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Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case–control study

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ABSTRACT

Objective: The objective of this study was to identify determinants for tuberculosis (TB) among HIV-infected adults in Northwest Ethiopia.

Design: Case–control study.

Setting: Three hospitals and 10 health centres in Northwest Ethiopia.

Participants: A total of 446 individuals consented to participate in the study (150 cases and 296 controls). Cases were HIV-infected adults diagnosed with active TB, and controls were HIV-infected adults without active TB.

Main outcome measure: The link between TB and determinants was assessed using logistic regression. Determinants were categorised as sociodemographic, host-related, clinical and environmental.

Results: Smoking (adjusted OR (AOR) 5.47; 95% CI 2.26 to 13.22), presence of a TB patient in the family (AOR 2.66; 95% CI 1.25 to 5.66), alcohol consumption (AOR 2.49; 95% CI 1.29 to 4.80) and chewing khat (AOR 2.22; 95% CI 1.11 to 4.41) were independent determinants for increased occurrence of TB. Highly active antiretroviral therapy (HAART) (AOR 0.25; 95% CI 0.13 to 0.51), isoniazid preventive therapy (IPT) (AOR 0.22; 95% CI 0.11 to 0.41) and cotrimoxazole preventive therapy (AOR 0.32; 95% CI 0.19 to 0.55) had a protective effect against TB.

Conclusions: HIV-infected adults with substance abuse (tobacco smoking, khat chewing and alcohol) should be prioritised for TB screening. This study reaffirmed that HAART and IPT are some of the best strategies for reducing TB occurrence in HIV-infected adults. These findings provide impetus to intensify tracing of TB household contacts.

Strengths and limitations of this study

- This is the first multicentre case–control study in Northwest Ethiopia to investigate determinants for tuberculosis (TB) in HIV-infected adults.
- The study identified determinants for TB that will be important for prioritising TB screening, treatment, prevention and control.
- This study reaffirmed that highly active antiretroviral therapy and isoniazid therapy are some of the best strategies for reducing TB among HIV-infected adults in resource-limited settings.
- As we used a retrospective case–control approach, no temporal relationship could be established and the study design did not allow proof of causation.

INTRODUCTION

The advent of HIV was a massive setback for the prevention and control of tuberculosis (TB).[1] TB is the leading cause of morbidity and mortality among people with HIV.[2] There is a strong synergy between TB and HIV infection in HIV high-burden countries particularly in resource-limited settings where the impacts of both diseases are more significant.[3]

One-third of the world's population is infected with TB.[2] In 2013, an estimated 9.0 million people developed TB; 1.1 million were HIV infected.[4] Ethiopia ranks as the seventh most TB burdened country in the world.[5]

In resource-limited settings, the healthcare systems are overwhelmed by the preventive, therapeutic and diagnostic challenges of the 'HIV–TB syndemic'. In Ethiopia, the dual epidemics have drained resources and overburdened the already very limited health work-force.[1] HIV increases life time risk of developing TB.[6] However, HIV is not the only determinant for developing TB; various others contribute to TB–HIV co-infection. Previous studies have identified sociodemographic,[7 8] clinical,[9 10] life style[11 12] and environmental[13] determinants for TB. However, among HIV-infected adults, the determinants for TB are still not well described, particularly in a resource-limited setting. Determinants for TB among HIV-positive adults vary from one setting to another. Therefore, a context-specific study in a high-burdened TB/HIV region is indicated. This study aims to assess the

determinants for TB among HIV-infected adults in Northwest Ethiopia.

METHODS

Study design

We conducted a multicentre case–control study from 12 May to 5 June 2014 in Northwest Ethiopia. All governmental health institutions in 10 districts were included (ie, Bahir Dar, Dangella, Kossober, Fnote Selam, Bure, Dur Betie, Deber Tabor, Wereta, Addis Zemen and Nefas Mewcha).

Participants

Cases were HIV-infected adults diagnosed with active TB and on TB treatment during the data collection period. The diagnosis of active TB was based on one or more TB diagnostic investigations (sputum microscopy, X-ray, histopathology, culture or molecular). Controls were HIV-infected adults without TB. All controls were actively screened for TB to rule out TB. The screening procedure included history taking for four symptoms at each visit (cough, weight loss, night sweating and fever). If the patient presented with any one of these symptoms, this patient was a suspected TB case and was investigated according to the national guidelines for TB–HIV.[1] In hospitals, sputum microscopy, histopathology and radiology examinations are used as the TB diagnostic tools. In health centres, sputum microscopy is the main-stay TB diagnostic tool, and patients are sent for other diagnostic evaluation to hospitals and private institutions where the diagnostic tools are available.

Sample size calculation

The sample size was calculated using Epi Info V.7 software. The study was designed to have 80% statistical power with a level of significance at 5% and a case to control ratio of 1:2. Assuming the proportion of low CD4 cell count was 5.9% for the controls and 13.9% for the cases,[13] the calculated sample size was 144 for cases and 287 for controls using the two-proportions formula. Allowing for a non-response rate of 10%, the resulting sample size was 474 (158 cases and 316 controls). The sample size was calculated for exposure status of different variables: cotrimoxazole preventive therapy (CPT), isoniazid preventive therapy (IPT) and CD4. We took the largest sample among these exposure variables.

Sampling procedures

A total of 52 health institutions provide HIV care services in 44 districts of Awie, West Gojjam and South Gondar Zones.[14] Ten districts were randomly selected, and all health institutions in the 10 districts were included in the study. Three hospitals and 10 health centres were included. HIV-infected adults diagnosed with confirmed active TB were recruited as cases, while those without active TB were recruited as controls. Study subjects who were unable to give informed consent and subjects with suspected but unconfirmed TB were excluded. All TB–HIV co-infected patients attending HIV care clinics and those who were receiving TB treatment were included. Controls were allotted on the basis of the number of cases available in each facility, with a control to case ratio of 2:1, and sampled by systematic random sampling with a sampling interval of five.

Data collection and analysis

Data were collected from two sources. Trained nurses who were in charge of an HIV care clinic conducted face to face interviews with study participants by using structured questionnaires that were prepared in English, translated into Amharic and back translated, and pretested for consistency and ease of understanding. The primary data were collected to assess sociodemographic variables (age, sex, educational and marital status) and host-related variables (cigarette smoking, khat chewing and alcohol consumption). A person with substance abuse (chewing khat, alcohol consumption or smoking) was defined as an individual who is currently using the substance or has a history of regular substance abuse. Environmental determinants included the presence of flooring, latrine and separate kitchen in the house. Trained nurses also collected data from patient's' records to assess clinical variables: highly active

Table 1 Sociodemographic and host-related determinants of HIV-infected adults in Northwest Ethiopia, 2014

Variable	Cases	Controls	Total
Sex			
Male	69 (46)	108 (36.5)	177 (39.7)
Female	81 (54)	188 (63.5)	269 (60.3)
Education			
No formal education	46 (30.7)	120 (40.5)	166 (37.2)
Primary	48 (32)	78 (26.4)	126 (28.3)
Secondary	42 (28)	60 (20.2)	102 (22.9)
Tertiary	14 (9.3)	38 (12.8)	52 (11.6)
Marital status			
Married	53 (35.3)	141 (47.6)	194 (43.5)
Divorce/widowed	50 (33.3)	98 (33.1)	148 (33.2)
Never married	47 (31.3)	57 (19.3)	104 (23.3)
Smoking			
Yes	25 (16.7)	12 (4)	37 (8.3)
No	125 (83.3)	284 (96)	409 (91.7)
Khat chewing			
Yes	44 (29.3)	37 (12.5)	81 (18)
No	106 (70.7)	259 (87.5)	365 (82)
Alcohol			
Yes	49 (32.7)	49 (16.6)	98 (22)
No	101 (67.3)	247 (83.4)	348 (78)
Previous history of TB			
Yes	41 (27.3)	50 (16.9)	91 (20.4)
No	109 (72.7)	246 (83.1)	355 (79.6)

Values are n (%).
TB, tuberculosis.

antiretroviral therapy (HAART), CD4 cell count, CPT and IPT. Data collection procedures were supervised by medical officers.

Data were entered into Epi-info V.7 and analysis was performed with SPSS V.20. Frequencies and proportions were used to describe the study subjects in relation to the studied variables. OR (95% CI) and p value were used to measure strength of association and identify statistically significant results. Logistic regression models were applied to assess the relationship between determinants and TB. Confounding variables were identified by applying logistic regression models. Multivariable analysis (backward stepwise) was used. The Hosmer–Lemeshow test was applied and the fit of the model was checked: a poor fit of the model if the p value is <0.05 and good fit if the p value is >0.05. In this study the model adequately fitted the data and the p value was 0.34.

Ethics considerations

Ethical approval from the Heidelberg Ethics Commission was obtained. In addition, ethical approval from the country in which the research was conducted—Amhara Regional Research and Ethical Core Process, Bahir Dar, Ethiopia—was granted. Written permission to conduct the study was obtained from each health institution involved in the study. Since there were illiterate participants, the data collectors informed each study participant about the informed consent sheet. Informed oral consent was obtained from each study participant. The data collectors documented the participant's consent on the informed consent sheet. This consent procedure was approved by the ethics commission.

RESULTS

Sociodemographic and host-related determinants of HIV-infected adults

A total of 446 subjects (150 cases (33.6%), 296 controls (66.4%)) out of 474 eligible participants responded and consented to participate in this study, resulting in an overall response rate of 94.1% (94.9% for cases and 93.7% for controls).

The median age of the cases was 32 years (IQR 27–39), and that for controls was 33 years (IQR 28–39). A higher percentage of women was observed in both groups: 81 (54%) in the case group and 188 (63.5%) in the control group (table 1).

Bivariate analysis

Although, in bivariate analysis, male patients were 1.48 times more likely to have TB than female patients, the association was not statistically significant. Married patients (crude OR (COR) 0.45; 95% CI 0.27 to 0.75)

Table 2 Sociodemographic and host-related determinants for developing tuberculosis among HIV-infected adults in Northwest Ethiopia, 2014

Variable	Cases	Controls	COR	95% CI	p Value
Sex					
Male	69 (46)	108 (36.5)	1.48	0.99 to 2.12	0.053
Female	81 (54)	188 (63.5)	1		
Education					
No formal education	46 (30.7)	120 (40.5)	1.04	0.51 to 2.09	0.912
Primary	48 (32)	78 (26.4)	1.67	0.82 to 3.39	0.157
Secondary	42 (28)	60 (20.2)	1.90	0.9 to 3.93	0.084
Tertiary	14 (9.3)	38 (12.8)	1		
Marital status					
Married	53 (35.3)	141 (47.6)	0.45	0.27 to 0.75	0.002*
Divorce/widowed	50 (33.3)	98 (33.1)	0.61	0.37 to 1.03	0.068
Never married	47 (31.3)	57 (19.3)	1		
Smoking					
Yes	25 (16.7)	12 (4)	4.73	2.30 to 9.72	<0.0001*
No	125 (83.3)	284 (96)	1		
Khat chewing					
Yes	44 (29.3)	37 (12.5)	2.9	1.77 to 4.75	<0.0001*
No	106 (70.7)	259 (87.5)	1		
Alcohol					
Yes	49 (32.7)	49 (16.6)	2.44	1.54 to 3.86	<0.0001*
No	101 (67.3)	247 (83.4)	1		
Previous history of TB					
Yes	41 (27.3)	50 (16.9)	1.85	1.15 to 2.96	0.01*
No	109 (72.7)	246 (83.1)	1		

*Indicates significant difference.
Values are n (%).
COR, crude OR; TB, tuberculosis.

were less likely to develop TB than patients who had never been married. Cases were more likely to be smokers (COR 4.73; 95% CI 2.3 to 9.72), khat chewers (COR 2.9; 95% CI 1.77 to 4.75) or alcohol drinkers (COR 2.44; 1.54 to 3.86). Study participants who had a history of TB (COR 1.85; 95% CI 1.15 to 2.96) were more likely to develop TB. However, educational status was not a determinant for TB (table 2).

HAART (COR 0.33; 95% CI 0.19 to 0.56), CPT (COR 0.35; 95% CI 0.22 to 0.53) and IPT (COR 0.30; 95% CI 0.18 to 0.50) had a protective effect against TB. Subjects with a separate kitchen in the house (COR 0.61; 95% CI 0.40 to 0.93) were less likely to develop TB. HIV-infected adults with a TB patient in the family (COR 1.99; 95% CI 1.11 to 3.57) were more likely to develop TB. However, flooring and a latrine in the house were not determinants for developing TB (table 3).

Multivariable analysis

To identify independent determinants for TB, a multivariable logistic regression model was used. After adjustment for possible confounders, some variables remained in the multivariable model: chewing khat (adjusted OR (AOR) 2.22; 95% CI 1.11 to 4.41), being a smoker (AOR 5.47; 95% CI 2.26 to 13.22) and drinking alcohol (AOR 2.49; 1.29 to 4.80) were independent determinants for increased TB occurrence. However, HAART (AOR 0.25; 95% CI 0.13 to 0.51), CPT (AOR 0.32; 95% CI 0.19 to 0.52) and IPT (AOR 0.22; 95% CI 0.11 to 0.42) had an independent beneficial protective effect against TB. Subjects with a separate kitchen in the house (AOR 0.48; 95% CI 0.28 to 0.83) were less likely to develop TB. Patients who live with a TB patient in the household (AOR 2.66; 95% CI 1.25 to 5.66) were more likely to develop TB. Patients whose CD4 cell count was <200 cells/μL (AOR 7.22; 95% CI 3.39 to 15.37) were more likely to develop TB. However, sex, marital status and a previous history of TB did not remain in the multivariable model (table 4).

DISCUSSION

This study showed that HIV-positive adults receiving HAART, CPT and IPT were less likely to develop TB, but smoking, alcohol consumption, khat chewing, presence of a TB patient in the family, and CD4 count <200 cells/μL were independent determinants for increased TB occurrence.

Similarly to the finding of another study, this study also showed that level of education was not a determinant for TB occurrence.[7] Hence, increasing the level of

Table 3 Clinical and environmental determinants for developing tuberculosis among HIV-infected adults in Northwest Ethiopia, 2014

Variable	Cases	Controls	COR	95% CI	p Value
HAART					
Yes	114 (76)	268 (90.5)	0.33	0.19 to 0.56	<0.0001*
No	36 (24)	28 (9.5)	1		
CPT					
Yes	83 (55.3)	231 (78)	0.35	0.22 to 0.53	<0.0001*
No	67 (44.7)	65 (22)	1		
IPT					
Yes	22 (14.7)	107 (36.1)	0.30	0.18 to 0.50	<0.0001*
No	128 (85.3)	189 (63.9)	1		
CD4 cell count (cells/μL)					
≤200	87 (58)	61 (20.6)	5.53	2.96 to 10.35	<0.0001*
200–500	46 (30.7)	169 (57.1)	1.05	0.56 to 1.97	0.86
≥500	17 (11.3)	66 (22.3)	1		
TB patient in the family					
Yes	25 (16.7)	27 (9.1)	1.99	1.11 to 3.57	0.021*
No	125 (83.3)	269 (90.9)	1		
Separate kitchen					
Yes	96 (64)	220 (74.3)	0.61	0.40 to 0.93	0.024*
No	54 (36)	76 (25.7)	1		
Floor of the house					
Mud/soil	123 (82)	240 (81)	1.06	0.64 to 1.76	0.814
Cement	27 (18)	56 (19)	1		
Latrine					
Yes	136 (90.7)	267 (90.2)	1.05	0.53 to 2.06	0.875
No	14 (9.3)	29 (9.8)	1		

*Indicates significant difference.
Values are n (%).
COR, crude OR; CPT, cotrimoxazole preventive therapy; HAART, highly active antiretroviral therapy; IPT, isoniazid preventive therapy; TB, tuberculosis.

Table 4 Independent determinants for tuberculosis among HIV-infected adults in Northwest Ethiopia, 2014

Variable	COR (95% CI)	p Value	AOR (95% CI)	p Value
HAART				
Yes	0.33 (0.19 to 0.56)	<0.0001	0.25 (0.13 to 0.51)	<0.0001
No	1		1	
CPT				
Yes	0.35 (0.22 to 0.53)	<0.0001	0.32 (0.19 to 0.55)	<0.0001
No	1		1	
IPT				
Yes	0.30 (0.18 to 0.50)	<0.0001	0.22 (0.11 to 0.41)	<0.0001
No	1		1	
Smoking				
Yes	4.73 (2.30 to 9.72)	<0.0001	5.47 (2.26 to 13.22)	<0.0001
No	1		1	
Khat				
Yes	2.9 (1.77 to 4.75)	<0.001	2.22 (1.11 to 4.41)	0.023
No	1		1	
Alcohol				
Yes	2.44 (1.54 to 3.86)	<0.0001	2.49 (1.29 to 4.80)	0.006
No	1		1	
TB patient in the family				
Yes	1.99 (1.11 to 3.57)	0.021	2.66 (1.25 to 5.66)	0.011
No	1		1	
Separate kitchen				
Yes	0.61 (0.40 to 0.93)	0.024	0.48 (0.28 to 0.83)	0.010
No	1		1	
CD4 cell count (cells/μL)				
<200	5.53 (2.96 to 10.35)	<0.0001	7.22 (3.39 to 15.37)	<0.0001
200–500	1.05 (0.56 to 1.97)	0.86	1.31 (0.63 to 2.74)	0.461
≥500	1		1	

AOR, adjusted OR; COR, crude OR; CPT, cotrimoxazole preventive therapy; HAART, highly active antiretroviral therapy; IPT, isoniazid preventive therapy; TB, tuberculosis.

school training may not necessarily bring successful behavioural change to TB prevention and control in this source population.

Married HIV-positive adults were also less likely to develop TB than those who were never married, consistent with a previous study.[8] Other studies have shown that the prevalence of marriage is higher in higher-income societies[15] and that TB and poverty are inter-related.[16]

HIV-positive patients with low CD4 count were more likely to develop TB, consistent with a previous study.[7] In addition, our findings indicating that IPT had a protective effect against TB were also consistent with a previous research report.[17] IPT reduces the mycobacterium load and reduces the progression of latent TB to active TB.[9] However, increased mycobacterial load is coupled with progressive impairment of the mycobacterium-specific T cell response.[18]

Study participants receiving HAART were less likely to develop TB, as found previously.[10] This may be due to a strong relation between increased HAART coverage and decreased viral load.[11] Lowering of viral load was also linked with reduced occurrence of active TB.[19]

We found that CPT has a protective effect against TB. This was consistent with a previous study.[13] CPT has beneficial effects in enhancing CD4 count as well as reducing viral load.[20]

Cigarette smoking induces immune impairment and damages ciliary clearance.[21 22] In the present study, smoking was an independent determinant for TB, as found previously.[23]

Khat chewing is linked with immune modulation.[12] No published study has detected khat chewing as an independent determinant for TB in HIV-infected adults. However, in this study, khat chewing was an independent determinant for TB.

Our findings show that study subjects who consumed alcohol were more likely to develop TB, in agreement with previous studies.[24–26] Alcohol can modulate the immune response. Long-term alcohol consumers have been shown to have impaired immunity.[27]

A past history of TB was found to be a determinant for increased TB occurrence, but only in the bivariable analysis. This may be explained by the low TB case detection rate in Ethiopia.[2] The established TB case detection mechanisms may have overlooked some TB patients. A proportion of TB patients may remain undiagnosed—that is, they may die from other diseases or die without visiting a healthcare centre; the detected proportion of reoccurrence might be low. Therefore the prevalence of reoccurrence was underestimated.

This study has the following potential limitations. As we used a retrospective case–control approach, a temporal

relationship could not be established and the study design could not prove causation. TB has the possibility to spread to other people who are not household members, but this study considered only family members as close TB contacts. Information bias related to substance use (chewing khat, smoking or alcohol consumption) might have also affected information accuracy.

CONCLUSION

HIV-infected adults with substance abuse (tobacco smoking, khat chewing and alcohol) should be prioritised for TB screening. This study reaffirmed that HAART and IPT are some of the best strategies for reducing TB occurrence in HIV-infected adults. These findings provide impetus to intensify tracing of TB household contacts.

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Contributors All the authors conceived and designed the experiments, performed the experiments, analysed the data, contributed materials/analysis tools, and wrote the paper.

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Competing interests None declared.

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Correction

Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case–control study. *BMJ Open* 2016;6: e009058. The first name of the third author was misspelt. The correct spelling is Annelies Wilder-Smith.

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