

Determinants of Active Tuberculosis among HIV-Positive Adults Attending Clinical Care in Ambo general hospital and Gedo hospital, West Shoa Zone, Oromia, Ethiopia (unmatched case-controlstudy)

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ABSTRACT

Background: Diseases and conditions that weaken immunity, such as malnutrition, smoking, alcoholism, HIV/AIDS and diabetes, are factors that facilitate the development of active TB disease. The rapid growth of the HIV pandemic in many developing countries has resulted in an equally dramatic rise in the estimated number of new TB cases. The Objective of this study was to assess the determinants of active TB among HIV-positive adults attending clinical cares in Ambo general and Gedo hospitals, West Shoa zone. **Methods and materials**: A facility based unmatched case control study design was employed using Systematic Random Sampling method from May to August/ 2015. A total sample size of 123 TB/HIV co-infected patients from Cases and 246 HIV infected without TB infection patients from control groups were selected for the study. Data were entered to computer by Epi data version 3.2.1 and transferred to SPSS version 16 software package for analysis. To measure the strength of association between dependent and independent variables, odds ratio with a 95% confidence interval was done. Finally, logistic regression was done to control possible confounders and to identify independent predictors of active TB among HIV positive patients. **Results:** Active TB among HIV-positive adults was significantly associated with lack of formal educational (AOR 3.23, 95%CI 1.60, 6.81), under nourished (lower BMI <18.5) (AOR 2.62, 95%CI 1.23, 5.95), advanced WHO clinical stages (AOR 2.89, 95%CI 1.12, 4.96) and CD4+count<200/µL (AOR 2.5 95%CI 1.18, 4.97) and being married is the protective factor (AOR .20 95%CI 0.11, 0.50)

Conclusion and Recommendation: lack of formal education, under nourished, advanced WHO clinical stages and CD4+ count <200/ µL were the independent predictors for active

TB among HIV positive patients. People with TB/HIV co-infection are important targets for interventions such as early diagnose and treatment of opportunistic infection and giving health education to prevent and control it.

INTRODUCTION

The term tuberculosis (TB) describes a broad range of clinical illnesses caused by *Mycobacterium tuberculosis* (or less commonly *Mycobacterium bovis*). Drugs that can cure most TB patients have been available since the 1950s, yet TB remains the world's most important cause of death from an infectious agent, besides the human immune deficiency virus (HIV) with which it is intimately linked [1]. In 1993 the World Health Organization(WHO) declared TB to be a global public health emergency and tuberculosis continues to be an immense global public health problem. Tuberculosis can affect virtually every organ, most importantly the lungs and is typically associated with granuloma formation [2].

Global targets for reducing the burden of disease caused by TB have been set for 2015 and 2050. The target set within the context of the millennium development goals (MDGs) is to halt and reverse the incidence of TB by 2015 and by 2050 the global incidence of TB disease will be less than one case per million people per year [3]. Tuberculosis control demands are a comprehensive and sustained response complementing measures to address the social, host and environmental factors that increase the risk of developing active TB. Poor people bear most of the burden of illness, suffering and death caused by TB. The Stop TB Strategy should therefore be viewed as a key component of broader international, national and local strategies to alleviate poverty [4].

The rapid growth of the HIV pandemic in many developing countries has resulted in an equally dramatic rise in the estimated number of new TB cases. HIV-related TB continues to increase even in countries with well-organized national TB control programmes (NTPs) that are implementing Directly Observed Treatment, Short-course [5]. Full DOTS implementation is clearly insufficient to control TB where HIV is fuelling the TB epidemic and control of HIV infection must therefore become an important concern for National Tuberculosis control programmes. Cognizing of this, TB/HIV collaborative activities have been incorporated as major components of the Stop TB Strategy and the Global Plan to Stop TB [6].

Tuberculosis and HIV/AIDS are commonly called the "deadly duo" and referred to as HIV/TB. HIV weakens the immune system and so people are more susceptible to catching TB if they are exposed. People Living with HIV/AIDS (PLWHA) are up to 50 times more likely to develop active TB in a given year than HIV-negative people. TB bacteria accelerate the progression of HIV to AIDS. Some TB infections are "latent," that is a person may have the TB-causing bacteria but they are dormant. A person with latent TB is not sick and not infectious. However, latent TB can progress to active TB. "Active TB infection" means that the TB bacteria are multiplying and spreading in the body. Human immune deficiency virus is responsible for the increase in active TB cases in sub-Saharan Africa and increases the risk of rapid TB disease progression. Worldwide, more than 13 million individuals are co-infected with HIV and TB. Approximately, 70% of those co-infected reside in sub-Saharan Africa[7].

Tuberculosis has been a major public health problem in Ethiopia since the 1950s. Ethiopia ranks 7th out of the world's 22 high-burden countries for TB.

Efforts to implement TB/HIV collaborative activities in Ethiopia started in 2001. The FMOH responded by establishing a national TB/HIV advisory committee with members from TB and HIV/AIDS programs, including representatives from academic and research institutions and associations [8].

More than one third of the global population is latently infected with *mycobacterium tuberculosis*, the bacterium that causes TB disease. Each individual with TB disease will infect an average of 10 to 15 persons if they go undiagnosed and untreated and the cycle of transmission continues [9]. In 2009, there were an estimated 9.4 million incident cases of TB globally (equivalent to 137 cases per 100,000). The absolute number of cases continues to increase slightly from year to year, as slow reductions in incidence rates per capita continue to be outweighed by increase in population [10].

Tuberculosis is the single most important threat and a leading killer among people living with HIV. At least one in four deaths among people living with HIV can be attributed to TB and many of these deaths occur in resource-limited settings [11]. A total of 1.7 million People died from TB in 2009, including 380,000 people living with HIV, equal to 4,700 deaths per day. Not only is TB the largest cause of death amongst persons living with HIV/AIDS, but it also has important implications related to drug interactions and toxicity when a person is on both TB and HIV medications [12].

According to the Ethiopian Ministry of Health hospitals statistics data, tuberculosis is the leading cause of morbidity, the third cause of hospital admission after deliveries and malaria, and the second cause of death after malaria in Ethiopia. Tuberculosis is an obstacle to socio-economic development; 75% of people affected by TB are within the economically productive age group (15-54 years) [13].

In Ethiopia, the introduction of provider initiated counseling and testing in most public health facilities has increased HIV screening among Tuberculosis patients from 16% in 2007 to 38% in 2009. A total of 56,040 Tuberculosis patients were tested for HIV, of which, 11,118 (20%) were found to be HIV positive. The proportion of HIV-positive patients who were screened for Tuberculosis increased from 25% in 2007 to 55% in 2009. Furthermore, in the fiscal year from July 2008 through June 2009, 68% of HIV-positive Tuberculosis patients were put on Cotrimexazole Prophylaxis Therapy (and 41% of HIV-positive Tuberculosis patients started Anti Retroviral Treatment [14].

According to Ambo general Hospital and Gedo hospital, in 2012 the number of clients following care in Anti Retroviral Treatment clinic was increasing. The total number of clients following care in the Ambo general hospital was 7000 People Living with HIV (3000 on pre-Anti Retroviral Treatment and 4000 on Anti Retroviral Treatment care) and 700 People Living with HIV (300 on pre- Anti Retroviral Treatment and 400 on Anti Retroviral Treatment care) in Gedo Hospital. Of this, 146 were Tuberculosis/HIV co-infected clients in the Ambo general hospital and 38 were Tuberculosis (TB)/HIV co-infected patients in Gedo hospital. Totally, according to the report of HIV/TB units of both facilities, 184 TB/HIV co-infected patients were on care [15].

As explained in the above paragraphs, some HIV infected people in the study area have developed active TB while others have not. Hence, being HIV-positive is not the only factor for developing active TB. Most of the studies that have been conducted so far on risk factors for TB have been done in developed countries and apart from the studies showing the effect of HIV infection, few studies have been carried out in resource-poor countries and, the factors that are responsible for the development of active TB among PLHIV are not well studied in the study area.

Objective of the Study

General objective

To assess the determinants of active tuberculosis among HIV-positive adults currently attending clinical care in Ambo General Hospital and Gedo hospital, West Ethiopia, December 2015.

Specific objectives

To identify the socio-economic factors associated with active tuberculosis among HIV-positive adults.

To assess the host factors associated with active tuberculosis among HIV-positive adults.

To assess the environmental factors associated with active tuberculosis among HIV-positive adult

METHODS AND MATEREIALS

This study was conducted in Ambo General Hospital and Gedo hospital. Ambo town is located at distance of 114km from the capital city of Ethiopia Addis Ababa. The hospitals give different clinical services for about more than 2 million people and have a separate anti-retroviral therapy clinic, which was established in 2004 to provide free anti-retroviral therapy [15]. The study was conducted from May to August 2015. A facility based unmatched case-control study was conducted to assess the determinants of active TB infection among people living with HIV at Ambo general and Gedo hospital. The source population is all adult People Living with HIV, attending clinical care in Ambo general and Gedo hospital from May to August 2015. **Cases** were TB/HIV co-infected adult who were on anti-TB treatment and and the controls were adult People Living with HIV without active TB who were attending clinical care in public health facilities of Ambo general and Gedo hospitals.

PLHIV whose age were greater than or equal to 15 years old, People Living with HIV with active TB of any site for cases and People Living with HIV without TB disease for controls were included in the study. Severely ill, mentally ill PLHIV and who could not respond to the interview, People Living with HIV who were transferred out to other health facilities and People Living with HIV with suspected TB but not confirmed were not included in the study.

Sample Size

Sample size was calculated considering the "proportion of presence of TB patient in the family" among the control as a key variable. Open Epi Version 2.3 software, sample size and power calculation for unmatched case control study was used to calculate the sample size needed.

p_2= proportion of presence of TB patient in the family among controls = 17.8%[25].

From similar study OR=2.2 (25)

Confidence level = 95%, Power = 80%, Population allocation ratio: n_2:n_1 = 2:1

Where, n_1 = Sample size of who developed active TB and

n_2 = Sample size of who did not have active TB.

A ratio of 2:1 was used to increase the power of the study and representativeness of patient attending ART clinic. From Fleiss continuity correction statistical methods for proportions sample size: n_1 = 112 and n_2 = 224 total sample sizes = 336. To allow for possible non-response during the actual survey, 10% non respondent rate was considered to get a final sample size of 369 [123 for n_1 and 246 for n_2].

Sampling Procedure

Based on the eligibility criteria list of cases and controls were prepared using unique identification number from ART clinic records. The study subjects were selected from constructed sampling frame of cases and controls. By using computer generated random number cases and controls were selected proportional to the number of patients on care in each hospitals during the study period. Finally, 123 TB/HIV infected patients were selected as cases and 246 HIV infected people without TB infection were selected as controls.

Data Collection Technique

The data were collected using a structured questionnaires adopted from similar studies. The data collection was made by face-to-face interview. The interview was conducted after having the consent of the study subject in another room near to ART clinic to ensure privacy and good discussion between the trained data collectors and study participants. Additional data were retrieved from the records.

Data Quality Control

The pre-test was held at Holeta health center with similar setting on 10% of cases and 10% of controls of the representative sample before the actual data collection took place to minimize

error. Two days intensive training was given for the data collectors and supervisors on the objectives of the study and how to interview, how to fill the questionnaire and handle questions asked by patients during interview.

Data Processing and Analysis

After the data were collected, completeness and consistency was checked manually and the data were entered to computer by Epi data version 3.1. After data were cleaned, it was transferred to SPSS version 16 software package for analysis. Frequencies and percentages were calculated for all the categorical variables. Bivariate analysis was done to see the association between the dependent and independent variables. To measure the strength of association between dependent and independent variables, odds ratio with a 95% confidence interval was calculated. Finally, logistic regression was used to control possible confounders and to identify independent factors associated with active TB.

Ethical Considerations

A written letters were obtained from Coordinator of Research and Knowledge Transfer of the College of Medicine and Health Science and submitted to Ambo general hospital and Gedo hospital. Oral consent was obtained from each respondent after explaining the purpose of the study prior to data collection.

RESULTS

Socio-Demographic and Socio-economic Characteristics

The response rate of the study participants was 90.8%. Among the total 335(110cases and 225 controls) of study subjects 274(81.8%) were from Ambo general Hospital ART clinic and 61(18.2%) were from Gedo hospital ART clinic. The majority of the respondents (56.7%) were females. The mean age of the respondents was 35.2 ± 5.8 years. Three hundred (89.5%) of the respondents were from urban area. Majority (83.5%) of the respondents attended formal education of various categories. Among the cases 40(36.6%) of the respondents were attended no formal education and 15(6.6%) of the controls were attended no formal education.

One hundred seventy (50.7%) of the respondents were married and 83(24.8%) were divorced/widowed. Among the cases 50(45.4%) of the respondent were married and 48(43.6%) them were divorced/widowed (Table 1).

Distribution of Host Factors

Twenty eighty (25.5%) of the cases had previous history of TB when compared to 46(19.3%) of the controls. Thirty two (29.1%) of the cases and 50(22.2%) of the controls had history of TB patient in their family. Twenty of the cases (18.2%) had history of diabetic mellitus when compared to 16(7%) of the controls. Majority (81.8%) of the cases and 160(71.1%) of the controls were taking ART during the study period. Twenty five (22.7%) of the cases and 30(13.3%) of the controls had known history of pneumonia in the past 1 year before the diagnosis of active TB (see Table 2).

Clinical characteristics of the study participants

Two hundred twenty (65.7%) of the study participants were in WHO clinical stage I and II. Majority of 60(54.5%) the cases were in WHO clinical stage of III and IV. The mean of the haemoglobin level at the time of active TB diagnose in the cases were 11.2gm/dL ± 2.6gm/dL, while the mean of recent haemoglobin level in the controls were 12.6gm/dL±2.3gm/dL.

The mean of CD4 counts at the time of active TB diagnose in the cases were 250.6 cells/ µL ± 10.5cells/ µL. Forty (36.4%) of the cases had CD4 count of less than 200cells/ µL at the time of active TB diagnosis (Table 3).

Distribution of Environmental Factors

Seventy (63.6%) of the cases and 143(62.2%) of the controls house floor were made of soil. Sixty (54.5%) of the cases and 140(62.2%) of the controls had less than five adults in the house hold. Majority (82.2%) of the controls had disposed waste outside the compound when compared to 80 (72.7%) of the cases. .

The Independent Predictors of Active TB in Multivariable Analysis

Logistic regression was done to control possible confounders and to identify independent factors associated with active TB among HIV-Positive adults in the study area. All variables which had shown p-value<0.05 during the bivariable analysis were entered to the model.

The multivariable analysis revealed that the independent predictors for active TB were no formal education AOR 3.23 (1.60, 6.81), CD4+<200/ µL AOR 2.5 (1.18, 4.97), advanced WHO clinical stages AOR 2.89 (1.42, 4.96) and BMI AOR 2.621.23, 5.45) among HIV positive adults attending both hospitals.

DISCUSSION

This study assessed the determinants of socio-economic, host and environmental factors of active tuberculosis among HIV-positive adults. This study has provided pertinent information about risk factors associated with active tuberculosis among HIV-positive adults for decision makers and planners as well.

Lack of formal education had significant difference among the cases and the controls. Similar studies conducted in Nekemte referral hospital on case and control have similar finding [16]. Other findings reported from India, in Gambia, Jimma teaching Hospital and Metu Karl Hospital have shown similar findings [19, 20, and 21]. This revealed that as the level of education increases the level of understanding of the respondents about the cause and its prevention increase of TB. Eventually they might have protected themselves from the disease based on the knowledge they acquired from various sources. Moreover, lack of formal education may be a proxy for low socio-economic status and might have contributed to the risk of TB disease.

In this study CD4+ count less than 200/µl increased the risk of Tuberculosis by 2.5 fold. The study conducted in West Africa also showed 3.8 (1.6, 15.2) fold increase in the incidence of TB during the acute phase of HIV-infection [21]. A study conducted in United Kingdom also showed that most recent CD4+cell count was the strongest risk factor for active tuberculosis [17].

Under nutrition was a prominent risk factors of active TB in this study. Those who were under nutritional BMI< 18.5kg/m^2 were 2.62 times more likely to have active TB compared to those who had BMI $\geq$18.5kg/m^2. A case control study conducted in Nekemte referral hospital also indicated that those with BMI<18.5kg/m^2 were 3.6 times more likely to have active TB compared to those who had BMI>18.5kg/m^2 [16]. A study from South India showed that patients with active TB were eleven times more likely to have a body mass index less than 18.5kg/m^2 which shows greater risk than present study[20]. Similarly a higher proportion of cases had a BMI less than 18.5kg/m^2 compared to controls in studies done in Jimma Hospital and Metu Karl Hospital [19]. Nutritional status is one of the most important determinants of resistance to infection. It is well established that nutritional deficiency is associated with impaired immune functions. While malnutrition limits cell mediated immunity and increases susceptibility to infection, infection can lead to nutritional stress and weight loss, thereby weakening immune function and nutritional status. Patients with active TB were more likely

to be very thin (wasted) or have a lower body mass index less than 18.5 kg/m^2 compared to TB controls. The wasting commonly found in patients with active TB was most likely the result of a combination of factors, including decreased appetite and food intake, and increased losses and altered metabolism associated with the inflammatory and immune response.

In this study those with the advanced WHO clinical stages of III and IV HIV were 2.89 times more likely to develop active TB as compared to those in WHO clinical stage I and II. Similar study conducted in Nekemte referral hospital, Jimma and Karl hospitals also show that advanced WHO clinical stages(III and IV) increase the risk of active TB among HIV positive patients [16, 19]. Another study conducted in Tanzania also shows that HIV/TB co-infected patients in WHO clinical stage III and IV had 70% increased risk of active TB when compared to those in WHO clinical stages I and II [18].

Interestingly, this study also showed that being married decreased the risk of TB co infection by 20% when compared with single individuals. This can be seen in the view of marriage having a positive effect on health of an individual in a sense that those who get married and stayed together have advantages of better health as a result of positive psychological and social impacts [22].

CONCLUSION

This study has come up with the conclusion that there are multiple factors associated with active tuberculosis in TB-HIV co-infection. Among these factors, lack of formal education, under nourishment (lower BMI <18.5kg/m^2), <200/µl CD4+ count and advanced WHO clinical stages (stage III and IV) were found to be independent risk factors for active TB in HIV patients. Tuberculosis is a multifactorial disorder in which the environment interacts with host-related factors, contributing to the overall disease progress. Therefore, improved understanding of the effects of the socio-economic and host related factors on the development of TB disease has strong implications for tuberculosis prevention and control.

RECOMMENDATIONS

The finding of this study has important implications for both public health policy making and the clinical management of people living with HIV/AIDS in the study area.

Ambo general and Gedo hospitals and Ambo zonal health office need to focus on strengthening of TB prevention and control with the identification of specific targets, such as enhanced health education to increase awareness of community's on TB disease.

Competing interests

I declare that I have no competing interests

Authors' contributions

I Habtamu Oljira Desta and Meseret Ifa Wanjo were the Principal Investigators, participated in Conceptualized the study, designed the study instrument and conducted the data analysis and wrote the first draft and final draft of the manuscript and involve in a critical review of the manuscript.

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List of tables

Table 1: distribution of socio demographic factors of active TB among HIV positive adults in Ambo general and Gedo hospitals, West Shoa zone Oromia, Ethiopia, December 2015.

Socio-demographic variables	Cases (n=110) (%)	Controls (n=225) (%)
Sex		
Male	40(36.3)	105(46.7)
Female	70(63.7)	120(53.3)
Age		
20- 35 years	80(72.7)	160(71.1)
>35years	30(27.3)	65(28.9)
Educational status		
No Formal education	40(36.6)	15(6.7)
Primary education	30(27.3)	100(44.4)
Secondary education	10 (9.1)	60(26.6)
Tertiary education	10(9.0)	50(22.3)
Marital status		
Single	12(10.9)	70(31.1)
Married	50(45.4)	120(53.3)
Divorced/Widowed	48(43.7)	35(15.6)
Employment status		
Employed	36(32.3)	120(53.3)
Unemployed	74(67.7)	105(46.7)
Monthly income		
<930 ETB	71(63.6)	110(48.9)
≥930 ETB	39 (36.4)	125(51.1)
Residence		
Urban	95(86.4)	200(88.8)
Rural	15(13.6)	25(11.2)
Religion		
Orthodox	60(54.5)	140(62.2)
Protestant	40(36.4)	70(31.1)
Other	10(9.1)	15 (6.7)

Table 2: Distribution of Host factors in active TB among Ambo general and Gedo hospitals, West Shoa zone,Oromia, Ethiopia, December 2015.

Host factors	Cases (%) (n=110)	Controls (%) (n=225)
Smoking		
Never	80(72.7)	180(80.0)
Past	14(12.7)	20(8.9)
Current	16(14.6)	25(11.1)
Asthma		
Yes	20(18.2)	40(17.8)
No	90(81.8)	185(82.2)
Diabetic Mellitus		
Yes	20(17.2)	16(7.1)
No	90(81.8)	209(92.9)
Taking IPT		
Yes	30(27.2)	150(66.7)
No	80(72.8)	75(33.3)
Previous History of TB		
Yes	28(25.5)	40(17.8)
No	82(74.5)	185(82.2)
Presence of TB (Family)		
Yes	32(29.1)	50(22.2)
No	78(70.9)	175(77.8)
History of Pneumonia		
Yes	25(22.7)	30(13.3)
No	85(87.3)	195(86.7)
Taking ART		
Yes	70(63.6)	146(64.9)
No	40(36.4)	79(35.1)

Table 3: distribution of Clinical variables in active TB among Ambo general and Gedo hospitals West Shoa zone,Oromia West Ethiopia, December 2015.

Clinical factors	Cases (n=110) (%)	Controls (n=225)(%)
WHO Clinical stage		
Stage I & II	50(55.5)	170(75.6)
Stage III & IV	60(54.5)	55(24.4)
Haemoglobin level		
<10	25(22.7)	20(8.8)
10-12.49	63(57.3)	50(22.2)
≥12.5	22(20)	155(69.0)
CD4 count		
<200	40(27.7)	35(17.2)
200-499	50(51.3)	140(52.1)
≥500	20(21)	50(30.7)
BMI		
<18.5	50(45.5)	50(22.2)
≥18.5	60(54.5)	175(77.8)

Table 4: Distribution of environmental factors in active TB, among HIV positive adults in Ambo general and Gedo hospitals, West Shoa zone, Oromia, Ethiopia, December 2015.

Environmental variables	Cases (%)(n=110)	Controls (%)(n=225)
Wall of house		
Mud/mud brick	60(54.5)	150(66.7)
Cement	50(45.5)	75(33.3)
Separate kitchen		
Yes	56(50.1)	160(71.1)
No	54(49.9)	65(28.9)
Waste disposal site		
In the compound	30(27.3)	40(17.8)
Outside	80(72.7)	185(82.2)
Floor of house		
Earth	70(63.6)	140(62.2)
Cement	40(36.4)	85(37.8)
PPR		
<1	20(18.2)	60(26.7)
1-2	70(63.6)	100(44.4)
>2	20(18.2)	65(28.9)
Ceiling		
Yes	80(72.7)	150(66.7)
No	30(27.3)	75(33.3)
Number of Adult in HH		
1-5	60(54.5)	140(62.2)
>5	50(45.5)	85(37.8)
Number of windows		
0	20(18.2)	30(13.3)
1	50(45.5)	100(44.4)
>2	40(36.3)	95(42.2)

Table 6: Independent predictors of active TB in HIV infected adult among Ambo general and Gedo hospitals, West Shoa zone, Oromia, Ethiopia, December 2015.

Independent Predictor	COR	AOR	P-value
Educational status			
No Formal education	5.55[2.09, 9.90]	3.23 [1.60, 6.81]	0.02
Primary education	4.34[2.2, 7.24]	1.70 [0.78, 3.12]	0.10
Secondary education	1.35[0.78, 2.34]	1.14 [0.52, 2.46]	0.56
Tertiary education	1.00	1.00	
CD4 count			
<200	2.85[1.43, 4.88]	2.5 [1.18, 4.97]	0.04
200-499	1.12[0.44, 2.22]	1.00	
≥500	1.00		
WHO Clinical stage			
Stage I & II	1.00	1.00	
Stage III & IV	3.37[1.85, 6.84]	2.89 [1.42, 4.96]	0.02
BMI			
<18.5	2.92[1.53, 5.68]	2.62[1.23, 5.45]	0 .03
≥18.5	1.00		
Marital status			
Single	1.00	1.00	
Married	0.30[0.21, 0.80]	0.20[0.11, 0.50]	0.04*
Divorced/Widowed	1.73[0.99, 5.34]	1.63[0.79, 6.34]	0.072