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Rise in rifampicin-monoresistant tuberculosis in Western Cape, South Africa

F. K. Mukinda[*], **D. Theron**[†], **G. D. van der Spuy**[‡], **K. R. Jacobson**[§], **M. Roscher**[†], **E. M. Streicher**[‡], **A. Musekiwa**[¶], **G. J. Coetzee**[#], **T. C. Victor**[‡], **B. J. Marais**[**,††], **J. B. Nachega**[‡‡,§§], **R. M. Warren**[‡], and **H. S. Schaaf**[**,††]

[*]Department of Interdisciplinary Health Sciences, Clinical Epidemiology, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa

[†]Brewelskloof Hospital, Worcester, South Africa

[‡]Centre for Molecular and Cellular Biology, Stellenbosch University and the South African Medical Research Council (MRC), Cape Town, South Africa

[§]Massachusetts General Hospital, Boston, Massachusetts, USA

[¶]Biostatistics Unit, South African MRC, Cape Town, South Africa

[#]National Health Laboratory Services, Cape Town, South Africa

[**]Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, South Africa

[††]Desmond Tutu TB Centre, Faculty of Health Sciences, Stellenbosch University, South Africa

[‡‡]Department of Medicine and Centre for Infectious Diseases, Faculty of Health Sciences, Stellenbosch University, South Africa

[§§]Departments of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

SUMMARY

SETTING—Brewelskloof Hospital, Western Cape, South Africa.

OBJECTIVES—To verify the perceived increase in rifampicin monoresistant tuberculosis (RMR-TB) in the Cape Winelands-Overberg region and to identify potential risk factors.

DESIGN—A retrospective descriptive study of trends in RMR-TB over a 5-year period (2004–2008), followed by a case-control study of RMR and isoniazid (INH) monoresistant TB cases, diagnosed from April 2007 to March 2009, to assess for risk factors.

RESULTS—The total number of RMR-TB cases more than tripled, from 31 in 2004 to 98 in 2008. The calculated doubling time was 1.63 years (95%CI 1.18–2.66). For the assessment of risk factors, 95 RMR-TB cases were objectively verified on genotypic and phenotypic analysis. Of 108 specimens genotypically identified as RMR cases, 13 (12%) were misidentified multidrugr esistant TB. On multivariate analysis, previous use of antiretroviral therapy (OR 6.4, 95%CI 1.3–

Correspondence to: Fidele Kanyimbu Mukinda, Department of Interdisciplinary Health Sciences, Division of Community Health Sciences, Faculty of Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg 7505, South Africa. Tel: (+27) 21 938 9498. Fax: (+27) 21 938 9138. fidelekmukinda@gmail.com; H Simon Schaaf, Desmond Tutu Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Tygerberg 7505, South Africa. hss@sun.ac.za.

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31.8), alcohol use (OR 4.8, 95%CI 2.0–11.3) and age ≥40 years (OR 5.8, 95%CI 2.4–13.6) were significantly associated with RMR-TB.

CONCLUSION—RMR-TB is rapidly increasing in the study setting, particularly among patients with advanced human immunodeficiency virus (HIV) disease. Routine drug susceptibility testing should be considered in all TB-HIV co-infected patients, and absence of INH resistance should be confirmed phenotypically if genotypic RMR-TB is detected.

Keywords

rifampicin; monoresistant; tuberculosis; South Africa

IN SOUTH AFRICA, tuberculosis (TB) remains a major public health challenge, with an estimated TB incidence of 940 cases per 100 000 population in 2008.[1] South Africa adopted the DOTS strategy in 1996, but despite investments in TB control, progress toward reaching programme objectives has been slow. The case detection rate remains less than 60% (World Health Organization [WHO] target 70%; Africa region 50%, range 48–53%), while treatment success increased from 69% in 2004 to 76% in 2008, well below the 85% target.[2]

Rifampicin (RMP) is associated with the lowest occurrence of naturally occurring resistance mutations (2.25×10^{-10} mutations vs. 2.56×10^{-8} for isoniazid [H, INH]).[3]

RMP-monoresistant TB (RMR-TB) has been noted as a problem in the United States, particularly in TB-HIV (human immunodeficiency virus) co-infected individuals.[4–6] Most (>90%) RMP-resistant isolates were also INH resistant, and hence RMP resistance is frequently used as a proxy for multidrug-resistant TB (MDR-TB). In fact, most patients with RMR-TB are treated with MDR-TB regimens, even when the INH susceptibility results are unknown. In recent years, health professionals in the Cape Winelands-Overberg region have perceived an increase in RMR-TB, but remained uncertain if this was a real phenomenon or reflected underdetection of INH resistance by the newly introduced line-probe assays (LPAs). According to a WHO policy statement, LPAs are genotypic resistance tests and do not offer a complete replacement for conventional culture and drug susceptibility testing (DST).[7] As INH resistance is g enotypically far more polymorphic than RMP resistance and these tests detect only a select number of INH-resistant genes, it may incorrectly identify some MDR-TB cases as RMR.[8]

This study aimed to verify whether there has been a true increase in RMR-TB and to identify potential risk factors for the development of RMR-TB.

METHODS

The study had three separate components. Observed trends in RMR-TB diagnosed in the Western Cape Province over a 5-year period (from 2004–2008) were analysed using data from the National Health Laboratory Services (NHLS) database. For the Cape Winelands-Overberg region, data for the same time period were composed from routine NHLS data supplemented by data collected at the Brewelskloof Hospital, the regional MDR-TB referral hospital. To verify the true incidence of RMR-TB and to identify risk factors associated with RMR-TB, we retested a subset of samples by genotypic and phenotypic methods and performed a retrospective review of medical records of all cases with confirmed RMR- or INH-monoresistant TB (HMR-TB) for comparative purposes (case-control study).

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Study population

The retrospective review was conducted at the Brewelskloof Hospital. All RMR- and HMR-TB patients diagnosed between April 2007 and March 2009, aged >15 years and resident in the Cape Winelands-Overberg region were eligible for inclusion.

A confirmed RMR-TB case was defined as culture-positive for *Mycobacterium tuberculosis* with RMP resistance diagnosed both genotypically by LPA (GenoType® MTBDR*plus*, Hain Lifescience, Nehren, Germany) and phenotypically by liquid culture (Mycobacterium Growth Indicator Tube [MGIT] media containing 2 μg/ml RMP, BD, Sparks, MD, USA) in the absence of resistance to INH (confirmed by genotypic and phenotypic testing), ethambutol, streptomycin or pyrazinamide. Spoligotyping was performed using the internationally standardised method,[9] while DNA sequencing of the RMP resistance determining regions was performed as previously described.[10]

An HMR-TB case required a positive *M. tuberculosis* culture with INH resistance confirmed genotypically by LPA or phenotypically by culture and DST, without proven resistance to RMP or any other drug. All cases that failed to meet these criteria were excluded.

Data collection

Demographic and clinical information on all patients who met the entry criteria was retrieved from the medical records at the Brewelskloof Hospital and clinics in the Cape Winelands-Overberg region. This study explored the following variables: age, sex, HIV status, previous TB episode, number of TB episodes, previous TB treatment, duration and regimen, adherence to treatment, fixed-dose combinations (FDCs), cigarette smoking, alcohol intake, prison exposure and close contact with known drug-resistant cases. The definitions used are summarised in Table 1.

Statistical analysis

Stata 10.0 software (Stata Corp, College Station, TX, USA) and Microsoft® Office Excel® 7.0 (Microsoft, Redwoods, WA, USA) were used for statistical analysis. GraphPadPrism5 software (GraphPad Software Inc, La Jolla, CA, USA) was used for estimation of the doubling time.

To estimate risk factors for RMR-TB, we calculated odds ratios (ORs), 95% confidence intervals (CIs), *P* values and standard errors. For multivariate analysis, we calculated adjusted odds ratios (aORs) using logistic regression. For inclusion in the multivariate analyses, non-collinear variables were chosen with an observed $P < 0.05$ in univariate analysis. Tests for multicollinearity as well as interactions between variables were performed before inclusion of the variables in the final model; strongly correlated variables were excluded. For the final multivariate model, variables were chosen using a manual forward stepwise method. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test.

Ethics approval to perform the study was obtained from the Stellenbosch University (Ref No: N09/11/ 306), the Western Cape Department of Health (Ref No 19/18/RP 112/2009) and from the local health authorities at Brewelskloof Hospital.

RESULTS

Figure 1 reflects the numbers of RMR-TB cases diagnosed in the entire Western Cape Province and the Cape Winelands-Overberg region over the specified 5-year period, either by culture and phenotypic DST or by LPA. This figure demonstrates that RMR increased

markedly in both the province and the region during the study period, and although this occurred simultaneously with an almost total switch from phenotypic DST to LPA DST, the increase cannot be ascribed solely to the use of LPA DST. Table 2 provides a more detailed breakdown of drug-resistant cases diagnosed in the Cape Winelands-Overberg region, using routine NHLS data. The estimated doubling time of RMR-TB was 2.08 (95%CI 1.67–2.7, R^2 0.99) years for the Western Cape Province and 1.63 (95%CI 1.18–2.66, R^2 0.97) years for the Cape Winelands-Overberg region, using non-linear regression and an exponential growth model (R^2 indicates how well the data fit the regression model).

During the 2-year study period, risk factors for 184 RMR-TB cases were identified. Of these, 85 (46.2%) were recorded in both NHLS and Brewelskloof Hospital databases, 43 (23.4%) only at Brewelskloof and 56 (30.4%) only by the NHLS. Among the 184 RMR-TB cases identified, 76 (41.3%) could not be verified by retesting, as cultures were unavailable. Phenotypic DST identified INH resistance in 13 of 108 (12%) RMR-TB cases routinely diagnosed using LPA alone, reclassifying these as misidentified MDR-TB cases. In total, 95/108 (88%) RMR-TB cases for which cultures were available could be confirmed and sufficient data could be retrieved from 91 medical records. These 91 cases were included in the final comparative analysis (Figure 2). Spoligotyping and *rpo*B DNA sequence data were available for isolates from 30/91 patients. In combination, 21 different genotypes were identified.

The demographics and baseline characteristics of RMR-TB cases and HMR-TB cases are summarized in Table 3. On univariate analysis RMR-TB, compared to HMR-TB, was significantly associated with the following variables: age ≥40 years compared to <40 (OR 5.3, 95%CI 2.7–10.3), receiving a second (or third) retreatment regimen (OR 3.9, 95%CI 1.54–9.89), retreatment after default (OR 8.2, 95%CI 1.94–35.0) and retreatment after failure (OR 2.5, 95%CI 1.06–5.83), HIV infection (OR 1.83, 95%CI 1.01–3.31), antiretroviral therapy (ART) before RMR-TB diagnosis (OR 3.98, 95%CI 1.89–8.36), excessive alcohol use (OR 2.8, 95%CI 1.52–5.19) and recent diagnosis (OR 3.04, 95%CI 1.69–5.48; Table 4). We were not able to accurately document close exposure to drug-resistant source cases due to lack of information from medical records.

A multivariate analysis of the main risk factors for RMR-TB is reflected in Table 5. Being aged ≥40 years, ART before TB diagnosis, excessive alcohol use, being sputum smear-negative and being diagnosed in 2008 were identified as significant risk factors for RMR-TB compared to HMR-TB. The Hosmer-Lemeshow goodness-of-fit test ($\chi^2 = 57.36$, $P = 0.085$) confirmed good fit of the model.

DISCUSSION

We document an alarming increase in RMR-TB cases in the study setting over the past years. Despite being unable to verify all cases, it is clear that misclassification of MDR-TB cases due to limitations of the LPA test fails to fully explain the observed increase. Only 12% of independently verified RMR-TB cases were misclassified, while RMR-TB cases increased by more than three-fold during the study period. The estimated doubling time of 1.6 years in the Cape Winelands-Overberg region and 2.1 years for the whole Western Cape Province suggests that RMR-TB is a rapidly emerging phenomenon. Confirmed transmission of RMR-TB was documented in 12/91 (13.5%) confirmed cases, in agreement with a previous study from the United States in which transmission by close contact with an RMR-TB case was suggested in 13%.[5] This is supported by genotypic analysis of *M. tuberculosis* isolates from a subset of this study, which confirmed a high degree of genetic diversity, suggesting that RMR is primarily acquired.

The strongest association identified comparing RMR-TB to HMR-TB included advanced HIV disease, as reflected by ART prior to TB diagnosis and lower CD4 counts among RMR-TB cases. This may reflect increased vulnerability among immune-compromised HIV-infected patients to develop TB following infection with an RMR strain and reduced adherence due to concomitant TB and HIV treatment. It may also reflect an increased risk of transmission in health care facilities frequented by these patients. On the other hand, implementation of HIV treatment in United States resulted in the reduction of MDR-TB cases, and RMR-TB disappeared.[13]

The association between HIV infection status and RMR-TB has been documented in previous studies,[6,14–17] but the risk of transmission within HIV care facilities has not been investigated. However, the clonal spread of extensively drug-resistant TB (XDR-TB) documented during the Tugela Ferry outbreak in KwaZulu-Natal, South Africa,[18] emphasises the crucial importance of adequate infection control in all TB facilities, especially in those providing care to HIV-infected patients.

A 2006 survey in Bujumbura, Burundi, found MDR-TB and RMR-TB among new TB-HIV co-infected cases, but it could not establish whether this resulted from infection with a drug-resistant strain or acquisition of drug resistance.[19] Early identification and effective treatment of drug-resistant TB cases is essential to limit ongoing transmission of drug-resistant strains. Apart from its important public health benefits, early effective treatment will also improve individual patient outcomes. We suggest that routine DST (or LPA) testing should be recommended in all HIV-infected patients diagnosed with TB and in all retreatment patients. While a history of recent (during the past 2 years) close contact with a drug-resistant case or with someone who died from TB is rarely considered in adults, it clearly identifies a potential risk group in whom routine DST (or LPA) should be considered. The WHO recommends the use of LPA because of its high specificity (≥99%) and sensitivity (≥97%),[7] although this can range from 70% to 90% depending on the prevalence of particular mutations,[20] and the proficiency of laboratory staff. However, discordant findings have been reported between LPA and phenotypic DST, with LPA underdetecting INH resistance by 9.6%,[21] while phenotypic DST methods may underdetect the presence of low-level RMP-resistant strains, even with proficient laboratories.[22]

There is a significant association between RMR-TB and treatment failure or default after previous treatment, as previously reported,[23] especially in chronic cases (i.e., those with more than one retreatment episode). Failure of WHO Category I and II regimens may reflect inadequate drug regimens (i.e., inadequate drugs, doses or duration of treatment);[24] however, during the current study period only quality-assured FDC tablets were used and given in doses that were in accordance with current WHO recommendations.[25] It is possible that a large percentage of previously treated cases represent primary (or transmitted) RMR-TB that was not diagnosed during the initial episode. Following infection with an RMR strain it is expected that treatment failure rates would be increased following standard first- and second-line treatment due to reduced bactericidal activity and inadequate sterilisation. The current increase in RMR-TB cases may thus reflect ongoing transmission of these strains at the community level, as a legacy of the poor quality drugs used previously.[26]

The question of potential drug-drug interactions between ART (particularly efavirenz) and RMP should be considered, given that all co-treated RMR-TB patients received an efavirenz-containing regimen, suggesting the benefit of drug monitoring of TB-HIV co-infected patients on combination therapy.[27] Malabsorption of RMP and INH in HIV-infected patients with or without diarrhoea has been reported,[28,29] and may be a contributing factor to consider, although the pharmacokinetics of RMP may be variable even without HIV.[30] Our study suggests that excessive alcohol use is another important risk factor for

RMR-TB, and it is well documented that alcohol abusers are less likely to complete their full course of treatment.[31] Alcohol abuse is a particular problem in the study setting. Other important risk factors identified in previous studies include homelessness and prior incarceration, which were not recorded in our study.[6,32]

The study is limited by its retrospective design and incomplete patient records, but it still provides important 'real-life' data that allow a better understanding of what is happening in routine TB care. It is evident that routine collection of TB patient information should be improved to ensure that all essential clinical data are systematically recorded. This should include information on treatment duration and regimens used during previous TB episodes and close contact with possible drug-resistant TB cases. Medical records of all RMR-TB cases referred from clinics were found at Brewelskloof Hospital, but for HMR-TB cases medical records were reviewed from clinics, which may have introduced information bias: however, the quality of the data appeared similar, as a standardised data collection form was used. Regardless of these limitations, we are confident that the study findings are not a consequence of systematic bias and that our conclusions are valid for the study setting.

In conclusion, we describe rapidly increasing rates of RMR-TB in the Western Cape Province of South Africa. This seems to be strongly correlated with more advanced HIV disease, previous TB treatment and excessive alcohol use. DOTS should be reinforced to increase treatment adherence, while DST should be provided for all, with special emphasis on TB-HIV co-infected patients, retreatment cases, cases with a history of drug-resistant TB exposure, and in those cases where LPA indicates MDR-TB or monoresistance to RMP or INH. Further study is needed to assess the treatment outcome of RMR-TB cases, with and without HIV infection. Critical re-assessment of measures to improve airborne infection control is essential, particularly in facilities providing HIV care.

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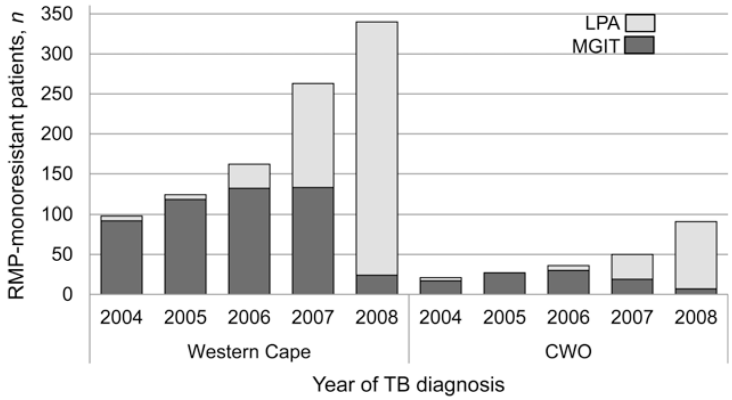

Figure 1.
RMP-monoresistant cases recorded at the routine diagnostic laboratory over a 5-year period. RMP = rifampicin; LPA = line-probe assay (genotypic test); MGIT = Mycobacteria Growth Indicator Tube (phenotypic test); CWO = Cape Winelands-Overberg region; TB = tuberculosis.

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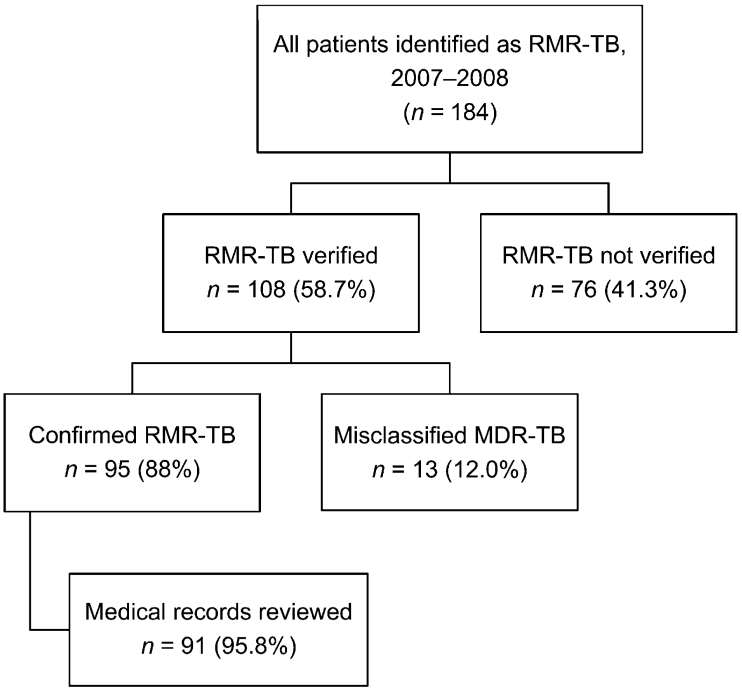

Figure 2.
Flow diagram of all RMR-TB cases included in the analysis. RMR-TB = rifampicin-monoresistant tuberculosis; MDR = multidrug-resistant.

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Table 1

Summary of definitions used

TB episode: a patient with symptomatic disease due to *Mycobacterium tuberculosis* (bacteriologically confirmed)
New case: a patient who has never had treatment for TB or who has taken TB treatment for <4 weeks
Retreatment case: a patient who received previous TB treatment for ≥4 weeks and either relapsed, defaulted or had treatment failure • Relapse: a patient who received previous treatment and was declared cured or treatment completed at the end of treatment who again presents with TB • Default: a patient who completed at least 1 month of treatment and returns after having interrupted treatment for ≥2 months, and is still smear- or culture-positive or has signs of active TB on clinical or radiological assessment • Failure: a patient who is still sputum smear- or culture-positive at the end of the treatment period and is started on a retreatment regimen
Good adherence to treatment is defined as taking all the medication, as prescribed, for the entire length of time (completing >80% of doses) *
Excessive alcohol use: consumption of >2 drinks per day for men, or >1 drink per day for women; a standard drink being equal to 14 g (0.6 ounces) of pure alcohol that may be found in 12 ounces of beer, 8 ounces of malt liquor or 5 ounces of wine[12]

* Adapted from South African national tuberculosis guidelines, 2008.[11]

Table 2

RMP- and INH-monoresistant, MDR-TB and drug-susceptible TB cases diagnosed in the Cape Winelands-Overberg Region, South Africa

Year	INH *n* (%)	RMP *n* (%)	MDR-TB *n* (%)	Susceptible *n* (%)	Not classified *n* (%)*	All cases *n*
2004	239 (6.6)	31 (0.9)	355 (9.8)	3001 (82.4)	15 (0.4)	3641
2005	204 (5.8)	25 (0.7)	348 (9.9)	2915 (83.3)	6 (0.2)	3498
2006	257 (5.8)	48 (1.1)	459 (10.4)	3631 (82.2)	20 (0.5)	4415
2007	296 (5.7)	86 (1.7)†	600 (11.6)	4130 (79.5)	81 (1.6)	5193
2008	105 (2.4)‡	98 (2.3)§	192 (4.4)‡	3461 (80.0)	471 (10.9)	4327

*Not tested for INH and/or RMP.

†36 and

§7 of these were diagnosed by the NHLS but were not recorded in the NHLS database.

‡The drop in INH and MDR-TB cases in 2008 is proportionately greater than the drop in cases tested, reflecting the introduction of genetic resistance testing (line-probe assay), which misses a significant proportion of INH resistance.

RMP = rifampicin; INH = isoniazid; MDR-TB = multidrug-resistant TB; TB = tuberculosis; NHLS = National Health Laboratory Services.

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Table 3

Demographics and baseline characteristics of rifampicin- and isoniazid-monoresistant cases

	RMP-monoresistant (*n* = 91) *n* (%)	INH-monoresistant (*n* = 114) *n* (%)
Age, years		
<40	15 (16.9)	59 (51.8)
≥40	74 (83.1)	55 (48.2)
Not recorded	2 (0)	0
Sex		
Male	47 (51.7)	73 (64.0)
Patient category		
New	12 (13.5)	27 (24.3)
Retreatment		
After default	31 (34.8)	28 (25.2)
After failure	11 (12.4)	3 (2.7)
After relapse	35 (39.3)	53 (47.8)
Unknown	2 (0)	4 (0)
Number of previous TB episodes		
0 (new)	12 (13.6)	27 (27.8)
1	45 (51.1)	51 (52.6)
2	26 (29.6)	15 (15.5)
≥3	5 (5.7)	4 (4.1)
Unknown	3 (0)	17 (0)
Treatment adherence	(*n* = 78)	(*n* = 83)
Yes	42 (56.0)	51 (64.6)
No	33 (44.0)	28 (35.4)
Unknown	3 (0)	4 (0)
Sputum smear status		
Positive	42 (48.8)	74 (64.9)
Negative	44 (51.2)	40 (35.1)
Not reported	5 (0)	0
TB classification		
Pulmonary	85 (93.4)	114 (100)
Extra-pulmonary	6 (6.6)	0
HIV co-infection		
Positive	36 (40.9)	30 (28.0)
Negative	52 (59.1)	77 (72.0)
Not reported	3 (0)	7 (0)
On ART		
ART before TB diagnosis	17 (60.7)	2 (20)
ART after TB diagnosis	11 (39.3)	8 (80)
Unknown	1 (0)	2 (0)
Alcohol		
Yes	39 (65.0)	24 (51.1)
No	21 (35.0)	23 (48.9)
Unknown	31 (0)	67 (0)
Smoking		
Yes	33 (61.1)	36 (81.8)
No	21 (38.9)	8 (18.2)
Unknown	37 (0)	70 (0)
Study year		
2007	25 (27.5)	61 (53.5)
2008	66 (72.5)	53 (46.5)

TB = tuberculosis; HIV = human immuno deficiency virus; ART = antiretroviral treatment.

Table 4

Univariate logistic regression of risk factors for rifampicin- compared to isoniazid-monoresistant TB

Risk factor	Crude OR	95%CI	*P* value	Standard error
Age, years				
<40	1			
≥40	5.3	2.7–10.3	0.001	1.8
Sex				
Male	0.60	0.34–1.05	0.075	0.17
Female	1			
Weight *	0.995	0.97–1.02	0.711	0.02
Patient category				
New	1			
Retreatment				
After default	8.2	1.94–35.0	0.004	6.25
After failure	2.5	1.06–5.83	0.035	1.08
After relapse	1.5	0.67–3.32	0.334	0.61
Previous TB episode				
Yes	2.24	1.09–4.59	0.028	0.8
No	1			
Number of episodes				
0 (new TB)	1			
1	1.99	0.90–4.37	0.089	0.8
2	3.9	1.54–9.89	0.004	1.85
≥3	3	0.64–12.36	0.171	2.12
Treatment adherence				
Yes	1.06	0.61–1.84	0.840	0.299
No	1			
Sputum smear status				
Positive	0.46	0.26–0.81	0.007	0.13
Negative	1			
HIV co-infection				
Positive	1.83			
Negative	1	1.01–3.31	0.045	0.55
On ART				
Yes	3.98	1.89–8.36	<0.001	1.51
No	1			
ART				
Before TB diagnosis	12.86	2.89–57.33	0.001	9.8
After TB diagnosis	1			
Smoking				
Yes	1.23	0.69–2.21	0.481	0.37
No	1			
Excessive alcohol use				
Yes	2.8	1.52–5.20	0.001	0.88
No	1			
Study year				
2007	1			
2008	3.04	1.69–5.48	0.001	0.9

* Compared as continuous variable.

TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; ART = anti retroviral treatment.

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Table 5

Multivariate logistic regression of risk factors for rifampicin- compared to isoniazid-monoresistant TB

Risk factor	Adjusted OR	95%CI	*P* value	Standard error
Older age				
≥40 years	5.8	2.44–13.57	<0.001	2.5
ART before RMR/				
HMR-TB	6.4	1.3–31.8	0.023	5.2
Excessive alcohol use	4.8	2.01–11.31	<0.001	2.1
Sputum smear-negative	3.0	1.4–5.0	0.006	0.1
More recent diagnosis				
Study year 2008	4.01	1.81–8.90	0.001	1.6

TB = tuberculosis; OR = odds ratio; CI = confidence interval; ART = antiretroviral treatment; RMR-TB = rifampicin-monoresistant TB; HMR-TB = isoniazid-monoresistant TB.