PREVALENCE OF DRUG RESISTANT TUBERCULOSIS AMONG PATIENTS AT HIGH-RISK FOR HIV ATTENDING OUTPATIENT CLINICS IN DELHI, INDIA

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Abstract. We sought to determine tuberculosis (TB) prevalence including multidrug resistant (MDR)-TB among a cohort of high risk patients at two directly observed treatment short course (DOTS) clinics in Delhi, India. We also aimed to compare the sensitivity of acid-fast bacilli (AFB) smear tests for patients with HIV using sputum cultures as the gold standard. A cross-section study was conducted among adult patients (≥18 years old) with prolonged cough (greater than two weeks), night sweats, fever, and/or weight loss suspected of pulmonary TB between February and March 2006. Sputum samples were obtained and processed for 165 patients; 53 (32.1%) were culture positive for TB. Patients with TB were predominantly male (92.1%), young (median age of 32 years), and the HIV-seroprevalence was high (41.5%). In the multivariable analysis adjusted for age, HIV infection was significantly associated (POR=2.0, $p<0.05$) with the presence of TB disease. Among *Mycobacterium tuberculosis* isolates recovered from 53 cases, 25 (47.2%) were resistant to ≥1 first line anti-TB drugs and 7 (13.2%) were MDR-TB. The sensitivity of AFB smears among HIV negative and positive participants was 35.5% and 18.0%, respectively. Our findings demonstrated that the sensitivity of AFB smears to detect TB among HIV positive patients was low. Additionally, we found that even in regions where population drug resistance estimates are low, sentinel surveillance of MDR-TB in high-risk populations is useful to prioritize target groups in need of additional prevention, monitoring and health outreach.

Keywords: tuberculosis, multidrug resistance, HIV, DOTS

INTRODUCTION

The World Health Organization (WHO) estimates that there were 9.4 million new tuberculosis (TB) cases in 2009 and 1.3 million deaths due to TB worldwide (WHO, 2010). India alone accounts for an estimated 1.6-2.4 million new cases each year. Between 1998-2006 India's Revised National TB Control Program (RNTCP) increased directly observed treatment short course (DOTS) coverage by 50% reaching full national geographic

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availability by March 2006 (RNTCP, 2007). Despite improvements in the availability of DOTS, in 2008 India reported 54 TB cases per 100,000 persons and the estimated new smear-positive incidence rate was 75 cases per 100,000 persons per year, yielding a case detection rate of 72% (Borgdorff, 2004; RNTCP, 2009). While the general epidemiology of TB in India is well described, the prevalence of TB and multidrug resistant (MDR)-TB among high-risk groups, such as those with HIV and substance users, is limited.

In 2009, WHO estimated that 4.9% of TB cases globally were MDR-TB, or resistant to at least rifampin and isoniazid (WHO, 2009). Estimating the prevalence of MDR-TB among marginalized populations (such as persons who inject drugs and persons living with HIV) is important because they may contribute to bridge transmission routes with the general population, prevention and treatment may be difficult to provide for them, and consequently mortality is often high (Lawn and Zumla, 2011). HIV/TB co-infections challenge TB control in India and globally although it is estimated that <1% of the population of India is HIV-infected (Ministry of Health and Welfare, 2006; Cohen, 2007). However, the prevalence of HIV infection in India is expected to increase given widespread risk factors such as sex work and injection drug use (IDU) (Kumar *et al*, 2006). Among adult TB patients in India, WHO estimates an HIV prevalence of 5.2%, (RNTCP, 2009) but higher rates have been found in some provinces of India; for example in Karnataka, Andhra Pradesh, Maharashtra, and Tamil Nadu (Ministry of Healht and Welfare, 2006).

The relationship between emerging HIV epidemics and the impact on prevalence of MDR-TB remains uncertain in India. The purpose of our study was to assess the prevalence of and risk factors for TB and drug resistant TB, including MDR-TB among an urban, high risk Indian population in Delhi. We also sought to describe the resistance patterns to DOTS TB medicines and determine the sensitivity and specificity of AFB sputum smears with sputum culture as the "gold standard," by HIV status.

MATERIALS AND METHODS

Study population and setting

Approval for this study was obtained from the Ethical Review Board of Sharan, New Delhi, India, and the Institutional Review Boards (IRB) at the University of Illinois at Chicago, Chicago, IL, USA, and Emory University, Atlanta, GA, USA.

Between February and March 2006, study participants were recruited from two urban clinics in northern Delhi, both administered by Sharan, a non-governmental health organization. Sharan offers multiple social and health services at several sites throughout the metropolitan Delhi area including DOTS screening and treatment. Sharan targets a Delhi population at "high-risk" by providing services to persons with multiple behavioral risk factors for HIV and TB (substance abuse, IDU, homelessness) in a community setting where background prevalence of HIV and TB is high. The two non-governmental Sharan clinics from which study participants were recruited provided a variety of health services including needle exchange, buprenorphine drug substitution, primary medical care, HIV care and support services, and for those with TB, provision of DOTS. Persons attending clinics for any services were screened by physicians and referred to the study if they were ≥18 years old and

were suspected of having pulmonary TB based on the following signs and symptoms: prolonged cough (greater than two weeks), night sweats, fever, and/or weight loss. All participants provided written informed consent.

Data collection

Study participants were interviewed by trained Sharan staff using a standardized WHO questionnaire (WHO, 2003) designed to identify risk factors for MDR-TB, the survey was translated into Hindi, and back translated into English to ensure accuracy. The instrument collected information on demographics, previous TB diagnosis and treatment, drug use behavior, and basic socioeconomics. All study participants had previously received HIV counseling and testing at Sharan, the standard of care at the clinics. Medical records of HIV status were available for all study participants; tests were performed between 2003 and 2005. TB diagnoses were determined by sputum collection and microscopy. All enrolled patients had sputum samples collected and tested for AFB smear and culture. Participants diagnosed with TB were considered "first episode" if they had no self-reported history of a prior TB diagnosis or treatment. All AFB smear positive and/or culture positive patients for *M. tuberculosis* were referred to Indian government DOTS programs with assistance from Sharan outreach workers.

Specimen collection and laboratory processing

Following the face-to-face interviews, participants provided sputum samples collected in sterilized 50 ml containers. Study participants were instructed to return to submit two additional sputum samples on consecutive mornings and were offered a 15 Indian Rupees (approximately USD 0.35) meal coupon for each sputum sample provided. The samples were transferred daily to the All India Institute of Medical Sciences (AIIMS) in sealed heat-protective containers. The AIIMS Division of Clinical Microbiology, Department of Laboratory Medicine, conducted AFB sputum smear microscopy, culture and drug susceptibility testing on each sputum sample collected. All sputa were digested and decontaminated following a standard protocol (Gupta *et al,* 2002). Briefly, equal volume of sodium hydroxide (NaOH, 1% final concentration) containing N-acetyl cysteine (NALC) was added. After 15 minutes of incubation the suspension was neutralized with phosphate buffer (pH 6.8), and concentrated by centrifugation; the pellets obtained were re-suspended in sterile phosphate buffer for further use in various test protocols. From a portion of this suspension, smears were prepared and stained with Ziehl-Neelsen acid-fast staining (Gupta *et al*, 2002).

Specimens were inoculated on both solid medium (Lowenstein-Jensen agar) and broth-based automated system (MGIT 960, Beckton-Dickinson, San Jose, CA) and incubated at 37°C (Mukherjee *et al,* 2004). Susceptibility testing to first line anti-TB drugs (isoniazid, rifampin, ethambutol and streptomycin) was performed at AIIMS using the MGIT960 as previously described (Singh *et al,* 2007). *M. tuberculosis* isolates resistant to at least isoniazid and rifampin were considered MDR-TB.

Statistical analysis

Data were entered into Microsoft Excel and exported for analysis into Statistical Package for the Social Sciences (SPSS for Windows, Rel 16.0.1 2007; SPSS, Chicago, IL). All analyses were performed without personal identifying informa-

tion from patients. Descriptive analyses were conducted to characterize the study population, compare demographic and risk factor variables, and present TB outcome measures. Chi-square univariable analyses were used to determine potential associations between demographic and risk factor variables with TB outcomes (culture positive and any resistance). Prevalence odds ratios (POR) and 95% confidence intervals were calculated. Binomial logistic regression models were used to examine the independent associations of variables significant ($p<0.05$) in the univariable analysis, and control for known or suspected confounders.

Sensitivity and specificity were calculated using standard epidemiological formulas (Mausener and Bahn, 1974). In these analyses we considered AFB culture the "gold standard." Concordant AFB smear and culture results were considered as true positives/true negatives. Discordant results where the AFB smears were negative but cultures were positive were considered false negative smears; there were no instances in which AFB smears were positive and cultures negative.

RESULTS

Of the 173 participants with signs and symptoms suggestive of pulmonary TB, AFB smear microscopy and culture test results were available for 165 (95.4%); 8 patients did not have sputum specimens processed due to handling errors. A total of 136 (82%) patients submitted 2 or more sputum samples for analysis. Of the 165 study participants, 53 (32.1%) were culture positive for *M. tuberculosis* (Table 1). Fifty-one patients (30.9%) were HIV-seropositive and 22 (13.3%) were TB and HIV co-infected. Risk factors for HIV were high among the clinic patients, including homelessness (37.3%), substance abuse (86.2%) and IDU (71.3%).

Persons with HIV infection (POR 2.0; 95%CI 1.0-4.1) and those who were married (POR 2.2; 95%CI 1.0-4.8) were significantly ($p<0.05$) more likely to have TB (Table 1). A multivariable analysis was conducted to determine which factors independently associated with laboratory confirmed TB. After controlling for age and HIV status, marital status was not associated with TB. However, after controlling for age, the odds of having culture confirmed TB among those with HIV was twice the odds compared to HIV-negative patients (Table 2). No other sociodemographic or substance abuse factors were significantly associated with TB disease (Table 2).

Susceptibility testing to first line anti-TB drugs was performed on all 53 *M. tuberculosis* isolates (Table 3). Overall, 25 (47.2%) of 53 isolates were resistant to one or more anti-tuberculosis agents (isoniazid, rifampin, ethambutol, or streptomycin). Fourteen isolates (26.4%) were mono-resistant to isoniazid, and 13 (24.5%) to rifampin. Seven isolates (13.2%; 95%CI 5.5-25.5%) were MDR, all among patients previously treated for TB. Social-demographic factors and HIV status were not statistically associated with any resistance outcome in univariable analysis (data not shown).

All AFB smear positive specimens grew positive TB cultures. Crude AFB sensitivity was 28.3% and specificity 100%. Of the 15 AFB smear positive patients, 11 were HIV negative and 4 HIV positive (Table 3). Using the TB culture as the gold standard, this study found sensitivity and specificity of AFB smear among HIV positive to be 18.0% and 100%, respectively; among HIV negative patients, the sen-

Table 1
Univariable analysis of social and demographic variables associated with culture-confirmed tuberculosis among patients at high-risk of HIV in Delhi, India.

Characteristic	Total *N*=165 *n* (%)	Culture (+) *N*=53 *n* (%)	Culture (-) *N*=112 *n* (%)	Crude POR (95% CI)	Wald *p*-value
Age (yrs)					
18-39	119(72.1)	35 (66.0)	84 (75.0)	1	
40-65	46 (27.9)	18 (34.0)	28 (25.0)	1.54 (0.76-3.14)	0.23
Mean (SD)	33.3 (9.7)	32.3 (9.1)	35.5 (10.7)		
Median	32	31.5	33		
Sex					
Male	152 (92.1)	48 (90.6)	104 (92.9)	1	
Female	13 (7.9)	5 (9.4)	8 (7.1)	1.35 (0.42-4.36)	0.61
Marital status					
Unmarried	126 (77.8)	36 (67.9)	90 (82.6)	1	
Ever married	36 (22.2)	17 (32.1)	19 (17.4)	2.24 (1.05-4.78)	**0.04**
Occupation					
Service	20 (13.6)	7 (13.2)	13 (11.6)	1	
Manual	95 (64.6)	30 (56.6)	65 (58.0)	0.86 (0.31-2.37)	0.77
None	32 (21.8)	13 (24.5)	19 (17.0)	1.27 (0.40-4.05)	0.69
Unknown	18 (10.9)	3 (5.7)	15 (13.4)	0.37 (0.08-1.74)	0.21
Sleep location					
House	45 (29.4)	16 (30.2)	29 (25.9)	1	1
Footpath	57 (37.3)	19 (35.8)	38 (33.9)	0.91 (0.40-2.06)	0.81
Shelter	51 (33.3)	15 (28.3)	36 (32.1)	0.76 (0.32-1.78)	0.52
Unknown	12 (7.3)	3 (5.7)	9 (8.0)	0.61 (0.14-2.56)	0.49
Any drug use[a]					
No	22 (13.8)	10 (19.2)	12 (11.2)	1	
Yes	137 (86.2)	42 (80.8)	95 (88.8)	0.53 (0.23-1.23)	0.17
IDU[b]					
No	45 (28.7)	18 (35.5)	27 (25.5)	1	
Yes	112 (71.3)	33 (64.7)	79 (74.5)	0.63 (0.30-1.29)	0.2
HIV status					
Negative	114 (69.1)	31 (58.5)	83 (74.1)	1	
Positive	51 (30.9)	22 (41.5)	29 (25.9)	2.03 (1.02-4.05)	**0.04**
Previous TB Tx					
No	23 (14.6)	10 (19.2)	13 (12.4)	1	
Yes	134 (85.4)	42 (80.8)	92 (87.6)	0.59 (0.24-1.46)	0.26

[a]Lifetime drug use; [b]Lifetime history of injection drug use.

sitivity was 35.5% and specificity 100%. Considering only culture-confirmed TB cases, the odds of having an AFB-positive smear among patients without HIV was 2.4 times the odds among HIV-positive patients, although the difference in sensitivities by HIV status was not statistically significant (p=0.18).

Table 2
Social and demographic multivariable factors associated with culture-confirmed tuberculosis among a high-risk Indian population in Delhi.

Characteristic	Adjusted OR (95% CI)
HIV status	
Negative	1
Positive	2.02 (1.01-4.05)
Age (yrs)	
18-39	1
40-65	1.53 (0.75-3.15)

Adjusted OR measured the log odds of culture positive TB for each characteristic while controlling for the other.

DISCUSSION

The current study found a high prevalence of active pulmonary TB disease among a high risk group of urban Indians who attended two urban health clinics in Delhi, India. Nearly a third of patients with symptoms suggestive of pulmonary TB (53 of 165) were culture positive for *M. tuberculosis*. Furthermore, we documented a high prevalence of substance abuse among those seen in the clinic and nearly a third who had symptoms and were screened for TB were HIV co-infected; >40% of those with a positive culture for TB were HIV-infected.

To our knowledge, this is the first study of its kind in Delhi to report drug resistant TB prevalence among a study population where substance abuse and HIV were common. Drug resistant TB was common among those found to have TB disease in our study, almost half of the patients with TB disease were resistant to ≥1 first line anti-TB drugs, and 13.2% had MDR isolates. All MDR participants had a history of prior treatment and therefore are considered secondary drug resistant cases. These data suggest that TB patients with a prior history of treatment should be screened for sensitivities to first line drugs, confirming RNTCP 2012 policy guidelines. The high level of MDR-TB in this study population demonstrates the need to further characterize the prevalence of MDR-TB in subpopulations at high risk for HIV.

Although no representative nationwide surveys have been performed in India, several sentinel surveys across the country reported MDR prevalence between 11.8-49.0% among previously treated cases (Paramasivan *et al*, 2002; Shah *et al*, 2002; Pereira *et al*, 2005; Joseph *et al*, 2007; Sharma *et al*, 2011). Prevalence data on MDR-TB in major urban cities like Delhi are scarce, but a recent study reported a prevalence of 5.0-12.7% (Angrup *et al*, 2011) and previous studies reported 33-47% prevalence among re-treatment cases (Hanif *et al*, 2009). While the present study explored MDR among those at high-risk for HIV and TB, including illicit substance users, this initial enhanced surveillance indicates resistance is likely to be present throughout similar populations in Delhi and India; for example, there are an estimated 1.1 million persons who are

Table 3
First line anti-tuberculosis drug susceptibility patterns and HIV status from 53 culture positive *M. tuberculosis* isolates collected from patients attending two outpatient clinics in Delhi, India.

Drug resistance	Total *N* (%)	HIV diagnosis		
		Positive, *n*	Negative, *n*	*p*-value*
Total number of patient isolates tested	53 (100%)	22 (41.5%)	31 (58.5%)	NA
Smear positive	15 (28.3%)	4 (18.1%)	11 (35.5%)	0.18
Fully susceptible	28 (52.8%)	12 (54.5%)	16 (51.6%)	0.64
Resistance to any drug[a]				
INH	14	6	8	0.56
RMP	13	3	10	0.14
EMB	8	2	6	0.29
SM	11	4	7	0.49
Monoresistance				
INH	4	1	3	0.45
RMP	1	0	1	0.59
EMB	3	1	2	0.63
SM	2	2	0	0.17
Polydrug resistance[b]				
2-drug resistance				
INH+RMP	3	2	1	0.37
INH+EMB	1	1	0	0.41
INH+SM	2	1	1	0.66
RMP+SM	3	1	2	0.63
3-drug resistance				
INH+RMP+EMB	1	0	1	0.59
INH+RMP+SM	1	0	1	0.59
Resistance to all drugs				
INH+RMP+EMB+SM	2	0	2	0.34
Resistance to INH or RMP[c]	20	7	13	0.36
Multidrug resistance (MDR)[d]	7	2	5	0.39

[a]With or without resistance to other drugs; [b]RMP+EMB and INH+EMB+SM patterns not detected (0 cases); [c]Resistance at least to INH or RMP; [d]Resistance at least to INH and RMP.
INH, isoniazid; RMP, rifampin; EMB, ethambutol; SM, streptomycin
*Exact binomial *p*-value, expected counts by distribution of HIV status.

injection drug users in India and 30-35,000 in Delhi alone (Dorabjee and Samson, 2000; Aceijas *et al*, 2006). Monitoring the level of MDR among HIV-seropositive and injection drug users in dense urban areas is important to prevent potential outbreaks and reduce mortality in the general population. Participants in this study likely have interactions with many injection drug users (among whom HIV prevalence is high) and prisoners, representing a potential bridge of transmission for

MDR-TB. Given the preliminary evidence of high prevalence of both MDR-TB and retreatment cases among injection drug users in Delhi, greater priority should be given to DOTS centers that can outreach to drug users and HIV positive persons.

Using culture as the gold standard, the sensitivity of AFB smears in this population was very low (28.3%) and even lower among the HIV positive participants (18.2%), although this difference was not statistically significant. These findings are consistent with previous studies evaluating AFB smears that reported sensitivities ranging of 22-43% (Burdash *et al*, 1976; Lipsky *et al*, 1984; Maloney *et al*, 2006). Other reports have also found that HIV-infected persons are less likely to be smear-positive than HIV uninfected persons (Finch and Beaty, 1997).

The low level of AFB smear positive results among pulmonary patients with laboratory confirmed TB in this study indicates that standard DOTS diagnosis (*ie*, smear microscopy alone) does not adequately detect many patients with pulmonary TB and does not allow the detection of drug resistant TB. More than 71% of TB patients in our study would not have been detected by the standard AFB smear test alone. In our study, 41.5% of HIV-seropositive patients had pulmonary TB, all but four tested AFB smear negative but culture positive. Most TB cases among HIV patients would not have been detected in similar resource-limited areas where smear microscopy is typically the only available diagnostic method. While the prevalence of HIV-infected patients in this setting was high, the possibility of TB cases being undiagnosed by AFB smear is a serious concern for all populations.

With the second largest DOTS program in the world, India's national TB program cannot afford the consequences of MDR-TB epidemics. Expanding MDR surveillance to cover all of India should continue to be the goal, and introducing sentinel surveillance among HIV high-risk groups may lead to more efficient control of TB resistance. Given the need for TB drug sensitivity testing and the low sensitivity of smear microscopy among HIV positive TB patients, performance of cultures on all patients with suspected TB should be the goal for standard diagnosis even in resource poor areas. The development of empirically tested guidelines for surveillance and treatment of MDR-TB in resource poor settings and among those at high risk of HIV infection is greatly needed.

This study is subject to potential random and systematic errors. Because prior TB treatment history was only available by self-report and not validated, misclassification by previous treatment was possible. Study participants represent a convenience sample and selection occurred over a two month period of time; consequently, the study was limited to patients who became ill and sought care during this time period. In addition, the total number of patients screened was not recorded and only those patients referred to the study were known. Quality assurance data were not collected and therefore the criteria used to refer participants could not be systematically reviewed. The prevalence of MDR is subject to random error due (reflected in the reported confidence interval) to relatively few samples, and the extent to which these estimates can be generalized to other populations is unknown.

In summary, TB control in India has achieved major accomplishments in the previous decade. The societal-level eco-

nomic and epidemiologic transitions in India offer new opportunities to continue to improve and expand TB treatment. This study demonstrates that high-risk groups in resource poor areas of Delhi present a major challenge to TB control in the form of MDR. Even in regions where population drug resistance estimates are low, sentinel surveillance of MDR-TB in high-risk populations is useful to prioritize target groups in need of additional prevention, monitoring and health outreach. Future surveillance studies are needed to identify other groups with high prevalence of MDR-TB and strategies to diagnose TB among HIV positive patients who do not have access to gold standard culture tests should be prioritized. Our findings suggest that where culture methods are not available to diagnose TB, a positive AFB smear should not be required for patients to begin anti-TB therapy, especially when risk factors for HIV are present and background prevalence of TB is known to be high.

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