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ORIGINAL RESEARCH

Factors Affecting Survival Rates Among Adult TB/HIV Co-Infected Patients in Mizan Tepi University Teaching Hospital, South West Ethiopia

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Background: Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection was responsible for approximately 300,000 deaths worldwide in 2017. Despite this burden of death, factors associated with the survival of TB-HIV co-infected patients were not adequately studied; and some of the existing evidences are inconsistent. This study was aimed to identify factors associated with survival rates of TB/HIV co-infected patients.

Methods: The current study was a retrospective analysis of data extracted from 364 TB/HIV co-infected patients treated at Mizan Tepi University Teaching Hospital, Ethiopia, during the years 2007–2017. Time to event was measured from the date of TB treatment initiation till death, loss to follow-up or completion of treatment. Since the event was death, patients lost from follow-up and those on follow-up were considered as censored. Using Cox-regression, the 95% CI of hazard ratio (HR) and P-value <0.05 were used to identify the significant variables in multivariable analysis.

Results: All the 364 patients were followed up for 1654 person-months. There were 83 (22.8%) deaths and the majority, 38 (45.8%), were occurring within the first two months of anti-TB treatment initiation. The overall incidence rate and median survival time were 5.02 per 100 person-months (95% CI: 4.05, 6.22) and 10 months, respectively. Not using CPT (adjusted hazard ratio [AHR] =1.72; P=0.023), bedridden functional status (AHR=2.55; P=0.007), not disclosing HIV status (AHR=4.03; P<0.001) and CD4 < 200 cells/mm^3 (AHR=6.05; P<0.001) were factors associated with survival rates of TB/HIV co-infected patients.

Conclusion: Our finding signals that care and attention should be given to the victims of these synergistic diseases. There is room to improve the survival of the patients if those with low CD4 count and bedridden functional status are closely monitored; and if CPT is promptly initiated with encouraging HIV status disclosure.

Keywords: TB/HIV, co-infection, survival rate, MTUTH

Introduction

TB/HIV co-infection synergistically increases the adverse effects of both diseases and complicates a number of factors such as epidemiology, pathology, clinical presentation, treatment, and prevention.[1]

It has also social, economic and political crises as consequences.[2,3] The most common consequences are stigma, high susceptibility to other comorbidities like mental disorders, cost of care, increased number of orphans and decreased productivity due to long time illness and absence from the workplace.[2,3] In most of the

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situations, this co-infection affects the productive segment of the population and increases the crisis by many folds, especially for low-income countries like Ethiopia.[4]

For people living with HIV/AIDS (PLWHA), the risk of developing TB is estimated to be between 17–23 times greater than those without HIV infection in 2017. Globally, the proportion of HIV-positive patients died during the TB treatment was 11%, in the same year.[5,6]

TB was the leading cause of death among people with HIV and there were about 300,000 people died from HIV-associated TB in 2017, in which the masses of deaths (84%) occurred in Africa.[6]

Ethiopia is among the 30 high TB/HIV burden countries and out of the TB patients with known HIV status, about 11% were HIV co-infected. It was estimated that there were about 3600 deaths due to TB-HIV co-infection in 2017.[5,7] On the top of the knowledge gap, the problems of lay beliefs, misconceptions, and prejudices regarding TB/HIV co-infection are other devastating issues in Ethiopia; since these all might contribute to delay from care and in turn for poor survival among co-infected patients.[8–10]

Currently, there is no published study in the study area on factors associated with survival rate of TB/HIV co-infected patients; although it is nearest to Gambella region, which is among the regions with higher TB/HIV co-infection in Ethiopia and from where also a significant number of TB/HIV co-infected patients come to Mizan-Tepi University Teaching Hospital (MTUTH).

In addition, studies conducted in the North West and the southwest part of Ethiopia identified inconsistent predictors.[11,12] This study was aimed to identify the factors associated with the survival rate of TB-HIV co-infected adult patients in MTUTH.

Methods

Study Design and Setting

A retrospective analysis of data was done for TB/HIV co-infected patients enrolled from July 2, 2007, to July 1, 2017, at Mizan Tepi University Teaching Hospital. Each patient was followed up retrospectively from the date of TB treatment initiation till death, loss to follow-up or completion of treatment. Since the event was death, patients lost from follow-up and those on follow-up were considered as censored. The hospital is found in Mizan-Aman town, which is 593 km to South West of Addis Ababa, the capital of Ethiopia. The hospital started offering free ART services in 2006. About 5946 PLWHA were enrolled till January 2019 and among these 1830 were active. Assessment for TB was being done routinely for every HIV patient. Similarly, if their test results become positive, all TB patients were supported to know their HIV status and linked to the ART clinic.

Study Population and Sampling Techniques

All adult TB/HIV co-infected patients, who received care from MTUTH and being on anti-TB from July 2, 2007, to July 1, 2017, were included. Patients who started ART earlier than six months before the diagnosis of TB and later than two months after the diagnosis of TB were excluded. Stopping ART for any reason during TB treatment is one of the exclusion criteria since it is the known risk factor that increases death by many folds. Additionally, incomplete registries, transfer-out, and death on the same day of anti-TB treatment initiation were excluded.

The sample size was determined using the online calculator for test time-to-event data for the Cox proportional hazard.[13] The CD4 count ≤50 is a known predictor of mortality and used to classify the groups into two (ie subjects with CD4 count ≤50 cells/mm^3 and subjects with CD4 count >50 cells/mm^3).[4,14] Using the parameters (power=80%, type one error rate=5%, hazard ratio=2.31, overall probability of event=13% and proportion of sample in group of subjects with CD4 count ≤50 cells/mm^3=38.7%) from previous study,[15] the sample size became 364. The samples were selected by simple random sampling technique after listing the medical registration number of all 670 eligible records as a sampling frame.

Data Extraction Technique and Data Quality Control

Data were extracted using a data extraction tool adapted from national ART and anti TB treatment standard registries. Data sources were standard registries of ART and anti-TB treatments, electronic format, patient medical record (card) and intake forms. Two trained nurses each from the ART and TB clinics of the hospital extracted the data. The trained supervisor supervises all the extraction processes. Both the supervisor and principal investigator daily checked the completeness and consistency of checklists during data extraction. Socio-demographic, clinical,

behavioral and health service-related baseline data were extracted from the sources.

Data Entry, Processing and Analysis

Data were entered into Epi data 3.1 and exported to SPSS version 21 for analysis. Exploration of the data was done to check the missing values, outliers, and proportionality of hazards over time. Continuous variables were described using means and medians with respective 95% CI; while categorical variables were described using counts, percentages and tables. The median survival time, survival probability and the incidence rate were determined. The association between the independent variables and outcome variable was assessed by the Cox-proportional hazard model, and hazard ratio (HR) was used as a measure of association. The survival status of TB/HIV co-infected patients was presented by the life table.

All variables with p-value ≤0.25 and/or clinical importance were candidates for the final model. By using a backward stepwise likely hood ratio technique and p-value <0.05 the final significant factors were identified.

Ethical Consideration

The study proposal was approved by an institutional review board (IRB) of Jimma University. A support letter was obtained from the IRB of Jimma University to MTUTH administrator's office. Confidentiality was assured strictly. In addition, patient identifiers (medical registration number and ART unique number) were replaced by a new identification number during data extraction and the name of the patients was not used.

Results

Characteristics of the Cohort

Among eligible 670 patients, 364 were included in the study. The mean age (±SD) of the participants was 30.52 (±9.03). From the total participants, 211 (58%) were females and 64 (30.3%) of them died during anti TB treatment giving the sex ratio (female to male) of death as 3.4 (64/19).

Similarly, among 150 (41.2%) married participants, 15 (10%) experienced death. Regarding the educational status more than one third, 133 (36.5%) had attended secondary school and out of them more than a quarter, 35 (26.3%) were encountered death (Table 1).

Participants with a baseline CD4 count of less than 200 cells/mm^3 were 124 (34.1%) and more than half, 73 (58.9%) of them died during the follow-up period. The significant proportion, 232 (63.7%) of the study participants had one or two opportunistic infections other than TB; among these, 57 (24.6%) had the outcome of death. The proportion of death among cotrimoxazole preventive therapy user participants [283 (77.7%)] was 15.9% (Table 2).

From the total subjects included in the study, the disclosure status of two participants was not recorded. About three fourth, 270 (74.6%) disclosed their HIV status to family or any other and out of these 18 (6.7%) have died. On the other hand, among the 92 (25.4%) participants who did not disclose their status to anybody, 65 (70.7%) were experienced death.

Survival Status and Associated Factors

Three hundred sixty-four participants were followed for a total of 1654 person-months. There were 83 (22.8%) deaths and 41 (11.3%) loss to follow-up. From the total deaths, 38 (45.8%) occurred within the first two months of anti-TB treatment initiation. The overall incidence rate of death was 5.02 per 100 person-months (95% CI: 4.05, 6.22). The median survival time was around the 10th month. Survivals at 2, 6 and 12 months after initiating TB treatment were 82.02%, 73% and 45% respectively (Table 3).

The factors significantly associated with the survival rate of TB/HIV co-infected patients were; not using CPT (AHR=1.72; 95% CI: 1.08, 2.74), bedridden functional status (AHR=2.55; 95% CI: 1.29, 5.06), not disclosing HIV status (AHR=4.03; 95% CI: 2.21, 7.35) and CD4 count of less than 200 cells/mm^3 (AHR=6.05; 95% CI: 2.83, 12.95) (Table 4).

Discussion

This study revealed that there were 22.8% deaths among TB/HIV co-infected patients during TB treatment and this finding is comparable to the studies done in Ethiopian towns, Jimma[11] and Bahirdar;[12] but higher than the Guinean finding.[16] The overall incidence rate was 5.02 per 100 person-months, which is comparable to a study done in Bahirdar.[12] The comparability of death rates in Ethiopian studies and higher than Guinean finding are suggestive for Ethiopia's rank of being among TB/HIV high burden countries in the world and the need of future high attention and priority particularly for the timely achievement of ending both epidemics.[7,17]

The majority of the deaths, 38 (45.8%) occurred within the two months of anti-TB treatment commencement. This is more than two times higher compared to finding from South

Table 1 Baseline Socio-Demographic Characteristics of Study Subjects in MTUTH, South West Ethiopia, 2007–2017

Variables	Category of Variables	N (%)	Status	
			Censor	Death
			N (%)	N (%)
Age	15–24	91 (25)	69 (75.8)	22 (24.2)
	25–34	160 (44)	120 (75)	40 (25)
	35–44	81 (22.2)	65 (80.2)	16 (19.8)
	≥45	32 (8.8)	27 (84.4)	5 (15.6)
Sex	Male	153 (42)	134 (87.6)	19 (12.4)
	Female	211 (58)	147 (69.7)	64 (30.3)
Educational status	No education	70 (19.2)	56 (80)	14 (20)
	Primary (grade 1–8)	80 (22)	55 (68.8)	25 (31.2)
	Secondary (grade 9–12)	133 (36.5)	98 (73.7)	35 (26.3)
	Tertiary (college/university)	81 (22.3)	72 (88.9)	9 (11.1)
Marital status	Never married	140 (38.4)	96 (68.6)	44 (31.4)
	Married	150 (41.2)	135 (90)	15 (10)
	Divorced	37 (10.2)	26 (70.3)	11 (29.7)
	Widowed	37 (10.2)	24 (64.9)	13 (35.1)
Occupation	Gov't employed	48 (13.2)	42 (87.5)	6 (12.5)
	Private organization employed	31 (8.5)	28 (90.3)	3 (9.7)
	Jobless	44 (12.1)	37 (84.1)	7 (15.9)
	Student	46 (12.6)	41 (89.1)	5 (10.9)
	Farmer	35 (9.6)	30 (85.7)	5 (14.3)
	Commercial sex worker	42 (11.5)	16 (38.1)	26 (61.9)
	Merchant	83 (22.8)	57 (68.7)	26 (31.3)
	Housewife	35 (9.6)	30 (85.7)	5 (14.3)
Place of residence	Within the catchment area	261 (71.7)	200 (76.6)	61 (23.4)
	Out of the catchment area	103 (28.3)	81 (78.6)	22 (21.4)
Having HIV-positive family member (n=362)[a]	No	100 (27.6)	78 (78)	22 (22)
	Yes	262 (72.4)	201 (76.7)	61 (23.3)

Note: [a]Two participants had no records on either they had HIV positive family members or not.

Africa.[16] The difference might be due to the dissimilarity of study designs and populations. The current finding is fairly comparable with a study conducted in Malaysia[18] and Cameroon.[16] This is suggestive for the need of appropriate management of drug interactions and overlapping toxicities of anti TB and ART drugs, immune reconstitution inflammatory syndrome (IRIS) and other OIs which were factors highly associated with early deaths in TB/HIV co-infected patients.[19–21]

The death among females was tripled compared to males in our study, and this might be the result of high social responsibility among females in the society due to which they may not take care of their health. This finding is higher than the Cameroonian finding[22] and the inconsistency might be attributable to the difference in sample size which was smaller in the previous study.

The survivals at 2, 6 and 12 months after initiating TB treatment were 82.02%, 73% and 45% respectively. This is lower than the Malaysian finding.[18] This might be due to the pioneering efforts in Malaysia to combat TB/HIV co-infection; which was evidenced by its early achievement of the first and third 90s of UNAIDS' 90-90-90 target.[23]

Patients who did not use CPT were nearly two times (AHR=1.72) at higher risk of death and in agreement with this, a study conducted in Bahirdar revealed that not taking CPT was significantly associated with mortality among TB/HIV co-infected patients during TB treatment.[12] Severe bacterial infections and malaria, which can be

Table 2 Clinical Characteristics of Study Participants in MTUTH, South West Ethiopia, 2007–2017

Variables	Category of Variables	N (%)	Status	
			Censor	Death
			N (%)	N (%)
CD4 count	<200 ≥200	124 (34.1) 240 (65.9)	51 (41.1) 230 (95.8)	73 (58.9) 10 (4.2)
ART regimen	First line Second line	343 (94.2) 21 (5.8)	267 (77.8) 14 (66.7)	76 (22.2) 7 (33.3)
Use of CPT	Yes No	283 (77.7) 81 (22.3)	238 (84.1) 43 (53.1)	45 (15.9) 38 (46.9)
OIs other than TB	No at all One or two At least three	105 (28.8) 232 (63.7) 27 (7.4)	93 (88.6) 175 (75.4) 13 (48.1)	12 (11.4) 57 (24.6) 14 (51.9)
ART failure history	Yes No	21 (5.8) 343 (94.2)	14 (66.7) 267 (77.8)	7 (33.3) 76 (22.2)
Functional status	Working Ambulatory Bedridden	139 (38.2) 149 (40.9) 76 (20.9)	126 (90.6) 137 (91.9) 18 (23.7)	13 (9.4) 12 (8.1) 58 (76.3)
WHO clinical stages	One Two Three Four	60 (16.5) 51 (14) 220 (60.4) 33 (9.1)	51 (85) 46 (90.2) 167 (75.9) 17 (51.5)	9 (15) 5 (9.8) 53 (24.1) 16 (48.5)

Abbreviations: ART, anti retroviral therapy; CPT, cotrimoxazole preventive therapy; CD4, Cluster of differentiation four; TB, tuberculosis; OIs, opportunistic infections; BMI, body mass index; WHO, World Health Organization.

successfully prevented by CPT, might be attributable to the higher risk of death among CPT nonusers.[14,24,25]

The majority, 70 (92.1%) of the bedridden patients were on first-line ART and the remaining 6 (7.9%) were on second-line ART. Though they were on ART, their risk of death was two and a half times (AHR=2.55) higher compared to those who had working functional status. This is similar to the findings of the studies conducted in Jimma and Ambo.[11,26,27] This might be due to the delayed presentation of bedridden patients to care after developing numerous infections and complications which were in turn associated with poor survival.[10,18]

The bidirectional and synergistic effect of TB and HIV infection has a profound impact on the survival of TB/HIV co-infected patients. Latent or active TB activates CD4 cells to be captured by HIV and HIV depletes CD4 cells, which in turn accelerates the progression of latent TB to active TB disease.[1,28] CD4 count of less than two hundred cells per cubic millimeter was significantly associated with poor survival of TB/HIV co-infected patients in this study (AHR=6.05). This is supported by previous findings from different parts of the world including Ethiopia. Although the current estimation is consistent with the findings from Bahirdar and Malaysia, it is higher compared to that of a study conducted in Brazil.[12,15,18] This might be due to the categorization CD4 count into small intervals in a previous study.

Failure to disclose status puts TB/HIV co-infected patients and their families at a higher risk of death. It prevents other at risk family members from being tested; and patients who do not disclose their status are highly likely to be lost to follow-up, as they cannot explain their ongoing need to visit health institutions.[29] In the current study, patients who did not disclose their HIV status to anybody were about four times (AHR= 4.03) at higher risk of death than those who disclosed their status. This is in line with the finding of the study done in Jinka, Ethiopia.[30]

Table 3 Overall Life Table of TB/HIV Co-Infected Patients in MTUTH, South West Ethiopia, 2007–2017

Time in Months	Number at Risk	Number of Events	Proportion of Events	Proportion Surviving	Cumulative Proportion Surviving[a]
0	354.5	38	0.11	0.89	0.89
2	295	24	0.08	0.92	0.82
4	177	11	0.06	0.94	0.77
6	52.5	3	0.06	0.94	0.73
8	16.5	5	0.3	0.70	0.51
10	9.5	1	0.11	0.89	0.45
12	8	0	0	1	0.45
14	8	0	0	1	0.45
16	6	1	0.17	0.83	0.38
18	2	0	0	1	0.38
20	0.5	0	0	1	0.38

Note: [a]The proportion of case surviving from the start of the table to the end of the interval.

Table 4 Multivariable Cox-Regression Analysis of Factors Associated with Survival Rate of TB/HIV Co-Infected Patients in MTUTH, South West Ethiopia, 2007–2017

Variables	Category of Variables	CHR	P-value	AHR	95% CI		P-value
Sex	Male	1		1			
	Female	2.74	0.000**	1.27	0.63	2.55	0.508
Educational status	No education	1		1			
	Primary	1.44	0.277	1.44	0.63	3.25	0.386
	Secondary	1.19	0.573	1.05	0.45	2.45	0.913
	Tertiary	0.48	0.088**	1.32	0.37	4.71	0.669
Marital status	Never married	0.81	0.515	0.85	0.45	1.61	0.623
	Married	0.244	0.000**	0.87	0.40	1.91	0.732
	Divorced	0.90	0.791	2.16	0.93	5.04	0.073
	Widowed	1		1			
Occupation	Gov't employed	1		1			
	Private organization employed	0.60	0.473	0.52	0.12	2.27	0.387
	Jobless	1.09	0.877	0.34	0.10	1.36	0.137
	Student	0.84	0.780	0.43	0.12	1.51	0.188
	Farmer	1.19	0.772	0.68	0.19	2.40	0.551
	Commercial sex worker	7.20	0.000**	1.10	0.39	3.09	0.861
	Merchant	2.64	0.032**	1.08	0.38	3.08	0.884
	Housewife	0.95	0.927	0.92	0.25	3.38	0.906
CPT use	Yes	1		1			
	No	4.21	0.000**	1.72	1.08	2.74	0.023*
ART failure history	Yes	1.06	0.887	1.03	0.85	5.24	0.761
	No	1		1			
WHO clinical stages	One	1		1			
	Two	0.62	0.390	1.05	0.31	3.59	0.935
	Three	1.50	0.259	1.23	0.59	2.69	0.555
	Four	3.85	0.001**	2.02	0.75	5.43	0.162
Functional status	Working	1		1			
	Ambulatory	0.91	0.823	0.93	0.41	2.11	0.861
	Bedridden	10.75	0.000**	2.55	1.29	5.06	0.007*
TB registration group	New	1		1			
	Previously treated	1.98	0.003**	0.88	0.52	1.49	0.634
Disclosure of status	Yes	1		1			
	No	13.97	0.000**	4.03	2.21	7.35	0.000*
BMI	<18.5	5.02	0.002**	0.84	0.24	2.94	0.787
	18.5–24.9	0.53	0.239**	0.52	0.16	1.66	0.267
	25–29.9	0.75	0.650	0.72	0.19	2.73	0.632
	>29.9	1		1			
Number of OIs other than TB	No at all	1		1			
	One or two	2.13	0.017**	1.37	0.62	3.02	0.439
	At least three	4.96	0.000**	1.06	0.40	2.83	0.902
CD4 count in cells/mm^3	<200	19.41	0.000**	6.05	2.83	12.95	0.000*
	≥200	1		1			

Notes: **Statistically significant at p≤0.25, *statistically significant at p<0.05

Abbreviations: CI, confidence interval; CHR, crude hazard ratio; AHR, adjusted hazard ratio; CPT, cotrimoxazole preventive therapy; CD4, Cluster of differentiation four; TB, tuberculosis; OIs, opportunistic infections; BMI, body mass index; WHO, World Health Organization.

This might be due to patients who did not disclose their status would not be comfortable to take their medications appropriately, could not get important family supports and would not visit health institutions in the opposite of recommendation; which might contribute to the unwanted outcome like ART failure and poor survival.[31] One of the main reasons for non-disclosure of the status is fear of stigmatization, and this needs a sustainable awareness creation in the community to bring positive attitudes toward TB/HIV co-infected patients and alleviate lay beliefs and misconceptions.[8,9]

Strength of the Study

Although they were insignificant in the final model, we have assessed the effect of new variables (ie which were not assessed previously for this particular study group), TB registration group and number of OIs other than TB on the survival of TB/HIV co-infected patients. In addition, we have also computed the overall life table of TB/HIV co-infected patients.

Limitation of the Study

Selection bias might be introduced; during the exclusion of incomplete registers and subjects with lost cards.

Conclusions

This study demonstrated a high proportion of deaths, particularly within the first two months of anti-TB treatment initiation; and it also identified the risk factors that can be addressed during the routine care. Our finding signals that attention should be given to the victims of these synergistic diseases. As a result, to improve the survival of TB/HIV co-infected patients, close monitoring of bedridden and low CD4 count patients, and prompt CPT initiation with encouraging HIV status disclosure are recommended to all concerned bodies.

List of Abbreviations

AHR, Adjusted Hazard Ratio; AIDS, Acquired Immuno Deficiency Syndrome; ART, Anti-Retro Viral Therapy; BMI, Body Mass Index; CD4, Cluster of Differentiation 4; CI, Confidence Interval; CPT, Cotrimoxazole Preventive Therapy; HIV, human immunodeficiency virus; HR, Hazard Ratio; IRB, Institutional Review Board; OIs, Opportunistic Infections; PLWHA, Peoples Living With HIV/IDS; TB, Tuberculosis; UNAIDS, The joint United Nations Programme on HIV/AIDS; WHO, World Health Organization.

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Disclosure

The authors have declared that no competing interests exist.

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