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ORIGINAL ARTICLE

THE EFFECT OF HIV CO-INFECTION ON TUBERCULOSIS TREATMENT IN A ZONAL REFERRAL HOSPITAL IN ETHIOPIA: A RETROSPECTIVE COHORT STUDY.

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ABSTRACT

Background*: TB/HIV co-infection remains a major public health challenge worldwide. TB co-infection with HIV exacerbates the challenges in diagnosis and treatment of patients. The occurrence of these two diseases together can potentiate one another. This study was designed to determine the effect of HIV co-infection on tuberculosis treatment among tuberculosis patients.*

Methods*: A retrospective cohort study was conducted on 1952 tuberculosis patients. A multinomial logistic regression model was executed to assess the association of TB treatment outcomes with HIV status and other covariates.*

Result*: TB/HIV co-infected patients had significantly lower cure rate than HIV-negative TB patients (10.3% vs 16.7%) with ARR=0.599, P<0.028 and 95%CI= 0.380-0.946. Treatment completion rate was significantly lower in TB/HIV co-infected patients than HIV-negative TB patients (41.2% vs 47.2%) with ARR=0.584, P=0.001 and 95% CI=0.431-0.792. But TB/HIV co-infected patients had significantly higher death rate than HIV-negative TB patients (10.2% vs 2.2%) with ARR=3.053, p<0.001 and 95%CI=1.736-5.378.*

Conclusion and recommendation*:9 The TB treatment outcome was significantly influenced by the HIV co-infection. HIV-positive tuberculosis patients' cure and completion rates were significantly lower while the death rate was higher as compared to the HIV-negative TB patients. Strengthening TB and HIV collaboration activities is important to improve treatment outcome of TB patients.*

Keywords: *Retrospective, tuberculosis, Cure, completion, death*

BACKGROUND

Tuberculosis is one of the top 10 causes of mortality and the leading cause from a single infectious agent. According to the WHO 2018 report, an estimated 10 million people developed TB disease in 2017 globally, 9% were living with HIV and from those living with HIV 72% were in Africa (1). Tuberculosis causes ill health among millions of people each year and ranks nearly parallel to the human immunodeficiency virus (HIV) as a leading cause of death globally (2). TB caused an estimated 1.3 million deaths among HIV negative people and 300,000 additional deaths among HIV positive people (1). WHO reported Ethiopia with the estimated HIV negative TB mortality of 25,000 and HIV positive TB mortality of 3600 in 2017 (1). The FMOH national population-based TB prevalence survey conducted in 2010/2011 reported the prevalence of 108 and 240 per 100,000 population of smear positive and all forms of TB respectively (3).

The 2015 Ethiopian national TB/HIV sentinel report described Tuberculosis and HIV/AIDS as closely interlinked and synergistic diseases with a TB/HIV co-infection rate of 17.6% (4). TB/HIV co-infection remains a major public health challenge worldwide. HIV co-infection with tuberculosis exacerbates the challenges in diagnosis and treatment of patients and poses a huge burden on health service providers and health facilities particularly in African countries (5).

HIV infection speeds up the progression of TB from latent to active TB and TB bacteria also accelerate the progression of HIV infection to AIDS (6). In patients co-infected with *M. tuberculosis* and HIV, compromised immunity and increased other opportunistic infections lead to untimely death, if not properly treated (6). The synergistic effect of TB/HIV co-infection can also affect the prevention and control of TB by increasing the number of suspects and patients, need for human and infrastructure resources, risk of nosocomial TB infection and the risk of multi-drug resistant (MDR) and X-MDR tuberculosis among health workers and others (7).

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Treatment outcome is the evaluation mechanism for the strength and weakness in relation to diagnostic, adherence and effectiveness of treatment in TB patients. Health institutions can use the evaluation output to identify gaps and take corrective actions. To this end, program managers, care providers, and decision makers can institute appropriate decision based on evidence found from these evaluations. Treatment outcome serves as a proxy indicator for the quality of TB treatment provided by a health care system. This study was designed to determine the effect of HIV-infection on treatment outcomes among the Tuberculosis patients registered for treatment in a zonal hospital from June 2008 to June 2014.

It is well established that TB and HIV have synergistic effects on disease progression and that HIV co-infection influences TB treatment outcomes. This study aimed to investigate the magnitude of the influence of HIV co-infection on TB treatment outcome in the study area, to identify other predictor variables that might influence TB treatment outcome and to determine the level of association of HIV co-infection and other covariates on TB treatment outcome in this study area and compare this with other studies.

METHODS

Study design and setting

A retrospective cohort study design was used to determine the effect of HIV co-infection on tuberculosis treatment. Debreberhan referral hospital is found in Amhara National Regional State, North Shoa zone. The hospital has 5 wards, 128 beds and more than 20 service giving rooms at the time of the data extraction. The TB treatment unit of the hospital was receiving newly diagnosed TB patients and transferred-in TB patients from other health facilities. All TB patients who were registered for TB treatment in the hospital benefitted from HIV counselling and testing and their HIV status was recorded as reactive, nonreactive or status unknown on the TB registration logbooks. Full confidentiality was maintained regarding patient records.

Populations

Source population: the source population of the study was all TB patients who were registered for anti-TB treatment in the hospital.

Study population: the study population was all TB patients who were registered for anti-TB treatment in the hospital in the period of June 2008 to June 2014.

Eligibility criteria

Inclusion criteria*:* all TB patients registered for anti-TB treatment in the hospital from June 2008 to June 2014 who were newly diagnosed in the hospital and transferred-in from other health facilities regardless of their stay on treatment were included in the study.

Exclusion criteria*:* TB patient records that did not contain TB treatment outcome and/or HIV status information were considered as incomplete and were excluded from the study.

Sample size determination and sampling

Sample size: Sample size was not calculated prior to the study. But the post hoc power analysis was computed after the data collection using the Gpower software (8). The power value was computed by using the extracted sample size of 1952, a medium effect size of 1.3, and a significance level of 0.05. The result showed a power value of > 0.99 which indicated that the extracted sample was large enough in order to detect the desired effect with the value of 99%.

Enrollment procedure*:* Debereberhan referral hospital was purposefully selected for the study since it was the only referral hospital in the zone at the time of the study. All TB patients who were registered for anti-tuberculosis treatment from July 2008 to June 2014 were included in the study. The TB treatment registration logbooks were reviewed and a total of 1990 registered TB patients were found in the specified period. But 38 of them were excluded from the study due to incomplete information. The remaining 1952 patients were taken as a final sample size to be included in the study. Of these, 600 patients were HIV-positive, 208 were of unknown HIV status and 1072 were HIV-negative TB cases.

Data extraction procedure and data quality: The investigator prepared the data extraction tool in an excel format prior to data extraction. Three data collectors and 2 supervisors participated in the data extraction. The principal investigator gave brief orientation for the research team on the objective of the study, the importance of data quality, and procedures of data extraction. Data completeness, correctness, and consistency of extracted data were checked by the supervisors every day. The investigator also checked the collected data before the data entry started.

Measurement of variables: TB treatment outcome is the dependent variable for this study.

Treatment outcome was assigned for all bacteriologically confirmed and clinically diagnosed TB cases as cured, treatment completed, treatment failed, died, lost to follow-up, and not evaluated based on the WHO definitions and reporting framework for tuberculosis (9). TB treatment was given based on the national treatment program of directly observed treatment short course (DOTs) which was 8 months of treatment (currently 6 months).

The TB cases were categorized into 3 cohorts as HIV-positive coded 1, HIV-status unknown coded as 2, and HIV-negative coded as 3. HIV-positive refers to TB patients tested for HIV antigen/antibody test and recoded as positive on the TB register in HIV result column. HIV status unknown refers to TB patients tested for HIV antigen/antibody test and recoded as indeterminate or not done or unknown on the TB register in HIV result column. HIV-negative refers to TB patients tested for HIV antigen/antibody test and recoded as negative on the TB register in HIV result column.

***Definition of terms**:* Cured: a patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear or culture negative in the last month of treatment and on at least one previous occasion. Treatment completed: - a patient who completed treatment without evidence of failure but with no result to show that sputum smear or culture result in the last month of treatment and on at least one previous occasion were negative either test were not done or because results are unavailable.

Treatment failure: a patient whose sputum smear or culture is positive at 7 months or later during treatment. Died: - a patient who dies for any reason during or before starting the course of treatment. Lost to follow-up: - a patient who did not start treatment or whose treatment was interrupted for the consecutive two months or more. Not evaluated: - a patient for whom treatment outcome not assigned. This includes cases "transferred out" to another treatment units as well as cases for whom the treatment outcome is not known for the reporting unit. Treatment success: - the sum of cured and treatment completed (9).

Data processing and analysis: The data extracted based on the inclusion criteria were entered into the template developed using EpiInfo version 3.5.1and exported to SPSS version 22. The data processing, management and analysis were conducted using the SPSS software. Descriptive statistics were run to show the general characteristics of the study subjects.

A multinomial logistic regression model was executed to assess the association of TB treatment outcomes with HIV status and other predictor variables. The variables with p-value of 0.2 and less with crude odds ratio was entered to the multivariable analysis. The variables that showed association with the TB treatment outcomes in the final model at significance level of 0.05 and confidence level of 95% were considered as statistically significant predictor.

Ethics approval and consent to participate

The ethical approval (Ref. № 310/775/07) was obtained from the National Research Ethics Review Committee (NRERC) of Ethiopia Ministry of Science and Technology prior to commencing of the study. Permission to access the TB patients' records was obtained from the Hospital administration following the ethical approval and based on a support letter from the Addis Ababa Science and Technology University.

RESULTS

Socio-demographic characteristics

A total of 1952 TB patients' records were included in the study. Of these, 600 (30.7%) were TB/HIV co -infected, 1072 (54.9%) were HIV-negative and 208 (14.3%) were of unknown HIV status. Among the HIV-positive TB patients 90.7% and 88.2% were on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) respectively. The majority of patients were urban residents, 1129 (57.8%). Of the total study subjects, 50.3% were female. The socio-economically productive group with the age of 15-34 years old was the most affected segment of the population and accounted for 53.5% of HIV positive TB and 52.6% of only TB cases (Table 1).

Table 1. General characteristics of the study subjects at Debreberhan referral hospital, Amhara region, Ethiopia, 2008-2014.

Characteristics	TB-HIV positive (n=600)	TB-HIV negative (n=1072)	TB-HIV status unknown (n=280)
	N (%)	N (%)	N (%)
CPT started			
Yes	544(90.7)	NA	NA
No	56(9.3)	NA	NA
ART initiated			
Yes	529(88.2)	NA	NA
No	71(11.8)	NA	NA
Sex			
Male	276(46.0)	551(51.4)	144(51.4)
Female	324(54.0)	521(48.6)	136(48.6)
Address			
Urban	404(67.3)	614(57.3)	111(39.6)
Rural	196(32.7)	458(42.7)	169(60.4)
Age category			
0-14	40(6.7)	145(13.5)	85(30.4)
15-24	87(14.5)	360(33.6)	71(25.4)
25-34	234(39.0)	204(19.0)	48(17.1)
35-44	167(27.8)	120(11.2)	30(10.7)
45-54	56(9.3)	118(11.0)	18(6.4)
55+	16(2.6)	125(11.6)	28(13.4)
Tuberculosis type			
Smear positive Pulmonary	126(21.0)	310(28.9)	49(17.5)
Smear negative pulmonary TB	407(67.8)	569(53.1)	181(64.6)

Table 1 continued

Extra pulmonary	**67(11.2)**	**193(18.0)**	**50(17.9)**
Treatment category			
New	529(88.2)	999(93.2)	248(88.6)
Relapse	24(4.0)	15(1.4)	5(1.8)
Failure	0(0.0)	1(0.1)	1(0.4)
Return after default	3({0.5)	3((0.3)	0(0.0)
Transferred in	17(2.8)	33(3.1)	19(6.8)
Others	27(4.5)	21(2.0)	7(2.5)
Treatment success			
Yes	309(51.5)	685(63.9)	83(29.6)
No	291(48.5)	387(36.1)	197(70.4)

ART- Antiretroviral therapy, CPT – co-trimoxazole preventive therapy, NA- Not applicable

Associated factors: TB/HIV co-infected patients had significantly lower cure rate than HIV negative TB patients (10.3% vs 16.7%) with ARR=0.599, P<0.028 and 95%CL= 0.380-0.946. Treatment completion rate was significantly lower in TB/HIV co-infected patients than HIV negative TB patients (41.2% vs 47.2%) with ARR=0.584, P=0.001 and 95%CL=0.431-0.792.

TB patients with HIV infection had significantly higher death rate than HIV negative TB patients (10.2% vs 2.2%) with ARR=3.053, p<0.001 and 95% CL=1.736-5.378. But treatment failure had no significant association with HIV infection (ARR=0.846, P=0.498 and 95%CI=0.521-1.374) (table 2).

Table 2. The multinomial logistic regression analysis output of TB treatment outcomes and associated factors in Debreberhan referral Hospital, Amhara region, Ethiopia, 2008 – 2014.

HIV status		**TB Treatment outcomes**					
		Cured	Completed	Died	Failed	Loss to follow-up	Not evaluated
TB-HIV positive	N (%)	62(10.3)	247(41.2)	61(10.2)	2(0.3)	52(8.7)	176(29.3)
	ARR	0.599	0.584	3.053	0.874	0.846	1
	P-value	0.028	0.001	<0.001	0.836	0.498	--
	95%CI	0.380-0.946	0.431-0.792	1.736-5.378	0.246-3.106	0.521-1.374	--
TB-HIV status unknown	N (%)	13(4.6)	70(25.0)	20(7.1)	0(0)	18(6.4)	159(56.8)
	ARR	0.316	0.272	1.415	--	0.407	1
	P-value	<0.001	<0.001	0.547	--	0.005	--
	95% CI	0.176-0.567	0.189-0.393	0.620-2.464	--	0.217-0.765	--
TB-HIV negative	N(%)	179(16.7)	506(47.2)	24(2.2)	6(0.6)	87(8.1)	270(25.2)

Table 2 continued

	Reference						
Place of Residence							
Urban	N (%)	177(15.7)	602(53.3)	68(6.0)	4(0.4)	109(9.7)	169(15.0)
	ARR	4.651	5.768	4.005	1.526	4.965	1
	P-value	<0.001	<0.001	<0.001	0.376	<0.001	--
	95%CI	3.114-6.947	4.456-7.467	2.504-6.407	0.574-4.053	3.222-7.652	--
Rural	N (%)	77(9.4)	221(26.9)	37(4.5)	4(0.5)	48(5.8)	436(53.0)
	Reference						

The HIV-positive TB patients showed the highest proportion of death in all subgroups of HIV status. From a total number of 105 deaths, HIV-positive TB patients accounted for a proportion of 58.1%. (Figure 1)

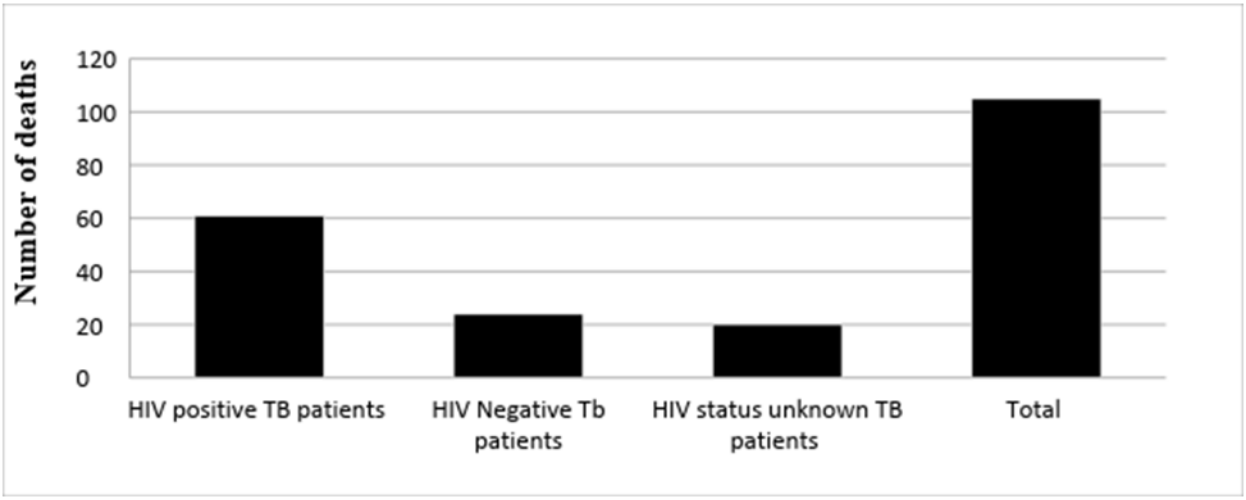

Figure 1. Distribution of TB death with respect to HIV status in Debreberhan referral Hospital, Amhara region, Ethiopia, 2008 – 2014.

DISCUSSION

In this study, the prevalence of TB/HIV co-infection among TB patients registered for treatment in Debireberhan referral hospital was 30.7%. This finding was high as compared with the studies conducted in Northern Ethiopia, Southern Ethiopia, Fenote Selam district hospital, and Mizan Aman General hospital which reported a TB/HIV co-infection prevalence of 4.3%, 10%, 22.1%, and 18.5% respectively(10-13). It was also higher than the prevalence reported from South Eastern Nigeria (17.2%)(2). But this finding was slightly lower than in the study conducted in Ethiopia that reported a prevalence of TB/HIV co-infection of 33%(14). However, the finding of this study was much lower than the study conducted in Northcentral Nigeria which reported a prevalence of 52% TB/HIV co-infection(15). According to the WHO global TB report of 2015, the proportion of TB patients who were known to be HIV-positive were highest in the African Region with a range of 10% in Ethiopia to 73% in Swaziland (5). The possible reasons for this discrepancy might be due to the differences of service quality on TB treatment, low initiation, and utilization of ART, the dual epidemic nature of TB and HIV in the areas, preference of patients to be served in referral hospitals, health infrastructure, economic status, social, and cultural issues.

The current study showed significantly lower TB treatment cure rates among HIV positive TB patients than among the TB only patients (10.3% vs 16.7%) with ARR=0.60, $p<0.03$ and 95% CI= 0.38-0.95. Similarly, HIV positive TB patients showed lower TB treatment completion rates than HIV negative TB patients (41.2% vs 47. 2%) with ARR=0.58, $p<0.001$, 95%CI=0.43-0.79. These findings were consistent with another study conducted in Northcentral Nigeria, which reported lower cure and completion rates of TB treatment in TB/HIV co -infected patients than in only TB infection cases (15). Similar studies conducted in South-Eastern Nigeria (2), India (16) and North-West Ethiopia (17) reported a lower TB treatment cure rate among HIV positive TB patients. Another study conducted in North-West Ethiopia showed lower overall Treatment success rate in HIV positive patients (18).

Moreover, the risk of death was more than 3 times higher in HIV-positive TB patients (10.2% versus 2.2%) than in HIV-negative TB patients with ARR=3.05, $p<0.001$ and 95%CI=1.74-5.38. Likewise, the study conducted in Northcentral Nigeria reported a higher proportion of death in HIV-positive than in HIV-negative TB patients (15).

The other studies conducted in North-West Ethiopia (17), South-Eastern Nigeria(2), North-Eastern Thailand (19), India (16), Western Ethiopia (20), Southern Ethiopia (21), also showed significantly higher outcomes of death in HIV-positive TB patients when compared with HIV-negative TB patients.

The possible explanations for the increased death occurrences among HIV infected TB patients might be due to the nature of HIV infection that suppresses the immune system. HIV infection is the most powerful known risk factor that enhances morbidity, mortality, and opportunistic infections among TB patients (6). TB and HIV are synergistically interacting and exacerbate the problem of diagnosis and treatment (22).

This nature of the two diseases can raise the frequency of premature death of TB patients when occurring concurrently. In the same way, the occurrence of this high death rate of HIV positive TB patients during their TB treatment might be due to immunosuppression, repeated and multiple opportunistic infections and late/no initiation and use of antiretroviral treatment. The occurrence of this higher death rate in HIV positive TB cases might also be associated with poor/ no implementation of the WHO policy on TB/HIV collaborative activities which is important to reduce the burden of HIV in TB patients by improving HIV counseling and testing, provision of co-trimoxazole and early initiation of ART services (23).

The high prevalence of HIV co-infection in TB patients can lead to low TB treatment cure and completion among HIV-Positive TB patients and the frequency of occurrence of death remains high. As a consequence, it poses diagnostic and therapeutic challenges, increases the risk of MDR and X-MDR-TB, nosocomial TB infection, drug-resistant strain TB transmission and high rate of TB recurrence among others (7).

In this study the place of residence showed significant association with TB treatment outcome; urban residents had higher treatment cure and completion rates than rural residents. The death rate was also higher among urban residents. The reasons are not clear. This difference might be due to the higher proportion of rural residents who were not evaluated for treatment outcome because rural residents were transferred out to other health facilities.

Limitations of the study

The data for this study were extracted from the TB register where the variables might not be sufficient enough to show the potential predictors exhaustively. This may introduce incorrect association due to confounding effect of unavailable variables. The excluded cases because of incomplete information might also cause selection bias if their characteristics are different from the included cases. The inference of the result may not be practical in health facilities outside the Debreberhan referral hospital that the nature of patients and level of facilities may have systematic difference. So, the interpretation of the findings may need to consider these limitations.

CONCLUSION

The prevalence of TB/HIV co-infection in this study was high compared with most of the study findings conducted in Ethiopia as per the reviewed literature. TB treatment outcome was significantly influenced by the HIV co-infection. The HIV-positive tuberculosis patients' cure and completion rates were significantly lower while the death rate was higher as compared to the HIV-negative TB patients. The place of residence showed significant association with TB treatment outcome. Strengthening TB and HIV collaboration activities is important to improve treatment outcome of TB patients in general and HIV positive TB patients in particular.

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