Original article

Survival of HIV-TB co-infected adult patients under ART in Ambo Referral Hospital, Ethiopia

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Abstract

Background: HIV infection is the greatest risk factor for acquiring TB infection and developing the disease. TB enhances HIV replication by accelerating the natural evolution of HIV infection; it is the leading cause of sickness and death of people living with HIV.

Objectives: To estimate the survival of HIV/AIDS co-infected patients and to identify predictors of survival based on data obtained from Ambo referral hospital, West Shoa Zone in Oromia Regional State, Ethiopia.

Methods: This retrospective study was conducted based on data collected in 501 cases of HIV-infected TB patients of age 15 years and above who started anti-TB treatment between September 1, 2006 and August 31, 2011 and followed until February 29, 2012. The Kaplan-Meier method and the log-rank test were used to compare the survival experience of different categories of patients. The Cox regression model was employed to identify predictors of mortality.

Results: A total of 79 deaths occurred during the follow up period of 78.66 months. Of these 49 patients died within the first nine months after initiation of the anti-TB treatment and the remaining 30 died after finishing the treatment; the last death occurred at 67.83 months. The overall median survival of the 79 death cases was 27.7 months. The Cox regression analysis showed that initial weight, TB site (pulmonary or extra-pulmonary), WHO clinical stage, functional status and CD4 count were significant risk factors. The most important predictors associated with higher risk of death at 0.05 level of significance were: low initial weight, low CD4 count, WHO stages III and IV as well as ambulatory and bedridden physical conditions.

Conclusion: A careful monitoring of the health status of patients with low initial weight, low CD4 cell count, advanced WHO stages III & IV, ambulatory and bedridden functional status is necessary to improve the survival of HIV-TB co-infected patients at initiation of and during anti-TB treatment. [*Ethiop. J. Health Dev.* 2013;27(2):88-93]

Introduction

According to a WHO report of 2009, the people living with HIV (PLWHIV) are estimated to have a 20 times higher risk of developing TB disease compared to people living without HIV infection in countries with an HIV prevalence of at least 1%. The global impact of the converging dual epidemics of TB and HIV remains as one of the major public health problems or challenges of our time. WHO reported that 9.27 million of the estimated new cases of TB of which occurred in 2007, 31% were in sub-Saharan Africa and about 1.37 million (14.8%) of these being among PLWHIV. About 79% HIV-positive TB incident cases, occurred in Africa in 2007. In the same year, there were 456,000 TB-related deaths among HIV-positive patients accounting for 23% of the global HIV/AIDS mortality. Southeast Asia was the second most affected region with 11% of global new TB cases in 2007 (1).

The latest WHO report on global TB control indicated that there were an estimated 8.8 million incident cases and 1.4 million deaths from TB in 2010, where 1.2 million (12–14%) of the new TB cases were amongst HIV-infected people in 2010, and TB caused the death of an estimated 0.35 million HIV-infected people. The proportion of HIV-TB-co-infected persons is highest in Africa; Africa accounted for overall 82% of TB cases among people living with HIV worldwide in 2010 (2).

HIV infection is the most common predictor of TB incidence, and the other way round, TB is a common opportunistic infection in sub-Saharan Africa. Thus, the countries in the sub-region continue taking the leading position in HIV/TB morbidity and mortality rate, where the TB epidemic was primarily driven by HIV infection. Ethiopia is one among these countries most heavily affected by HIV and TB co-infection. The World Health Organization ranked Ethiopia as seventh among the 22 high burden countries with TB where the estimated annual incidence and prevalence, respectively, were 379 and 643 cases per 100,000 populations (3). The prevalence of HIV among TB patients was estimated as high as 41% (4, 5). The WHO global report 2008 estimated that in Ethiopia 40% of TB patients tested for HIV were found to have been HIV-positive. In Ethiopia routine data obtained from 44 locations in the year 2005/6 showed that about 41% of TB patients were HIV-positive. In addition, another routine data set collected in 2006/07 estimated that some 31% of TB patients were HIV-positive (6). TB was the cause of 76,000 deaths in Ethiopia, out of which 30% were among HIV-positive patients (1). In addition to rate of mortality caused by the co-infection the extent of the negative impact on the

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quality of livelihood resulting from mental disorders was studied (7, 8).

Given the above introduction about HIV-TB co-infection, its prevalence and rates of mortality in the developing world in general and in Ethiopia, in particular, this study had the objectives to estimate survival and identify risk factors of HIV-TB co-infected patients during TB treatment.

Methods
This was a retrospective study based on 501 cases of HIV-infected TB patients of age 15 years and above who received anti-TB treatment in Ambo referral hospital, in Ambo, Oromia Regional State, Ethiopia between September 1, 2006 and August 31, 2011 and followed until February 29, 2012.

The Hospital started providing free ART service in 2006. It had a separate ART clinic and units for ART follow up for PLWHIV. Data about HIV infection were extracted from the available medical registers that were designed by the Federal Ministry of Health (FMOH) for uniformity of use in the country in order to document relevant clinical and laboratory variables. The registers included the Pre-ART register (register of patients at their first visit), the ART register (registration after ART initiation), and the follow-up patient form. The hospital also has a separate clinic and units for TB treatment and follow-up. Data regarding TB treatment and follow-up were recorded in standard register forms prescribed by FMOH. For this study, both ART and TB registers were thoroughly reviewed to record information about HIV infected persons who started ART and had been under anti-TB treatment.

The Hospital top management gave approval to access the patient register forms upon a request made by Addis Ababa University. The data were collected by a data clerk from the hospital and a statistician. Patient intake and follow up forms were cross examined for inconsistencies so that data quality could be ensured. After coding and cleaning of the data the analysis was done using SPSS, SAS, and STATA software.

The response/outcome variable of this study was survival time. In this study the length of survival time an adult HIV-TB co-infected patient had lived (measured in months) from start of anti-TB treatment until the date of death. The predictor/explanatory variables included in the study were: age (in years), sex (male, female), marital status (never married, married, other status), body weight (in kgs.), level of education (no education/illiterate, primary, secondary or above), substance (smoking, alcohol) use (no, yes), CD4 cells count (cells/mm^3), site of TB, WHO clinical stages (stages I, II, III and IV), functional status (working, ambulatory, bedridden), and type of regimen (D4T-based, AZT-based). A person (a patient in this case) who is able to perform usual work in and out of the house, perform normal activities, play or go to school (for children) is considered as working. On the other hand a patient who is capable of performing activities for daily living is considered as ambulatory while one who is unable to perform such activities is bedridden (6). Combinations of drugs that contain the regimen AZT and D4T in the treatment of TB co-infection are labeled as AZT-based and D4T-based, respectively.

Tuberculosis site means locality of the disease in the human body. It is a known fact that TB can affect virtually any tissue or organ but most commonly it affects the lungs; it also occurs in other sites most commonly pleura, lymph nodes, spine, joints, genito-urinary tract, the nervous system or abdomen, and it represents 14% of all TB cases in the world and 12% of all TB in high burden countries. TB infection is broadly classified into pulmonary tuberculosis (PTB) (accounting for 85% of all tuberculosis cases) and, extra-pulmonary tuberculosis (EPTB) (comprising 15% of all tuberculosis cases). Pulmonary tuberculosis is further classified into smear-positive PTB accounting for 75-80% of all PTB and smear-negative PTB that accounts for about 20-25% of all PTB cases worldwide (6). For the data used in this study it was not possible to distinguish between smear-positive and smear-negative PTB cases Hence, on account of the background provided above, it is believed that most of PTB cases were likely to be smear-positive.

Results
Among the study subjects 248 were females and 253 were males; 291 were married, 97 were never married, and the marital status of 113 was not established;114 were illiterate, 216 had primary level of education, 141 completed at least high school education; while 306 had no habit of substance use the remaining 195 were exposed to substance use; 181 and 320, respectively, had EPTB and PTB; 120, 44 and 337 had ambulatory, bedridden and working functional status; WHO clinical stages III and IV prevailed in 307 and 95 cases, respectively, while 99 cases were in WHO stages I and II. There were 215 and 286 subjects, respectively, to whom regimen types AZT and D4T were prescribed (Table 1).

The overall median age, weight and CD4 cell count of the HIV-TB co-infected patients after initiation of anti-TB treatment were: 31 years (inter-quartile range 27-38 years), 48 kgs. (inter-quartile range 42.5-54 kgs.) and 137 cells/mm^3 (inter-quartile range 65-226 cells/mm^3) with median survival time 27.7 months (inter-quartile range 9.56-44.60 months). For the deceased patients the median age, weight and CD4 cell count after initiation of anti-TB treatment were: 30 years (inter-quartile range 26-35 years), 42 kgs (inter-quartile range 30.5-49 kgs) and 69 cells/mm^3 (inter-quartile range 40-106 cells/mm^3) with median survival time 7 months (inter-quartile range 4.86-14.56 months) (Table 2).

Table   1: **Distribution of the categorical socio-demographic and health predictors/variables of HIV-TB co-infected patients taking anti-TB treatment in Ambo referral hospital, Ambo, Ethiopia, 2012 (n=501).**

Demographic and health Predictors/variables		Status of censoring or event			
		Total	Death	Censored	Death (%)
Sex	Female	248	41	207	16.5
	Male	253	38	215	15.0
Marital status	Never Married	97	20	77	20.6
	Married	291	39	252	13.4
	Others	113	20	93	17.7
Level of education	No Education	144	21	123	14.6
	Primary	216	35	181	16.2
	Secondary or above	141	23	118	16.3
Substance use (tobacco, alcohol)	No	306	46	260	15.0
	Yes	195	33	162	16.9
TB site	EPTB	181	17	164	9.4
	PTB	320	62	258	19.4
Functional status	Ambulatory	120	27	93	22.5
	Bedridden	44	19	25	43.2
	Working	337	33	304	9.8
WHO clinical stage	Stage I or II	99	5	94	5.1
	Stage III	307	49	258	16.0
	Stage IV	95	25	70	26.3
Regimen type	AZT-based	215	30	185	14.0
	D4T-based	286	49	237	17.1

Table   2: **Summary statistics related to the continuous variables included in the study of HIV-TB co-infected patients taking anti-TB treatment in Ambo referral hospital, Ambo, Ethiopia, 2012 (n=501)**

Patient Status	Continuous Variable	Min.	Max	Median	Q_1	Q_3
Censored	Survival time	1	78.66	31.89	15.37	46.51
	Age	17	78	31	27	38
	Weight	15	78	49	44	55
	CD4 count	6	699	159	80	244.75
Death	Survival time	9.20	67.83	7.03	4.86	14.56
	Age	19	57	30	26	35
	Weight	16	64	42	30.5	49
	CD4 count	2	514	69	40	106
Overall	Survival time	0.9	78.66	27.7	9.56	44.6
	Age	17	78	31	27	38
	Weight	15	78	48	42.5	54
	CD4 count	2	699	137	65	226

From the total of 501 patients included in this study 79 subjects (15.8%) died during the follow-up time. Of these 49 patients died within the first nine months after initiation of the anti-TB treatment; the remaining 30 died after finishing the treatment. The minimum and maximum survival lengths among the latter group were 9.2 months and 67.8 months, respectively.

A log-rank test was performed to check for existence of any significant differences in survival experience between/among various levels of the categorical variables included in the study. The results showed no significant differences in survival experiences between/among the categories of sex, marital status, education, substance use, and regimen and, therefore,

they were *statistically* non-significant for consideration in the subsequent analysis. On the other hand, differences in survival were observed among the categories of TB site, functional status and WHO clinical stage. These and the remaining two continuous variables namely, weight and CD4 cell count were included for consideration in the Cox multiple regression model. We note, however, that in the result provided below a comparison about survival differential will be made between the baseline CD4 count and a higher category where a 50 cells/mm^3 increase of CD4 count for ease of understanding the risk.

The bivariate regression analysis with single factors/predictors indicated that not all were important to

be included in the multivariable analysis stage on the basis of the selection/elimination with the lax criterion of 0.25 level of significance. This selection process gave rise to a Cox regression model that included only five covariates namely, weight, TB site, functional status, WHO clinical stage and CD4 count; these were found significant at 0.05 level. Further checks for confounding and interactions showed that there were no confounders and interaction terms. The regression model with the above covariates was accepted as a provisional model. After further checking for the validity of the provisionally accepted model the model containing the five main effects covariates was accepted as the final model (Table 3).

Table 3: **Results of the multiple Cox regression analysis about HIV-TB co-infected patients taking anti-TB treatment in Ambo referral hospital, Ambo, Ethiopia, 2012, (n=501)**

Factors/variables	Sig.	Estimated Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Weight	<0.0001	0.915	0.891	0.939
TB site – PTB	0.0033	2.330	1.326	4.096
Ref. group (EPTB)				
Functional Status	0.0080			
Ambulatory	0.0098	2.057	1.190	3.555
Bedridden	0.0062	2.423	1.285	4.568
Ref. Group (working)				
WHO	0.0105			
WHO III	0.0250	2.918	1.144	7.442
WHO IV	0.0032	4.416	1.647	11.839
Ref. group (WHOI/II)				
CD4	<0.0001	0.992	0.988	0.995

In the remaining part of this section interpretations of the results are given using estimated hazard ratios and their respective estimated 95% confidence intervals.

Weight: The estimated hazard ratio for weight, $\overline{HR} = 0.915$ [95% CI: 0.891-0.939, p<0.0001]. Suppose we took an increment of weight by five kgs to make comparisons. Then, the estimated hazard ratio for a five kgs increase in initial weight is $0.64 = \exp(-0.08927 \times 5)$. This means that the risk of death of a patient whose weight was 5kgs higher than another patient in the immediate lower weight category was 36% lower controlling for other covariates.

CD4 cell count: For CD4 cell count the estimated hazard ratio, $\overline{HR} = 0.992$ [95% CI: 0.988-0.995, p<0.0001]. For appropriateness of interpretation we took the estimated hazard ratio for a 50 cells/mm^3 increase in the baseline CD4 cell count which is $0.657 = \exp(-0.00838 \times 50)$. This means that patients whose CD4 cell count was higher by 50cells/mm^3 died at hazard rate lower by 34.3% relative to the next immediate lower category of CD4 cell count group controlling for other variables in the model.

TB site: The estimated hazard ratio of PTB compared to EPTB was $\overline{HR} = 2.33$ [95% CI: 1.326 - 4.096, p=0.0033] revealing that the rate of dying among patients with PTB was 2.33 times higher than among EPTB patients controlling for other variables in the model.

Functional status: Patients with ambulatory and bedridden functional status had $\overline{HR}=2.057$ [95% CI: 1.190-3.555, p=0.0098] and $\overline{HR} = 2.423$ [95% CI: 1.285-4.568, p=0.0062], respectively. These results showed that the risk of death in ambulatory and bedridden patients were, respectively, 2 times and 2.4 times higher than for patients with working functional status. Patients with bedridden status for comparison to ambulatory had $\overline{HR} = 1.18 = \exp(0.885-0.721)$ indicating that bedridden patients were 18% more likely to die than those with ambulatory functional status controlling for other variables in the model.

WHO stages: For patients in WHO stages III and IV the respective $\overline{HR} = 2.918$ [95% CI: 1.144-7.442, p=0.025] and $\overline{HR} = 4.416$ [95% CI: 1.647-11.839, p=0.0032] in comparison to that of stages I/II controlling for other variables in the model. This indicated that the hazards of death were, respectively, almost 3 times higher in stage III and 4.4 times higher in stage IV compared with the risk in stages I/II (both of which were similar). On the other hand, the estimated hazard ratio of stage IV compared to stage III is $1.51 = \exp(1.48525-1.07090)$ suggesting that patients in stage IV were about 50% more likely to die than patients in stage III controlling for other variables in the model.

Discussion
The current study found that initial weight, baseline CD4, TB site, functional status and WHO clinical stage were significant predictors of survival of HIV-TB co-infected patients under anti-TB treatment. In the following part we discuss findings obtained in similar research undertakings to find out if those findings corroborate or discord our results.

The impact of CD4 cell count on survival rate had been assessed by several studies the findings of which showed that the depletion of CD4 cell count was associated with

high risk of death. A retrospective cohort study (9) conducted in Ouagadougou, Burkina-Faso showed that CD4+ T-cell count < 50 cells/mm^3 at HAART initiation was associated with a two-fold higher risk of TB. A study conducted in southwest Ethiopia indicated that a CD4 lymphocyte count less than 200 cells/mm^3 was associated with the development of active TB in people living with HIV/AIDS (10). A study conducted in South Africa suggested that CD4+ T-lymphocyte count 200 cells/mm^3 was associated with progression of AIDS (11). A study conducted in Barcelona, Spain (12) revealed that survival was worst among patients with <200/mm^3 CD4 cells ($\overline{\overline{HR}}$ = 1.8, 95% CI 1.2-2.7) (12). A study conducted in Brazil indicated that CD4 count <200/mm^3 was a significant risk factor of death of HIV-TB co-infected patients (13). The finding of the current study was in agreement with the findings cited above.

A retrospective study conducted in Hawassa University referral hospital, Ethiopia, showed that bedridden functional status was one of the major risk factors that shortened the longevity among PLWHIV co-infected with TB (14). The current study indicated that being ambulatory and bedridden functional status significantly affected the survival of HIV-TB co-infected patients.

According to the WHO (9), clinical stages III and IV had significant impact on survival by increasing the incidence of TB among PLWHIV. Advanced WHO clinical stages accelerated mortality among TB patients living with HIV (10). The findings in (15) indicated that WHO clinical stage was identified as a risk factor of HIV-TB co-infection. The current study also showed that advanced WHO clinical stages III and IV were risk factors of mortality among HIV-TB co-infected patients.

Initial weight was reported as a risk factor of TB activation among PLWHIV (10). A study conducted in South Africa suggested that initial weight predicted mortality of HIV -TB co-infection (16). The current study also identified initial weight as a risk factor.

Several studies suggested that the occurrence of PTB was more frequent than EPTB among PLWHIV. Among HIV co-infected patients PTB was more serious than EPTB as a cause of death (15). A study conducted in Dar-es-Salaam, Tanzania, showed that, out of a total of 300 TB patients tested for HIV, in which 175 (58.3%) were HIV-infected 104 of the TB patients that were admitted died. About two-thirds of the patients, who died had PTB in which a significantly higher proportion of deaths occurred among HIV-infected TB patients (29.1% *versus* 15.2%) than among HIV-negative TB patients (p=0.005) (17). The findings of (18) based on a study in Manipur, India suggested that the site of TB was a risk factor of vulnerability of the HIV infected persons to TB. An ecological study made in Oromia regional state, Ethiopia showed associations between prevalence of HIV infection and the incidence of smear-positive tuberculosis, smear-negative tuberculosis and EPTB (19). The current study also identified PTB significantly affected the survival of HIV-TB co-infected patients.

Conclusion and Recommendations
This study provided some information about risk factors that impact the survival of HIV patients during TB treatment. It also identified the extent of risk of death caused by those factors during and after ant-TB treatment.

In this retrospective study the survival status and determinants of mortality of 501 HIV-TB co-infected patients who received anti-TB treatment at Ambo referral hospital was investigated. The patients received the treatment from September 1, 2006 to August 31, 2011, and were followed up until February 29, 2012. The minimum follow-up time was 0.9 month and the maximum was 78.66 months. The mortality rate was very high in the earlier months of the treatment period and stabilized in later stages. Initial weight, TB site, functional status, WHO clinical stage and baseline CD4 cell affected the survival of the patients significantly at 0.05 levels. Low initial weight, PTB, ambulatory and bedridden functional status, advanced WHO clinical stages (III and IV) and low baseline CD4 cell count were found to be highly associated with high rates of mortality.

The findings of the current study suggest that HIV-positive patients should be told about their health status after positive TB diagnoses in order to make them aware of the risk of not taking anti-TB treatment. For such patients medications and treatment must be affordable and easy to access. To that effect all concerned bodies in the country, especially FMOH and allied organizations, are expected to avail resources.

A limitation of the current study is the subtle assumption that all deaths were caused by HIV/TB co-infection.

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