0.05)
- These were summarized as number of effective drugs prescribed