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Research Article

TUBERCULOSIS INFECTION AMONG ADULT HIV PATIENTS ATTENDING ANTIRETROVIRAL THERAPY CLINIC AT UNIVERSITY OF GONDAR REFERRAL HOSPITAL OF ETHIOPIA

Mequanente Dagnaw[1*], Zewdu Baye[2], Yeneabat Birhanu[2], Meera Indracanti[1]
[1]Department of Biotechnology, Institute of Biotechnology, University of Gondar, Gondar, Ethiopia.
[2]School of Nursing, University of Gondar, Gondar, Ethiopia.
***Corresponding author: mequanente@gmail.com**
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ABSTRACT

Despite increased deliverance of antiretroviral therapy, morbidity and mortality from TB are still predominant among HIV/AIDS infected patients in Ethiopia. Thus, the current study aimed to determine incidence and predictors of tuberculosis among HIV infected patients at university of Gondar referral specialized teaching hospital, Ethiopia, 2018. Institutional based retrospective follow-up study was conducted among study population which was HIV infected individuals registered from September 2013 to September, 2018. The data were collected using structured data extraction form. The data were checked for completeness, cleanness and entered into Epi Info 7.0 and analyzed using SPSS version (IBM-23). Statistical significance was inferred at P-value ≤ 0.05. Adjusted odd ratio (AOR) with 95% confidence interval (CI) was used to determine predictors. Among 494 patients' charts were abstracted 275 (55.7%) and new TB cases were found. Cumulative and incidence density of tuberculosis was 6.875% and 55 per 100 person year respectively. Divorced Marital status, family size, tobacco user behavioral factors baseline, WHO clinical stage IV,CD4 count at present, CD4 count at diagnosis <200, drug adherence and hematocrit count, were important determinant/risk factors of tuberculosis among HIV infected patients. Relatively high tuberculosis cases were established among HIV infected patients.

Keywords: HIV infection, determinant, tuberculosis, Ethiopia.

INTRODUCTION

TB is a major public health problem and the most frequently diagnosed opportunistic infection worldwide. It is still the leading killer causing one in four deaths mostly in developing countries (Alene *et al*., 2013). TB and HIV are called a "deadly duo" as HIV weakens the immune system and makes them more susceptible to TB infection. On the other hand, TB increases the progression of HIV to AIDS stage. Globally, more than 13 million people are TB/HIV co-infected. Of these, about 70% are living in sub-Saharan Africa. Ethiopia ranked seventh among the 22 high TB burden countries in the world (Melkamu *et al*., 2013). According to a report (WHO, 2014), the prevalence and incidence of all forms of TB are 211 and 224 per 100,000 of the population, respectively. About 13% of all new TB cases are also HIV co-infected.

African region is the most affected with 25.7 million people living with HIV in 2017. The African region also accounts for over two thirds of the global total of new HIV infections (WHO, 2017).This study was conducted to generate data on the type, magnitude and predictors of opportunistic diseases among adults who were enrolled into the national HIV/AIDS care and treatment program (Weldegebreal *et al*., 2018).

MATERIALS AND METHODS

Study design

A five-year institution based retrospective follow up study was conducted at the University of Gondar referral specialized teaching hospital, Ethiopia. Currently, more than 12,000 patients were in active follow up, of which over 7000 have been initiated on highly active antiretroviral treatment (HAART) (Anon, 2019). Data was collected for the period September 2013 to September 2018 and data collection time was 1-30 December 2018.

Inclusion and exclusion criteria

All PLHIV aged 15 years and above and enrolled into the adult chronic HIV care at this hospital were included in the study. An individual with incomplete chart and diagnosed clinically without sputum examination, culture and chest X-ray were excluded from the study.

Measurements and study variables

The outcome variable in this study was the incidence rate of TB co-infection among HIV-positive patients, and it was calculated using the total duration of follow-up for the whole cohort in person-year (PY) of observation. For individuals who do not develop TB, the duration of follow-up from the time of enrolment for HIV care until the end was considered as TB-free. For those who developed TB, TB-free survival time was measured from the time of enrolment in the HIV care programs until the development of TB. An event of an incidence of TB in this study was considered as any form of TB that was diagnosed clinically or radio graphically and confirmed by laboratory examinations or by patients who had empirically started anti-TB treatment after enrolment. Incident TB case was diagnosed with sputum smear (+) (at least two), chest X-ray (suggestive of TB finding) and positive culture. Cumulative incidence of TB was calculated by dividing total new occurrence of TB to all total sampled patients. Incidence rate of TB was calculated by dividing all new occurrence of TB to total follow up time of patients in year. TB diagnosis was done using microscopic examinations of sputum smears, chest radiology, fine needle aspiration of lymphadenopathy, cytology with very high clinical grounds and Mycobacterium culture.

Sample size determination

The sample size was determined by using single proportion formula Z = 95% confidence interval, where P= prevalence of 28.9 %, D = 4% margin of error was taken.

$$n = \frac{(Za/2)^2 p(1-p)}{d2}$$

Where:

$Z_{a/2}$=1.96 is the critical point for the standard formal table, a=level of significant, n =sample size, d=4% of margin of error, $n = \frac{3.8416 * 0.289(1-0.289)}{(0.04)^2} = 494$

Random sampling was used through randomly generated number from patient's data of 2013-2018. A structured data extractions form was used which consists three parts, such as question based on socio-demographic characteristics, clinical factors, and co-morbidity. Variables of the study were dependent variable-new TB infections, independent variables-WHO clinical stage, residence, educational status, occupation, behavioral factors and drug adherence

Data processing

Data were cleaned and entered to Epi info version 7 software. Analysis was made using SPSS version 23 software package. Descriptive statistics was used to assess normality, outliers and identifying missing values. Bivariate analysis was performed to see the association between dependent and independent variables. To measure the strength of association, odds ratio with a 95% confidence level was calculated. Multivariable logistic regression was done by entering all variables with *P* value less than 0.20 in the bivariate analysis and the results were considered statistically significant at P-value< 0.05. The association between the dependent and independent variable was measured and tested using p-value and 95% CI for the significant level was considered at p-value <0.05. Finally, unconditional logistic regression with backward method was used to control possible confounders and to identify the determinant factors associated with TB/HIV co-infection.

Ethical consideration

The study was approved by the institutional review board of University of Gondar College of Medicine and Health Science. Personal identifiers were excluded during data abstraction. Since it was secondary data, obtaining informed consents from the participants was not possible, but the confidentiality of information was maintained by not recording their name from the chart and keeping the data anonymous.

RESULT AND DISCUSSION

Socio-Demographic characteristics

Four hundred ninety four records of HIV infected patients were analyzed. Almost more than half, 302 (61.1 %) of them were in the age group of 25 - 45 years. Over more than half (61.9 %) were females and the majority (79.4%) of them were urban dwellers. (Table1)

Table 1: Socio-demographic characteristics of HIV infective patient at university of Gondar referral hospital (Sep 2013-sep 2018).

Variable		Frequency	%
Sex	Male	188	38.1
	Female	306	61.9
Age years	18- 24	77	15
	25-45	302	61.1
	>45	115	23.3
Marital	Single	83	16.8

status	Married	144	29.1
	Divorced	219	44.3
	Window	48	9.7
Residence	Urban	392	79.
	Rural	102	20.6
Religion	Muslim	104	21.1
	Orthodox	366	74.1
	Others	24	4.9
Edu cation	No education	84	17
	Primary	115	23.3
	Secondary	103	20.9
	Tertiary	35	7.1
	No read/write	150	30.1
	Others	7	1.4

Base line clinical characteristics

One hundred ninety (38.5%) of them were at WHO clinical stage 4 during enrolment. The CD4 count during HIV diagnosis was 358 (72.5%) was <200 cell/µl. The predominant 36.9% hematocrit amount was 121(24.5%) (Table 2). Cumulative incidence and incidence rate of tuberculosis among patients was 68.75% and 55 per 100 person's year respectively. Bivariable logistic regression analysis of socio-demographic, clinical factors and comorbidity variables on incidence of TB revealed that marital status, family size, behavioral factors, WHO clinical stage, CD4 count at diagnosis and at present, HCT count, new Tb infections, INH prophylaxis and reason for change were determinants of incidence of TB, but all other variable like educational status, etc were not predict Incidence of Tuberculosis among HIV infected patients (Table 3).

Table 2. Clinical characteristics of HIV patients

Variable		Frequency	%
WHO clinical stage	I	78	15.8
	II	87	17.6
	III	139	28.1
	IV	190	38.5
CD4 at HIV diagnosis	<200	358	72.5
	200-500	121	24.5
	>500	15	3
	200-500	228	46.2
	<200	27	5.5
BMI (Kg/m2)	<18.5	289	58.5
	18.5-24.5	199	40.3
	>24.5	5	1.1
Hg B (g/dl)	<10	139	28.1
	>10	354	71.7
	41.5-50.4	87	17.6
	>50.4	13	2.6
New TB infection	Yes	275	55.7
	No	219	44.3
	Lung TB	175	35.4
	Extra lung TB	100	20.3
	No TB	219	44.2

Table 3. Predictors of tuberculosis among PLHIV patients in university of Gondar referral hospital.

Variable	Incidence of TB			AOR (95% CI)	p-value
	Yes	No	COR (95% CI)		
Marital status					
Single	24 (4.9)	59 (11.9)	1.912 (0.911, 4.015)		
Married	56 (11.3)	88 (17.8)	1.222 (0.613, 2.368)		
Divorced*	174 (35.2)	45 (9.1)	0.201(0.104, 0.388)	0.005 (0.000, 0..96)	0.00
Windowed	21 (4.3)	27 (5.5)	1		
Family size					
1-3	117 (23.7)	103(20.9)	1		0.031
4-5	120 (24.3)	96(19.4)	1.673 (0.915, 3.056)		
>5*	38 (7.7)	20(4)	1.520 (0.831, 2.782)	0.080 (0.008, 0.798)	
Behavioral factors					
Tobacco user*	26 (5.3)	20(4)	3.407 (0.83, 13.996)	0.010 (0.000, 6.157)	0.006
Alcohol user	57 (11.6)	52(10.6)	1.554 (0.976, 2.475)		
Both alcohol and tobacco user	21 (4.3)	22(4.5)	1.785 (0.924, 3.446)		
Chat chewing	16 (3.3)	20(4.1)	1.037 (0.505, 2.128)		
Others	16 (3.3)	23(4.7)	2.130 (1.045, 4.342)		
No	138 (28)	81(16.5)	1		
WHO clinical stage					
I	37 (7.5)	61(12.3)	1		
II	51 (10.3)	61(12.3)	534 (3.634, 11.755)		
III	80 (16.2)	70 (14.2)	4.740 (2.701, 5.319)		
IV*	107 (21.7)	27 (5.3)	3.468 (2.041, 5.892)	6.534 (3.631, 11.755)	0.000
CD4 count at present					
<100*	11 (2.2)	7 (1.4)	0.851(0.319, 2.271)	0.014 (0.00, 0.482)	0.018
101-200	25 (5.1)	19 (3.8)	1.0116 (0.530, 1.946)		
201-350	104 (21.1)	92 (18.6)	01.182 (0.808, 1.731)		
>350	135 (27.3)	101 (20.4)	1		
CD4 at HIV diagnosis					
>500	7 (1.4)	8 (1.6)	1		
200-500	21 (4.3)	100 (20.2)	2.543 (0.900, 7.186)		
<200*	247 (50)	111 (22.5)	10.596 (6.293, 17.842)	0.183 (0.119, 0.280)	0.00
Drug adherence					
Good	227 (46)	17 (36.3)	1		
Fair*	39 (7.9)	33 (6.7)	0.901 (0.321, 2.532)	0.009 (0.00, 0.419)	0.016
Poor	8 (1.6)	7 (1.4)	0.967 (0.317, 2.950)		
HCT count (%)					
<41.5	32 (6.8)	30 (6.1)	0.83 (0.030,0.227)		
41.5-50.4	30 (6.1)	57 (11.6)	0.298 (0.111,0.799)		
>50.4	8 (1.6)	5 (1.0)	1		
<36.9*	80 (16.2)	41(8.3)	0.605(0.232,1.577)	0.040 (0.002, 0.7440)	0.031
36.9-44.6	53 (10.8)	46 (9.3)	0.199 (0.049, 0.810)		
>44.6	7 (1.4)	22 (4.5)	0.163 (0.064, 0.413)		
Do not know	65 (13.2)	17 (3.4)	0.276 (0.108, 0.705)		
INH prophylaxis					
Yes	140 (28.3)	176 (35.6)	3.947 (2.623, 5940)		
No*	135 (27.3)	43 (8.7)	1	42.64 (3.252, 564.590)	0.004
Previous TB					
Yes *	260 (52.6)	158 (32)	0.149(0.082,0.272)	0.063 (0.008,0.498)	0.009
No	15 (3.0)	61 (12.3)	1		
Reason for change					
Due to toxicity	30 (6.1)	20 (4)	0.076 (0.23, 0.248)		
Due to comorbidity	48 (9.7)	6 (1.2)	0.14 (0.004, 0.054)		0.024
Due to treatment failure*	35 (7.1)	34 (6.9)	0.11 (0.036, 0.346)	0.003 (0.00, 0.467)	
Due to pregnancy	158 (32)	123(24.9)	0.089 (0.031,0.25)		
Others	0	1 (0.2)	1		
Do not know	4 (0.8)	35 (7.1)	1		

*significance of associated factors of incidence of TB.

Factors associated with TB in people with HIV

In multivariable logistic regression analysis, marital status, family size, behavioral factors, WHO clinical stage, CD4 count both at diagnosis and present, drug adherence, INH prophylaxis, HCT count, and reason for change were important risk factors for incidence of TB among HIV infected patients. Thus, an individual who was divorced was 0.995% more likely to develop tuberculosis among HIV than an individual who were widowed. Family size greater than five 0.92% times is more likely to develop TB than an individual 1-3, behavioral factors with tobacco user 0.99% more likely than those who were not used, WHO clinical stage is predictor for incidence of tuberculosis among HIV patients; accordingly HIV patients with clinical stage IV 6.5 times more at risk than individual who were enrolled to ART clinic on the first WHO clinical stage. An individual with hematocrit count 36.9% less was 0.96% more likely to acquire TB than an individual with >50.4% and due to treatment failure 0.96% more likely than others reason for change. Other clinical characteristics and co-morbidity were significant predictors of tuberculosis among HIV infected patients in bi variable analysis, but the association was diluted in multivariable analysis.

Total 275 (55.7%) patient developed TB which is more than 136 case conducted in Gondar (Alene *et al.,* 2013). The incidence of TB in our study is 55 case per/100 population which is higher than the estimated annual incidence of 191 case per 100,000 population and with prevalence of 224 cases per 100,000 (WHO, 2014).

This study used cumulative incidence of TB as outcome variable with cumulative incidence rate of tuberculosis among patients of 68.75%. It was higher than in formal of Tanzania, Dares Salaam (27.1%), in Debre Markos hospital, Ethiopia (44%) and at Arba minchi general hospital 21.4% and 5.36 per 100 PY respectively (Dalbo and Tamiso, 2016). However, the finding was higher than studies in Brazil which was 4.62% (Lannoy *et al*., 2008).

This study could establish association between TB and number of people in the household. Divorced marital status 0.995% more likely to develop TB than those widowed which is consistent with earlier studies (Méda *et al*., 2013). Base line WHO clinical staging was strong determinant for incidence of TB, accordingly HIV patients with clinical stage IV were 6.5 times more likely to develop tuberculosis than an individual who started following up on the first WHO clinical stage. The finding was supported by different study done in Ethiopia (Taha *et al.*, 2011; Kibret *et al.*, 2013).

Many studies found that a lower CD4 count was associated with a higher risk of TB (Kruk *et al*., 2011; Méda *et al.*, 2013) which are consistent with our findings where 0.82% CD4 cell count was significant determinant of TB among HIV infected patients. Similarly this study found that patients with hematocrit <36.9% is 0.96% are more likely risk of developing TB than those having >50% at base line. Hematologic complications were risk factors for the incidence of TB. This finding was in line with studies conducted in Ethiopia, Uganda, Tanzania and South Africa (Kerkhoff *et al*., 2015).

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