

Rifampicin-resistant *Mycobacterium tuberculosis* among tuberculosis-presumptive cases at University of Gondar Hospital, northwest Ethiopia

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Background: Various studies have reported that the emergence of drug-resistant tuberculosis poses a significant threat to tuberculosis-control programs worldwide. Rifampicin resistance is a surrogate marker of multidrug-resistant tuberculosis, since it reveals the presence of greater than 90% isoniazid resistance. Evidence on rifampicin-resistant *Mycobacterium tuberculosis* is scarce in the literature.

Objective: To determine the prevalence of rifampicin-resistant *M. tuberculosis* among tuberculosis-presumptive cases at the University of Gondar Hospital.

Materials and methods: A retrospective study was conducted at the University of Gondar Hospital from January 2013 to August 2015. Data were collected from registration books using a data-extraction format after securing ethical approval and checking the completeness of necessary information. Data were double-entered and rechecked to ensure accuracy and analyzed using SPSS version 20. Results were summarized using descriptive statistics. Associations were assessed using Fisher's exact test, and $P < 0.05$ was considered statistically significant.

Results: A total of 1,820 *M. tuberculosis*-presumptive patients were included in the study. The majority of the study participants were males (59.2%). The mean age of the participants was 36.6 ± 15.8 years. The preponderant age-group was 24–30 years, with 477 (23.5%) patients. The overall prevalence of *M. tuberculosis*-confirmed cases was 448 (24.6%, 95% CI 0.23–0.27). Of the 448 *M. tuberculosis*-confirmed cases, 71 (15.8%, 95% CI 1.12–1.19) were resistant to rifampicin. Rifampicin-resistant *M. tuberculosis* was observed among HIV seropositives (14 [18.7%]), males (45 [17.3%]), and previously treated tuberculosis patients (61 [16.5%]), although no significant association was found in this study.

Conclusion: The overall prevalence of *M. tuberculosis* and rifampicin resistance was found to be high in tuberculosis patients in this study. Therefore, early detection of drug-resistant *M. tuberculosis* should be strengthened for management of tuberculosis patients.

Keywords: University of Gondar Hospital, rifampicin-resistant, tuberculosis

Introduction

Tuberculosis (TB) is a chronic airborne infectious disease caused by the bacillus *Mycobacterium tuberculosis* (MTB). According to a World Health Organization (WHO) 2016 report, MTB remains a major public health problem, ranking above HIV/AIDS. It is one of the leading causes of morbidity and mortality among infectious diseases worldwide.¹ The best estimate of TB deaths in 2015 was 4 million, with an additional 0.4 million deaths resulting from TB disease among HIV-positive people. In terms of cases, there were 10.4 million new TB cases, of which 5.9 million were men, 3.5 million women, and 1 million children detected. Cases that remain undetected continue

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to suffer from TB disease and also transmit the disease to their contacts.^{1,2}

The prevention, diagnosis, and treatment of TB has become more complicated because of HIV-associated TB and multidrug resistant (MDR) TB. Many people die of TB owing to delayed diagnosis, which makes people, mainly in the sub-Saharan region, unable to reduce transmission significantly, and thus the epidemic continues.³ A global TB report estimated that there were about 230,000 (247 per 100,000 population) incident cases of TB in Ethiopia. In the same report, there were about 16,000 deaths (18 per 100,000) due to TB, excluding HIV-related deaths during the same period.⁴ Ethiopia ranks seventh among the world's 22 high-TB-burden countries, 10th among high-TB-pandemic countries, and fourth in sub-Saharan Africa.⁵

Worldwide emergence of MDR-MTB has been reported in both developed and developing countries.⁶ The incidence of MDR-TB is increasing, with almost half million estimated new cases in 2008.⁷ Ethiopia is one of the 27 high MDR-TB countries, ranked 15th with more than 5,000 estimated MDR-TB patients each year.⁸

Globally, the estimated prevalence of MDR-TB was 3.3% in newly diagnosed patients in the WHO 2015 report. This was higher (20%) in patients with a history of anti-TB treatment.⁵ MDR-TB is largely a consequence of poor supply management and quality of anti-TB drugs and inadequate or improper treatment, which is further worsened by HIV. Recent studies have indicated that on average, new HIV-positive TB patients are at increased risk of MDR-TB compared with HIV-negative patients.^{9,10} Poor infection-control practice has also been identified as a major contributing factor in the spread of drug-resistant TB.^{2,3} Based on the 2005 nationwide survey in Ethiopia, the prevalence of MDR-TB was 1.6% among new cases and 11.8% in the retreatment cases and rifampicin resistant was lower than 2% in new cases.¹¹

A history of previous TB treatment is the strongest risk factor for progress of MDR-TB. The risk of transmission of resistant strains from close contacts is rising, because of the growing burden of MDR-TB patients^{12,13} and extensively DR *Mycobacterium* spp.¹⁴

Smear microscopy is widely used for the rapid diagnosis of TB, but it does not detect DR-MTB or sensitivity. In individuals who are coinfecting with HIV, the detection rate varies between 20% and 50%.¹⁵ Results of mycobacterial culture turnaround require about 2–8 weeks, though this is not widely available in developing countries, including Ethiopia.^{15,16} This creates a diagnostic delay that hinders disease control, enhances transmission, and increases health-care costs.¹⁷

In Ethiopia, TB-case detection is mainly comprised of passive case finding, which is able to detect up to two-thirds of the annually estimated TB cases. TB screening among close and household contacts is one of the new approaches recommended by the national TB program to improve TB-case detection. This is usually carried out by sputum-smear microscopy and by GeneXpert MTB/RIF if the index-TB case is suspected to be a patient with DR-TB or who is at risk of harboring DR-TB.¹⁸ The national GeneXpert MTB/RIF implementation guideline recommends its use among presumptive MDR-TB cases that include symptomatic contacts of MDR-TB cases and presumptive TB cases among HIV-positive individuals and children below 14 years of age.¹⁹

GeneXpert is an automated real-time polymerase chain-reaction assay designed for the rapid and simultaneous detection of MTB and rifampicin resistance.^{20–22} Most rifampin-resistant MTB-complex strains have mutations in an 81-base-pair region of the *RPOB* gene that encodes the RNA polymerase β -subunit. This region is an ideal target for molecular tests for rifampin resistance.²³ The assay amplifies a MTB-complex-specific region of the *RPOB* gene, which is probed with molecular beacons to detect the presence of rifampicin resistance-determining mutations.²⁴

Continuous surveillance of the primary and acquired DR patterns of MTB is vital in assessing the efficacy of treatment regimens, as well as in detecting problems related to previous TB treatments. In Ethiopia, sputum-smear microscopy for acid-fast bacilli has been the backbone of TB-case detection in the past few decades. However, in developing countries, TB-culture and DR testing are not routinely carried out as part of the laboratory workup, owing to extreme economic disparities, low literacy, and impaired basic health-service delivery. Determining the prevalence of rifampicin-resistant MTB with advanced technology is critical to prevent drug resistance, like MDR-TB and extensively DR-TB. As far as the literature is concerned, little work has been done to document information systematically on the prevalence of rifampicin-resistant MTB using Xpert MTB/RIF in Ethiopia, particularly in Gondar. Therefore, this study aimed to determine the prevalence of rifampicin-resistant MTB among TB-presumptive cases at the University of Gondar Hospital, northwest Ethiopia.

Materials and methods

Study design, area, and period

A retrospective cross-sectional study was conducted from January 2013 to August 2015 at the University of Gondar Hospital TB DOTS (directly observed treatment,

short course) Clinic laboratory. the University of Gondar Hospital is found in Gondar town. The town is located in Amhara National Regional State 727 km from Addis Ababa, the capital. It offers a referral service for nearly 5 million inhabitants in northwest Ethiopia. The study population were all TB-presumptive (patients with clinical signs and symptoms suggestive of TB) patients who visited the hospital during the study period. Patients presumptive for pulmonary TB and who had full documentation in the registration book were included, whereas patients who had incomplete data, eg, age, sex, GeneXpert results, were excluded from the study.

Laboratory investigation

The TB DOTS Clinic operates under the national TB- and leprosy-control program of Ethiopia, in which the diagnosis of TB is followed by Xpert MTB/RIF assay for rifampicin resistance. Samples were processed by GeneXpert MTB/RIF assay. These were diluted and decontaminated, and the GeneXpert MTB/RIF assay was performed according to the manufacturer's manual. The Xpert MTB/RIF purifies and concentrates MTB bacilli from the samples. Genomic material is isolated from the captured bacteria by sonication and the genomic DNA subsequently amplified by polymerase chain reaction. Furthermore, the process identifies all the clinically relevant rifampicin resistance, inducing mutations in the *RPOB* gene in the MTB genome in a real-time format using fluorescent probes called molecular beacons. Internal quality controls (sample processing control and probe check control) were used during the assay.

HIV testing was done according to the national algorithm recommended by the Federal Ministry of Health of Ethiopia. Rapid HIV tests – HIV (1 + 2) rapid test strip and Stat-Pak – were run sequentially. Positive samples were confirmed with Stat-Pak. Discordant results were resolved using a third confirmatory testing kit: HIV1/2 Uni-Gold recombinant assay. Laboratory procedures were performed according to standard operating procedures.

Data collection and analysis

Data were collected retrospectively from registration books at the University of Gondar Hospital TB DOTS Clinic using a data-extraction format after checking the completeness of the data. Seven records of study participants with incomplete data and demographic characteristics were excluded from 1,827 study participants, resulting in 1,820. Data were analyzed using SPSS version 20. Results were summarized using descriptive statistics. Association between dependent

and independent variables were assessed using Fisher's exact test, and $P < 0.05$ was considered statistically significant.

Ethical clearance

Data was collected after ethical clearance had been obtained from the School of Biomedical and Laboratory Sciences, College of Medicine and Health Science, University of Gondar. After discussion of the purpose and aim of the study, permission was also obtained from the head of the University of Gondar Hospital TB clinic prior to data collection. To ensure confidentiality of participants' information, anonymous typing was used, whereby the name, identification number, and any other personal identifiers were not extracted during data collection. Also, the data was kept in a confidential manner. As secondary data were used, informed consent was not sought from the study participants.

Results

Sociodemographic and clinical characteristics

This retrospective cross-sectional study was conducted with a total of 1,820 presumptive TB cases. Among these, 742 (40.8%) were females and 1,078 (59.2%) males. The majority of the patients, 427 (23.5%), were in the age-group 24–30 years. Among total study participants, 315 (17.3%) were HIV-seropositive, 622 (34.1%) were HIV-seronegative, and the remaining 884 (48.6%) had unknown HIV status (Table 1).

Mycobacterium tuberculosis by sex and age

The overall prevalence of TB was 448 (24.6%, 95% CI 23%–27%). Based on the Xpert MTB/RIF assay, the highest positive finding (29.8%) of TB was observed in the age-group 24–30 years. The proportion of MTB was 24.1% in males and 25.3% in females. Rifampicin-resistant MTB was noted in 71 (3.9%). Based on Fisher's exact test, positive test results were strongly associated with age ($P = 0.001$) (Table 2).

Mycobacterium tuberculosis based on HIV status and TB-treatment history

Of the study participants, 315 (17.3%) were HIV-positive. HIV-TB coinfection was observed in 75 (23.8%), and 371 (24.5%) TB cases had a history of TB treatment. However, based on Fisher's exact test, both history of treatment and HIV status of the study subjects had no statistical association with the positive findings ($P > 0.05$) (Table 2).

Table 1 Sociodemographic and clinical characteristics of the study participants

Variables		n (total 1,820)	Percentage
Sex	Male	1,078	59.2
	Female	742	40.8
Age-group, years	<10	56	3.1
	10–16	61	3.4
	17–23	252	13.8
	24–30	427	23.5
	31–37	246	13.5
	38–44	238	13.1
	45–51	223	12.3
	52–58	118	6.5
>58	199	10.9	
History of treatment	Previously treated	1,515	83.2
	New cases	305	16.8
HIV status	Negative	621	34.1
	Positive	315	17.3
	Unknown	884	48.6
Year of diagnosis	2013	225	12.4
	2014	858	47.1
	2015	737	40.5

Table 2 *Mycobacterium tuberculosis* (MTB) among the study participants based on sex, age, history of TB treatment, and HIV status

Variables	MTB-positive cases, n (%)	MTB-negative cases, n (%)	Total	P-value
Sex				0.55
Male	260 (24.1)	818 (75.9)	1078	
Female	188 (25.3)	554 (74.7)	742	
Total	448 (24.6)	1372 (75.4)	1820	
Age-group, years				0.001
<10	5 (10.2)	44 (89.8)	49	
10–16	14 (20.6)	54 (79.4)	68	
17–23	65 (25.8)	187 (74.2)	252	
24–30	127 (29.8)	300 (70.2)	427	
31–37	77 (31.3)	169 (68.7)	246	
38–44	47 (19.8)	191 (80.2)	238	
45–51	51 (22.9)	172 (77.1)	223	
52–58	19 (16.1)	99 (83.9)	118	
>58	43 (21.6)	156 (78.4)	199	
Total	448 (24.6)	1,372 (75.4)	1,820	
TB-treatment history				0.78
Previously treated cases	371 (24.5)	1,144 (75.5)	1,515	
New cases	77 (25.2)	228 (74.8)	305	
Total	448 (24.6)	1,372 (75.4)	1,820	
HIV status				0.26
Positive	75 (23.8)	240 (76.2)	315	
Negative	167 (26.9)	454 (73.1)	621	
Unknown	206 (23.3)	678 (76.7)	884	
Total	448 (24.6)	1,372 (75.4)	1,820	

Rifampicin resistant *Mycobacterium tuberculosis* among TB-confirmed study participants

Of the 448 (24.6%) TB-confirmed cases, 71 (15.8%, 95% CI 1.12–1.19) were resistant to rifampicin. The proportion of MTB was higher 45 (17.3%) in males, and the predominant age-groups with rifampicin-resistant TB were 17–23 and 52–58 years, 16 (24.6%) and five (26.3%), respectively; 75 (23.8%) of the TB-confirmed subjects were HIV-positive. Rifampicin-resistant TB cases among HIV-positive subjects numbered 14 (18.7%). Rifampicin-resistant MTB subjects numbered 61 (16.4%) among previously treated TB patients (Table 3).

Mycobacterium tuberculosis according to year of diagnosis

A total of 1,820 study participants were included for Xpert MTB/RIF during 2013–2015. Of the participants enrolled,

Table 3 Rif-resistant MTB among confirmed TB patients based on sex, age, treatment history, and HIV status

Variables	MTB+/Rif-, n (%)	MTB+/Rif+, n (%)	Total TB positives, n (%)	P-value
Sex				0.32
Male	215 (82.7)	45 (17.3)	260 (58)	
Female	162 (86.2)	26 (13.8)	188 (42)	
Total	377 (84.2)	71 (15.8)	448 (100)	
Age-group, years				0.06
<10	5 (100)	0	5 (1.1)	
10–16	13 (92.9)	1 (7.1)	14 (3.1)	
17–23	49 (75.4)	16 (24.6)	65 (14.5)	
24–30	103 (81.1)	24 (19.9)	127 (28.3)	
31–37	67 (87)	10 (13)	77 (17.2)	
38–44	45 (95.7)	2 (4.3)	47 (10.5)	
45–51	46 (90.2)	5 (9.8)	51 (11.4)	
52–58	14 (73.7)	5 (26.3)	19 (4.2)	
>58	35 (81.4)	8 (18.6)	43 (10)	
Total	377 (84.2)	71 (15.8)	448 (100)	
TB-treatment history				0.54
Previously treated cases	310 (83.6)	61 (16.4)	371 (82.8)	
New cases	67 (87)	10 (13)	77 (17.2)	
Total	377 (84.2)	71 (15.8)	448 (100)	
HIV status				0.33
Positive	61 (81.3)	14 (18.7)	75 (16.7)	
Negative	146 (87.4)	21 (12.6)	167 (37.3)	
Unknown	170 (82.5)	36 (17.5)	206 (46)	
Total	377 (84.2)	71 (15.8)	448 (100)	

Notes: MTB+/RIF-, MTB-positive, but not Rif-resistant. MTB+/RIF+: MTB-positive and Rif-resistant.

Abbreviations: MTB, *Mycobacterium tuberculosis*; Rif, rifampicin.

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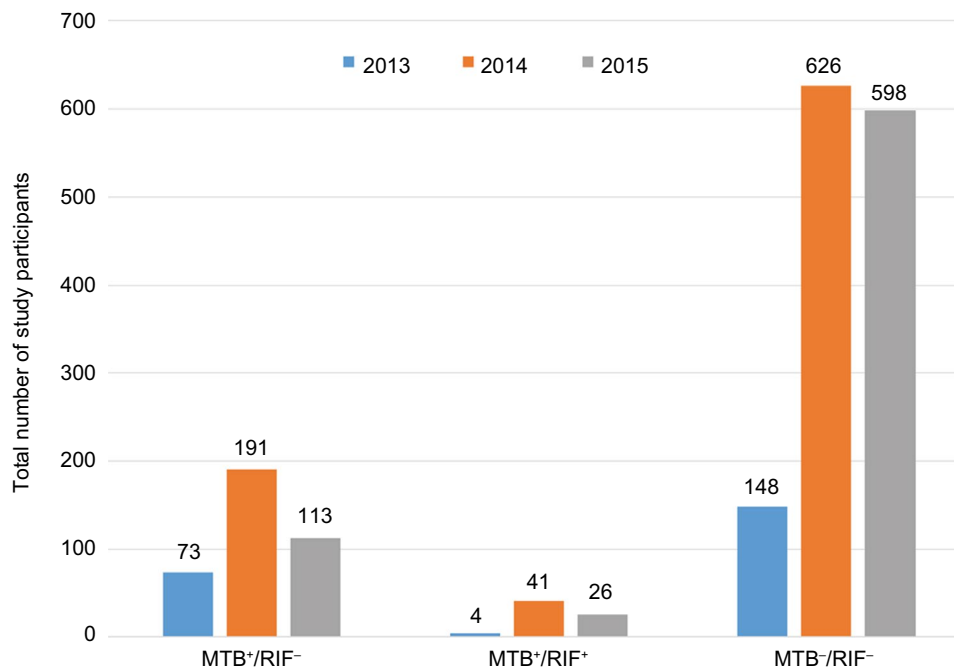


Figure 1 Rif-resistance MTB based on year of diagnosis.

Notes: MTB⁺/RIF⁻, MTB-positive, but not Rif-resistant. MTB⁺/RIF⁺: MTB-positive and Rif-resistant.

Abbreviations: MTB, *Mycobacterium tuberculosis*; Rif, rifampicin.

448 (24.6%) were positive for TB on GeneXpert, of which 71 (3.9%) were rifampicin-resistant. The trend in prevalence of TB was relatively higher in 2014 (Figure 1).

Discussion

The impact and management of rifampicin-resistant TB have not been deeply studied compared to MDR-TB, which is well known to be associated with poor TB-treatment outcome. This study reveals an overall prevalence of TB among presumptive cases of 448 (24.6%). This finding is higher than the previous studies conducted in southern Ethiopia (16.5%, 19.4%).^{25–27} However, our finding is lower than a study conducted in East Gojjam, Ethiopia of 124 (32.2%).²⁸ A probable reason for this variation might have been that we included presumptive cases to identify MTB, while other studies included identified cases of TB to check GeneXpert differences in study population. The method of diagnosis and study setting may account for the variation in prevalence across studies.

According to our study, the disease predominated slightly among females: 188 (25.3%). This is comparable with a study conducted in southern Ethiopia,²⁵ contrary reports from the WHO,^{1,4,5} and a population-based prevalence survey of TB in the Tigray region of Ethiopia, which confirmed TB was higher among males (352 of 100,000).²⁹ This difference in sex incidence might be due to health-seeking behavior,

environmental factors, and the higher exposure of males to different factors that pose a risk of acquiring the TB bacilli. Even if it is difficult to compare with previous reports directly, as different studies used different cutoff points for age-groups, based on our study result, TB was more prevalent among the productive age group of study participants (127 [29.8%]) and those with rifampicin resistance (16 [24.6%]). This is in agreement with studies conducted in Yirgalem Hospital in southern Ethiopia and the Agaro Teaching Health Center in southwestern Ethiopia.^{25,27} This might be due to more exposure to the outer environment, high workload, and wide range of mobility in younger age-groups.

We found higher levels of resistance to rifampicin, 71 (3.9%), among the participants, and 71 (15.8%) among TB confirmed cases, almost equivalent (3.4%) to the study conducted in Yirgalem, southern Ethiopia²⁵ and higher than other studies conducted in Ethiopia, where resistance was 2.5% in the northern, 1.7% in the east, 1.9% (primary resistance) in the northwest Ethiopia, and 2.59% in East Gojjam.^{25,28–34} This variation might be due to disparities in awareness of studied populations about drug resistance, access to health-care facilities, disorganized patient diagnosis, treatment, and follow-up, and poor patient adherence, which may have contributed to the higher prevalence of rifampicin-resistant TB in our study. The higher level of rifampicin resistance might be due to the fact that rifampicin is currently used for

the treatment of many other infectious diseases in this study area. Since rifampicin is the most vital drug to treat TB, the advent of resistance to this drug has enormous implications for TB-control programs.

Prevalence in this study was higher than studies conducted in South Africa during 2007–2009 with an overall proportion of rifampicin resistance 8.8%, studies in Kenya of 6.5%, India of 4.69%, and Iran of 7.4%, with an average rate of 5%–10%.^{35–38} On the other hand, our finding was lower than a study conducted in Nigeria (18.8%),³⁹ but comparable to a study conducted in Sudan (15.5%).⁴⁰ Probable reasons for this would be differences in patient selection, sample size (small samples could overrepresent the proportion), irregular supply of anti-TB drugs, poor TB case management (inadequate diagnosis, treatment, and follow-up), and poor treatment compliance. Also, rifampicin has several adverse effects that could result in patient nonadherence, and hence may lead to an increase in resistant strains.

Studies conducted in Iran and Nigeria revealed that none of the isolates was resistant to rifampicin alone.^{41,42} This might be due to a regular supply of anti-TB drugs and adequate diagnosis, treatment, and follow-up of TB patients. In the current study, males were more likely to have rifampicin resistance (45 [17.3%]). TB rates in South Africa have shown higher prevalence in males than in females.³⁵ This sex-incidence variation might be associated with high health-seeking behavior in males.⁴³

Studies around the world have shown significant variations in the prevalence of resistance to anti-TB drugs in patients previously treated for TB. Based on a 2005 nationwide survey, Ethiopia is also among the high-TB/HIV-burden countries, with a TB-HIV coinfection rate over 10%, with MDR-TB prevalence 1.6% and 11.8% among new and retreatment cases, respectively, and rifampicin resistance lower than 2% in new cases.¹¹ With respect to treatment history, the isolates showed different resistance patterns for rifampicin 61 (16.5%) for previously treated cases, and the remainder were new cases (ten [13%]) from TB-confirmed study participants.

Our study showed that there were high levels of drug resistance among those previously treated for TB. This finding is higher compared to other studies in Kenya, with prevalence of resistance of 9.9% and 0 for retreatment and new cases, respectively, and Bujumbura, Burundi, with 2% from new cases and 15% from previously treated cases,^{44,45} East Gojjam (2.59% among new cases, 0 among retreatment cases),²⁸ and western India (retreated cases 9% rifampicin-resistant).^{46,47} Other studies have reported an association

between previous history of TB treatment and anti-TB-drug resistance.^{48,49} In addition, a study in Palermo, Italy reported a wide heterogeneity among the MTB strains observed, which illustrates rapid changes in TB epidemiology.⁵⁰ This indicates the existence of ongoing transmission of DR strains, and could indicate weakness in TB prevention and control measures, as it is conveyed by resistance to rifampicin in new cases as well. This indicates that transmission of MDR-TB has a considerable role in this epidemic, and historical high frequency of treatment abandonment may contribute toward high levels of resistance.

In our study, the overall prevalence of TB was high, and the prevalence of HIV-TB coinfection was also high (23.8%). Rifampicin resistance in HIV-TB coinfecting participants was 18.7%, which is higher than a 2005 estimate of nationwide rifampicin resistance under 2% in new cases.¹¹ A high prevalence of rifampicin resistance among isolates from TB-HIV coinfecting patients has been also reported from Brazil.⁵¹ Resistance to specific anti-TB drugs among HIV-infected patients was evident in studies on global resistance rate to rifampicin alone (0.2%–9.1%).⁵¹ A survey of TB isolates collected in the US between 1993 and 1996 documented rifampicin monoresistance of 2.6% in HIV-positive cases and only 0.2% in HIV-negative cases.⁵² This might be due to HIV infection, which may lead to malabsorption of anti-TB drugs, especially rifampicin, with adverse effects leading patients to nonadherence and subsequent drug resistance and treatment failure. This study tried to assess a heretofore untouched area. This is very valuable and instructive, and could aid in comprehension for health professionals and policy makers to address the problem. Data incompleteness and poor document-retention systems were a limitation of this study, since it involved secondary data.

Conclusion

The prevalence of MTB and rifampicin resistance were high in this study. Therefore, early detection of DR-MTB should be strengthened for management of TB patients. HIV-coinfecting and previously treated patients were more likely to develop rifampicin resistance. Adequate treatment periods and observation of TB cases with strict implementation of directly observed treatments should be considered, and the HIV status of all patients and duration of treatment needs to be documented.

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Author contributions

KNJ and BB conceived and designed the study, performed analysis, interpreted data, and drafted the manuscript. MG, BG, HT, and AG assisted with the design, performed analysis and interpretation of data, and critically reviewed the manuscript. KNJ and BB are joint first authors of this article. All authors read and approved the submitted version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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