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Risk factors for multidrug-resistant tuberculosis in northwest Ethiopia: a case-control study

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Abstract

Ethiopia is one of 30-high burden multidrug-resistant tuberculosis (MDR-TB) countries globally. The aim of this study was to describe the characteristics of patients with MDR-TB and to investigate risk factors for MDR-TB relative to having drug-susceptible TB, in northwest Ethiopia. A hospital-based, unmatched case-control study was conducted. Cases were all MDR-TB patients (i.e. resistant to at least rifampicin and isoniazid) who were confirmed by culture and drug-susceptibility testing whilst enrolled on treatment at Gondar University Hospital. Controls were all drug-susceptible tuberculosis (DS-TB) patients who were confirmed by Gene Xpert MTB/RIF at Gondar University Hospital. Univariable and multivariable logistic regression models were used for comparisons, and odds ratios with 95% confidence intervals (CI) were computed to measure the strength of association between the dependent and independent variables. A total of 452 patients (242 MDR-TB and 210 DS-TB) were included in this study. The mean age of the study participants was 33 years (standard deviation (SD): ± 14 years). Approximately one fifth (78, 17%) of all study participants were human immunodeficiency virus (HIV) positive; 21% (51) of cases and 13% (27) of controls. Risk factors associated with MDR-TB were a history of previous TB

treatment (Adjusted Odds Ratio (AOR): 83.8; 95%CI: 40.7, 172.5), low educational status (AOR: 5.32; 95%CI: 1.43, 19.81); and ages less than 20 years (AOR: 9.01; 95%CI: 2.30, 35.25) and 21-30 years (AOR: 2.61; 95%CI: 1.02, 6.64). HIV infection was also significantly associated with MDR-TB among new TB patients (AOR: 5.55; 95%CI: 1.17, 26.20). This study shows that clinical and demographic features can be used to indicate higher risks of drug resistance in this setting.

Keywords: multidrug-resistant, MDR-TB, tuberculosis, Ethiopia

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least rifampicin and isoniazid, the two most effective first-line tuberculosis (TB) drugs (WHO, 2013). The emergence of MDR-TB has become a major public health problem in a number of countries and an obstacle to global TB control efforts (WHO, 2016). Treatment for MDR-TB is more lengthy, toxic, and expensive when compared to drug-susceptible TB, and cure rates are often lower at 52-75% (Alene, Viney, McBryde, Tsegaye, & Clements, 2017; Alene, Yi, et al., 2017; WHO, 2018) .

MDR-TB occurs in patients either due to the development of drug resistance during a course of first-line TB treatment (i.e. acquired MDR-TB) (Barroso et al., 2003), or due to the transmission of a drug-resistant strain from an infectious patient to a susceptible host (i.e. primary MDR-TB) (Amor, Nemser, Singh, Sankin, & Schluger, 2008; Dye, 2009; Law et al., 2008). Acquired MDR-TB, the most common type of MDR-TB in many settings, occurs as a result of sub-optimal first-line TB treatment, which is often related to health system or patient factors (Faustini, Hall, & Perucci, 2006; Han et al., 2005). There is increasing evidence that

primary MDR-TB is common and that many patients with MDR-TB had it from the start of treatment, highlighting the need for universal drug susceptibility testing (Dhedha et al., 2017; Ragonnet, Trauer, Denholm, Marais, & McBryde, 2017; Shah et al., 2017).

Globally, nearly half a million cases of MDR-TB are estimated to have occurred in 2017 (558,000 Rifampicin resistant (RR)/MDR-TB cases); the majority of these cases occurring among patients who have been previously treated for TB (WHO, 2018). In Ethiopia, the World Health Organization (WHO) estimated that MDR-TB comprises 2.7% of all new cases of TB and 14% among those who have been previously treated for TB (WHO, 2016, 2018). Previous studies have identified that sociodemographic (Barroso et al., 2003; Law et al., 2008; Nino Lomtadze et al., 2009), clinical (Balaji et al., 2010; Rajendra), and behavioral (Dzeyie et al., 2018) factors are associated with MDR-TB. Further, in some settings, human immunodeficiency virus (HIV) infection has been reported as a risk factor for MDR-TB and for deaths related to MDR-TB (Gandhi et al., 2006; Shah et al., 2007). A systematic review and metanalysis conducted in Ethiopia has showed that history of previous TB treatment was significantly associated with MDR-TB (Eshetie et al., 2017). However, this systematic review did not investigate potential clinical and demographic risk factors of MDR-TB. In Ethiopia - a high burden MDR-TB and HIV country - the incidence of TB has decreased over time following the implementation of a range of interventions, including the delivery of TB care by community health workers and directly observed therapy (DOT) (MOH, 2013; Yassin et al., 2013). However, the number of MDR-TB cases has increased over time and has become a challenge for the national TB control and prevention program (Alene, Viney, McBryde, & Clements, 2017; Alene, Viney, McBryde, Tsegaye, et al., 2017). Identifying clinical and demographic factors associated with MDR-TB is important for the provision of targeted preventive and control services. Therefore, the aim of this study was to identify sociodemographic and clinical factors associated with MDR-TB relative to drug-susceptible TB, and to describe the characteristics of patients with MDR-TB from northwest Ethiopia.

Results

Socio-demographic and clinical characteristics

A total of 452 study participants were included; 242 were cases who had MDR-TB, and 210 were controls who had DS-TB. The mean age of study participants was 33 years (standard deviation (SD)=14 years); 31 years for cases (SD =12.2 years) and 34 years for controls (SD

= 15.3 years). Of the total 452 study participants, nearly half (229, 50.7%) were from urban areas and two-thirds (284, 62.8%) were male (Table 1). Approximately one-fifth (78, 17%) of all study participants were HIV positive; 21% (51) of cases and 13% (27) of controls ($p=0.02$; Table 1).

Factors associated with MDR-TB

Univariable analysis

Table 2 shows the crude odds ratios (ORs) for factors associated with MDR-TB, comparing cases to controls. In the univariable analysis, demographic factors such as low educational status and occupation (i.e. daily laborer), and clinical factors such as a history of previous TB treatment, HIV co-infection and lower BMI were significantly associated with MDR-TB (Table 2). The variable average monthly income was not recorded for 45% of the cases and 40% of the controls, and this variable was not included in the multivariable analysis.

Multivariable analysis

In the final multivariable model, demographic and clinical factors such as age, educational status, history of TB treatment and HIV infection were significantly associated with MDR-TB. A history of previous TB treatment was strongly associated with MDR-TB (Adjusted odds ratio (AOR): 83.8; 95% confidence intervals (95% CI): 40.7, 172.5). In addition, educational status (i.e. being unable to read and write as compared to tertiary education) (AOR: 5.32; 95% CI: 1.43, 19.81), and ages less than 20 years (AOR: 9.01; 95% CI: 2.30, 35.25) and 21-30 years (AOR: 2.61; 95% CI: 1.02, 6.64) as compared to age 41 years or greater were significantly associated with MDR-TB. HIV infection was also significantly associated with MDR-TB among new MDR-TB patients only (AOR: 5.55; 95% CI: 1.17, 26.20) (Table 3).

Discussion

This case-control study identified factors associated with MDR-TB in northwest Ethiopia. Clinical factors such as a history of prior TB treatment and HIV infection as well as demographic factors such as a younger adult age group and a lower educational level were significantly associated with MDR-TB in northwest Ethiopia.

Our study showed that patients with a history of previous TB treatment were more likely to have MDR-TB than patients with no history of TB treatment. This finding is similar to the

findings of previous studies (Faustini et al., 2006; Mulu, Mekkonen, Yimer, Admassu, & Abera, 2015). Although MDR-TB can occur in patients due to the transmission of a drug-resistant strain from an infectious patient to a susceptible host (Amor et al., 2008; Dye, 2009; Law et al., 2008), the majority of the cases arise from inadequate treatment of TB that allows a drug-resistant strain to become dominant (Barroso et al., 2003; Caminero, 2010; Lomtadze, Aspindzelashvili, & Janjgava, 2009). Laboratory investigation such as drug-susceptibility testing (DST), line probe assays or Xpert MTB/RIF should be performed for all patients with TB in northwest Ethiopia in order to quickly screen for drug resistance at the time of diagnosis.

In our study, HIV infection was also significantly associated with MDR-TB among new TB patients. For HIV-positive patients, the odds of being diagnosed with MDR-TB were five times higher than the odds for HIV-negative patients. Previous studies have also reported that new HIV-positive TB patients are at increased risk of MDR-TB compared with HIV-negative patients (Mesfin, Hailemariam, Biadgign, & Kibret, 2014; van den Hof et al., 2015). The dual epidemics of HIV and MDR-TB may be the reason for the observed relationship between drug resistance and HIV infection. This might be particularly important in high MDR-TB and HIV burden counties such as Ethiopia (WHO, 2015). Integrated and enhanced efforts are necessary to provide routine diagnosis, effective treatment and high-quality care to HIV and MDR-TB co-infected patients as these group of patients are socially vulnerable and at increased risk of treatment failure and mortality (Alene et al., 2018; Gandhi et al., 2006). This finding reinforces the need for universal DST in high TB and HIV burden countries such as Ethiopia.

Another finding of our study was that patients with lower educational status were found to be at higher risk of being diagnosed with MDR-TB, compared to those with tertiary educational status. This is likely related to the fact that patients with lower educational status may have poor adherence to first-line TB treatment and then subsequently acquire MDR-TB. Reasons for non-adherence may be multiple. These patients may also be poor and least able to afford treatment. Our finding showed that educational status was significantly associated with MDR-TB in previously TB treated patients, but not with new TB patients. This might suggest that the provision of health education, support and counselling to TB patients will help to curb the widespread emergence of MDR-TB in the community (Li et al., 2015).

Our study also showed that the risk of MDR-TB is higher in age groups below 30 years. The association between MDR-TB and age group has been inconsistent in the literature, and is difficult to compare to other studies as these studies use different cut-off points for age groups, and others do not consider it at all (Suarez-Garcia et al., 2009). A systematic review conducted in European countries showed an association between MDR-TB and age under 65 years, but the association was weak and more heterogeneous for age groups under 45 years (Faustini et al., 2006). Other studies conducted in Bangladesh (Rifat et al., 2014), Malaysia (Elmi et al., 2014) and Hong Kong (Law et al., 2008) showed that being between 18 and 45 years of age was significantly associated with an increased risk for MDR-TB. Confounding factors such as behavioural factors, frequency of travel, adherence to treatment, the necessity of work and a reluctance to disrupt employment and history of previous TB treatment might explain the association between age and MDR-TB.

There are some limitations to this study. First, since our study was dependent on a review of the medical records of patients, several important risk factors such as adherence of patients to TB medication, comorbidities, and behavioural factors such as smoking and drinking alcohol were not assessed in the study. Second, as the number of MDR-TB cases who were enrolled at the hospital was small, we observed wide confidence intervals for some potential risk factors reflecting low power of the study. Third, selection bias is a particular problem inherent in case-control studies (especially in hospital-based studies), where comparability between cases and controls is a major concern.

In conclusion, we found that demographic and clinical factors such as lower age group, lower educational status, a history of prior TB treatment and HIV co-infection were significantly associated with MDR-TB in northwest Ethiopia. In light of these findings, improving public health education for all TB patients and expanding routine DST for patients with a history of previous TB treatment are recommended. Integrated efforts are also required to provide effective diagnosis and treatment to HIV and MDR-TB co-infected patients.

Methods

Study setting

The study was conducted at Gondar University Specialized Referral Hospital, located in Gondar city, in northwest Ethiopia. It has a DOT centre and a separate MDR-TB treatment centre which provide services for drug susceptible TB and MDR-TB patients, respectively.

The MDR-TB treatment centre was established in 2010. Tuberculosis is diagnosed using clinical signs and symptoms, sputum smear microscopy, molecular testing, radiology and histopathology (MOH, 2012). For the diagnosis of MDR-TB, culture and drug-susceptibility testing (DST), and Gene Xpert MTB/RIF are performed at the national and regional reference laboratories. Recently, Gondar University Hospital commenced using a Gene Xpert MTB/RIF test for the diagnosis of TB and DS-TB. Patients with evidence of rifampicin resistant (RR) or MDR-TB are enrolled into the MDR-TB treatment program (MOH, 2012).

DS-TB patients are treated with a combination of first-line TB drugs for six months. DS-TB patients with a history of previous TB treatment receive an eight-month regimen with the inclusion of streptomycin (MOH, 2012). Patients with drug-resistant TB including RR and MDR-TB are treated with a standardized second-line treatment regimen for 20 months (an 8-month intensive phase and a 12-months continuation phase). During the intensive phase, patients are admitted into the hospital until they become medically stable. The regimen during this phase contains pyrazinamide, ethambutol, an injectable second-line drug (i.e. capreomycin, amikacin or kanamycin), levofloxacin, prothionamide, (or ethionamide) and cycloserine. During the continuation phase, the injectable drug is discontinued and patients continue to take oral drugs including pyrazinamide, ethambutol, levofloxacin, prothionamide, ethionamide and cycloserine (Biruck Kebede et al., 2013; MOH, 2012). During the continuation phase, patients pick up their TB drugs every month from the treatment follow-up centres and treatment is self-administered.

Study design and population

A hospital-based, unmatched case-control study was conducted to identify risk factors associated with MDR-TB relative to DS-TB. Cases were all MDR-TB patients who were confirmed by culture and DST, enrolled at the MDR-TB treatment center, from September 2010 to August 2015. Controls were all DS-TB patients who were confirmed by Gene Xpert MTB/RIF and enrolled at the DOT clinic of the same hospital, between March to August 2018. DS-TB was used to define patients with culture positive for *Mycobacterium tuberculosis* that was not resistant to rifampicin and isoniazid

Variables

The dependent variable in the study was MDR-TB status (case or control). The independent variables were sociodemographic variables such as sex, age, residence, marital status,

educational status, occupation and average monthly income and clinical factors such as HIV status, site of TB, history of TB treatment, comorbidities, and body mass index (BMI) at the start of treatment.

Data collection and analysis

Data for the cases and controls were collected from the patient's medical and laboratory records from Gondar University Specialized Referral Hospital at the DOT and MDR-TB treatment centers, respectively. Categorical variables were summarised by counts and percentages, and continuous variables such as BMI, average monthly income and age were summarised by their mean and standard deviation (SD). Univariable logistic regression analyses were performed and crude odds ratios (COR) with 95% CI interval were reported. Collinearity between independent variables was assessed by variance inflation factors and pair-wise Chi-square tests. Variables with a high degree of association with other independent variables were excluded from the final models. Multivariable logistic regression models were then used to assess the association between independent and dependent variables. By assuming that the factors associated with MDR-TB among previously treated and new TB patients are different, two additional models were constructed. AOR with 95% CI were computed to measure the strength of association between the dependent and independent variables. Variables with a p-value <0.05 in the multivariable analysis were considered as having a statistically significant association with MDR-TB. The analyses were performed using STATA version 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The goodness-of-fit of the model was checked using the Hosmer-Lemeshow test. The test showed that our model fitted the data well (Pearson's chi-squared = 459.1; p-value= 0.2).

List of Abbreviations

AFB: Acid fast bacillus; BMI: Body Mass Index; AOR: Adjusted odds ratio; CI: Confidence interval; COR: Crude odds ratio; DOT: Directly observed therapy; DS-TB: drug-susceptible tuberculosis; DST: Drug susceptibility testing; ETB: Ethiopian Birr; IQR: inter quartile range; HIV: Human immunodeficiency virus; LPA: Line probe assay; MDR-TB: Multidrug resistant tuberculosis; RR: Rifampicin resistant; SD: standard deviation; TB: Tuberculosis

Ethics approval and consent to participate

Ethical approval was obtained from the Australian National University Human Research Ethics Committee (protocol number 2016/219), and permission to access the data was obtained from the University of Gondar. As this study used secondary data, informed consent was not obtained from the study participants.

Consent to publish

Not applicable

Availability of data and materials

The datasets supporting the conclusions of this article are available on request from KAA

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors contributed to this study, as required by the International Committee of Medical Journal Editors. KAA, conceived designed and prepared the draft manuscript. KV improved the drafted manuscript. MM collected the data and revised the drafted manuscript. KV, EM, MM, DJG, and AC advised on the data analysis and the development of the manuscript. All the authors revised the manuscript and approved the final version.

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Table 1: Socio-demographic and clinical characteristics of patients with multidrug-resistant tuberculosis patients (cases) and drug-susceptible tuberculosis (controls) from Gondar University Hospital, northwest Ethiopia.

Variables	Total (N=452), n (%)	MDR-TB (N=242), n (%)	DS-TB (N=210), n (%)	P-value
Sex				0.33
Male	284 (62.8)	147 (60.7)	137 (65.2)	
Female	168 (37.2)	95 (39.3)	73 (34.8)	
Age (years)				0.20
≤ 20	75 (16.6)	45 (18.6)	30 (14.3)	
21-30	186 (41.2)	93 (38.4)	93 (44.3)	
31-40	86 (19.0)	52 (21.5)	34 (16.2)	
≥41	105 (23.2)	52 (21.5)	53 (25.2)	
Residence				0.60
Rural	223 (49.3)	122 (50.4)	101(48.1)	
Urban	229 (50.7)	120 (49.6)	109 (51.9)	
Marital status				0.001
Single	193 (42.7)	94 (38.8)	99 (47.1)	
Married	204 (45.1)	105 (43.4)	99 (47.1)	
Divorced	36 (8.0)	28 (11.6)	8 (3.8)	
Widowed	9 (2.0)	5 (2.1)	4 (1.9)	
Separated	10 (2.2)	10 (4.1)	0 (0.0)	
Educational status				< 0.001
Unable to read and write	179 (39.6)	111 (45.9)	68 (32.4)	
Primary	129 (28.5)	77 (31.8)	52 (24.8)	
Secondary	76 (16.8)	32 (13.2)	44 (21.0)	
Tertiary	68 (15.0)	22 (9.1)	46 (21.9)	
Occupation				< 0.001
Government employee	33 (7.3)	22 (9.1)	11 (5.2)	

Self-employed	65 (14.4)	33 (13.6)	32 (15.2)	
Farmer	136 (30.1)	66 (27.3)	70 (33.3)	
Housewife	53 (11.7)	27 (11.2)	26 (12.4)	
Student	99 (21.9)	39 (16.1)	60 (28.6)	
Daily laborer	50 (11.1)	41 (16.9)	9 (4.3)	
Not-recorded	16 (3.5)	14 (5.8)	2 (1.0)	
Average monthly income (ETB), Median (IQR)	1000 (600-1500)	680 (400-1293)	1000 (1000-1500)	0.006
BMI, mean (SD)	17.32 (2.98)	16.98 (3.12)	17.71 (2.76)	0.01
HIV status				0.02
Positive	78 (17.3)	51 (21.1)	27 (12.9)	
Negative	374 (82.7)	191 (78.9)	183 (87.1)	
Site of TB disease				< 0.0001
Pulmonary	437 (96.7)	227 (93.8)	210 (100.0)	
Extra-pulmonary	15 (3.3)	15 (6.2)	0 (0.0)	
Previous TB treatment				< 0.001
Yes	259 (57.3)	225 (93.0)	34 (16.2)	
No	193 (42.7)	17 (7.0)	176 (83.8)	

BMI: body mass index; DS-TB: drug-susceptible tuberculosis; ETB: Ethiopia Birr; HIV: Human immunodeficiency virus; IQR: inter quartile range; MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis

Table 2: Demographic and clinical factors associated with multidrug-resistant tuberculosis at Gondar University Hospital, northwest Ethiopia

Variables	MDR-TB (N=242) n (%)	DS-TB (N=210) n (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Sex				
Male	147 (60.7)	137 (65.2)	0.82 (0.56, 1.21)	1.40 (0.66, 2.96)
Female	95 (39.3)	73 (34.8)	1.00	1.00
Age (years)				
≤ 20	45 (18.6)	30 (14.3)	1.53 (0.83, 2.78)	9.01 (2.30, 35.25)
21-30	93 (38.4)	93 (44.3)	1.02 (0.63, 1.64)	2.61 (1.02, 6.64)
31-40	52 (21.5)	34 (16.2)	1.56 (0.87, 2.77)	2.06 (0.78, 5.45)
>40	52 (21.5)	53 (25.2)	1.00	1.00
Residence				
Rural	122 (50.4)	101(48.1)	1.09 (0.76, 1.59)	1.19 (0.48, 2.94)
Urban	120 (49.6)	109 (51.9)	1.00	1.00
Marital status				
Not married	137 56.6)	111 (52.9)	0.86 (0.59, 1.25)	1.23 (0.55, 2.74)
Married	105 (43.4)	99 (47.1)	1.00	1.00
Educational status				
Unable to read and write	111 (45.9)	68 (32.4)	3.41 (1.89, 6.16)	5.32 (1.43, 19.81)
Primary	77 (31.8)	52 (24.8)	3.09 (1.67, 5.74)	2.74 (0.84, 8.96)
Secondary	32 (13.2)	44 (21.0)	1.52 (0.77, 3.01)	0.84 (0.27, 2.57)
Tertiary	22 (9.1)	46 (21.9)	1.00	1.00
Occupation				
Employee	55 (22.7)	43 (20.5)	0.28 (0.12, 0.64)	1.34 (0.33, 5.46)
Farmer	66 (27.3)	70 (33.3)	0.20 (0.09, 0.46)	0.34 (0.08, 1.44)
House wife	27 (11.2)	26 (12.4)	0.23 (0.09, 0.56)	0.87 (0.17, 4.43)
Student and others	53 (21.9)	62 (29.5)	0.19 (0.08, 0.42)	0.40 (0.09, 1.63)
Daily laborer	41 (16.9)	9 (4.3)	1.00	1.00

BMI, mean (SD)	16.98 (3.12)	17.71 (2.76)	0.92 (0.86, 0.98)	0.93 (0.85, 1.04)
HIV status				
Positive	51 (21.1)	27 (12.9)	1.81 (1.09, 3.01)	1.10 (0.46, 2.63)
Negative	191 (78.9)	183 (87.1)	1.00	1.00
Previous TB treatment				
Yes	225 (93.0)	34 (16.2)	68.5 (37.0, 126.7)	83.8 (40.7, 172.5)
No	17 (7.0)	176 (83.8)	1.00	
BMI: body mass index; CI: Confidence interval; DS-TB: drug-susceptible tuberculosis; HIV: Human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis				

Table 3: Factors associated with multidrug-resistant tuberculosis among previously treated and new TB patients at Gondar University Hospital, northwest Ethiopia

Variables	Previously TB treated patients Adjusted Odds Ratio (95% CI)	New TB patients Adjusted Odds Ratio (95% CI)
Sex		
Male	2.92 (1.16, 7.36)	0.10 (0.02, 0.45)
Female	1.00	1.00
Age (years)		
≤ 20	10.02 (1.75, 57.19)	7.46 (0.54, 192.9)
21-30	4.00 (1.27, 12.59)	1.58 (0.24, 10.16)
31-40	3.08 (0.97, 9.75)	1.21 (0.11, 11.86)
≥41	1.00	1.00
Residence		
Rural	1.36 (0.38, 4.92)	1.01 (0.18, 5.57)
Urban	1.00	1.00
Marital status		
Not married	1.17 (0.43, 3.17)	2.04 (0.35, 11.86)
Married	1.00	1.00
Educational status		
Unable to read and write	8.43 (1.52, 46.84)	4.06 (0.35, 47.18)
Primary	4.80 (1.03, 22.37)	0.98 (0.13, 7.15)
Secondary	1.40 (0.36, 5.50)	0.19 (0.01, 2.82)
Tertiary	1.00	1.00
Occupation		
Employee	1.68 (0.30, 9.53)	0.17 (0.01, 2.70)
Farmer	0.28 (0.04, 1.69)	0.22 (0.01, 3.68)
House wife	1.72 (0.24, 12.17)	0.07 (0.002, 1.96)
Student and others	0.42 (0.08, 2.26)	0.14 (0.01, 1.98)
Daily laborer	1.00	1.00
BMI, mean (SD)	1.01 (0.88, 1.17)	0.79 (0.65, 0.97)
HIV status		
Positive	0.70 (0.26, 1.90)	5.55 (1.17, 26.20)
Negative	1.00	1.00

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