Original article

Survival analysis of HIV-infected patients under antiretroviral treatment at the Armed Forces General Teaching Hospital, Addis Ababa, Ethiopia

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Abstract

Background: The introduction of ART dramatically improved the survival and health quality of HIV-infected patients in the industrialized world; and the survival benefit of ART has been well studied too. However, in resource-poor settings, where such treatment was started only recently, limited data exist on treatment results. Since the military across most countries of the world had been identified as one of the eight vulnerable and most-at-risk sub-populations to HIV/AIDS, it is worthwhile undertaking studies in the area.

Objectives: The objectives of this study were to estimate mortality rate and to identify survival predictors of patients taking ART based on data obtained from Armed Forces Teaching and General Hospital in Addis Ababa, Ethiopia.

Methods: The records of 734 patients enrolled in the Armed Forces General Teaching Hospital in Addis Ababa between September 2003 and August 2007 were reviewed, and a retrospective cohort study conducted. The Kaplan-Meier method and log-rank test were used to compare the survival experience of different categories of patients. The proportional hazards Cox regression model was employed to identify predictors of mortality.

Results: Of the 734 included in the current study, 86 (11.7%) died during the first 12 months. Of these 28 (32.6%) deaths occurred within the first three months after initiation of ART; another 15 died in the following three months of follow up; that is to say a total of 43 (50%) deaths occurred within six months. In the last six months 43 patients died; that makes the remaining 50% of the total. The most important predictors of mortality at 0.05 level of significance were low CD4 cell count at baseline, employment status, functional status, WHO clinical stages III and IV, TB co-infection, and opportunistic infections.

Conclusion: Based on the finding of the study it can be concluded that a careful monitoring of patients with low CD4 cell count, advanced WHO stages, history of opportunistic infections, ambulatory and bedridden functional status, co-infection with TB and being employed/unemployed must be undertaken in order to improve the survival of AIDS patients. [*Ethiop. J. Health Dev.* 2012;26(3):186-192]

Introduction

AIDS is one of about 30 new infectious diseases, some of the others being Legionnaires' disease, hepatitis C, bovine spongiform encephalopathy/variant Creutzfeld-Jakob disease, several viral hemorrhagic fevers, and so on. These have emerged as a result of profound world-wide changes in human ecology (1). HIV infection leads to low levels of CD4+ T cells that in turn make the body susceptible to opportunistic infections. According to the UNAIDS report, it was estimated that 33.2 million people lived with the disease worldwide, and that AIDS killed an estimated 2.1 million people, including 330,000 children. In 2008, an estimated 33.4 million people were living with HIV/AIDS worldwide; nearly 70% of these were found in sub-Saharan Africa (2).

According the report by (3) nearly three million people in low- and middle-income countries were receiving ART treatment. That is a 10 fold jump when compared with some 300,000 taking Acquired immunodeficiency syndrome (AIDS) drugs in the year 2003.

Survival patterns after HIV infection among African populations in the era before antiretroviral therapy (ART) form an important baseline for measuring future successes of treatment programs (4). Pre-antiretroviral therapy includes guidelines that attempt to address factors which are important in the holistic approach to patient management which could also influence the progression and outcome of disease including natural history of HIV infection, primary prophylaxis and immunization, nutrition, support and counseling (5).

The provision of ART decreased morbidity and mortality in people living with HIV/AIDS. It can also reduce mother-to-child transmission of HIV. In July 2003, the government of Ethiopia adopted a policy of ARV drug supply and use, paving the way for additional initiatives that facilitate access to free and low-cost ARVs. The epidemic has rigorously affected different sectors of development and also challenged the severely constrained health care system of the country. In January 2005 the government of Ethiopia launched the free ARV treatment initiative. About one million people were living with HIV in Ethiopia in the year 2008 (6).

Using a cross-sectional national data (1) a very high ART dropout rate of about 20.7% has been documented, which

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has been considered as a serious challenge to the national scaling up of the program. The study recommended that the extent of relevance of demographic, clinical and immunological correlates for survival in the Ethiopian setting had to be looked into. The finding in (7) based on the Ethiopian experience showed that patients who took HAART lived longer.

Eight vulnerable and most-at-risk sub-populations to HIV/AIDS were identified (8). These are military and other uniformed forces; long-distance truck drivers and other transport workers; fishermen and fisherwomen; female sex workers; refugees and internally displaced persons; prisoners; and females affected by sexual and gender based violence.

There is a claim that military personnel have a high risk of exposure to sexually transmitted diseases (STDs), including HIV/AIDS. In 1997, UNAIDS reported that sexually transmitted disease rates among armed forces are generally 2 to 5 times higher than in civilian populations; the difference could be even greater in times of conflict. By the same token, HIV/AIDS has been referred to as a pre-eminent security threat. The United Nations Security Council has met twice to discuss regional security instability in Africa due to the AIDS crisis.

Military preparedness (effectiveness) has suffered as a result of HIV/AIDS, which has caused illness and death among army personnel. There is a psychological effect, due to the anxiety and discrimination associated with HIV, both from inside the army and from the families of army personnel in their own communities. There are additional burdens for the medical and social services in the army, including the cost of campaigns to prevent new infections, counseling services for groups at risk and for those infected, care for people living with HIV/AIDS, and social support measures for them and their families. Military planners have long recognized the link between soldiers' well-being and military effectiveness, particularly the health and fitness of troops before and during deployment (9).

Based on a study in 21 countries of sub-Saharan Africa, it was concluded that HIV/AIDS prevalence in military (males) aged 15-24 was much higher than the general population of the same age and sex groups. The factors, which contribute to HIV infection and its transmission, were a direct result of the nature of military personnel (i.e., composed of young, male and sexually active individuals), long periods of being away from home and deployment to conflict zones (10).

In 2000 the U.S. National Intelligence Council estimated the following HIV/AIDS military prevalence rates: Angola 40 to 60%, Eritrea 10%, DRC (Zaire) 40 to 60%, Nigeria 10 to 20%, Tanzania 15 to 30%, Cote d'Ivoire 10 to 20%, and Congo Brazzaville 10 to 25%. Other recent estimates included the following: Lesotho 40%, Malawi 50%, Zimbabwe 55%, Botswana 40%, Namibia 33%, Zambia 35%, and South Africa 21% (11). Though HIV/AIDS is undoubtedly a threat to individual security, the argument/notion that it risks national security, and further, international security, is unwarranted (12).

Given the above background this study was undertaken with the two objectives: (i) to estimate mortality rate, and (ii) to identify predictors of the survival of HIV-infected army members and their dependants on ART based on data obtained from the Armed Forces Teaching and General Hospital in Addis Ababa, Ethiopia. It is hoped that the findings would be a contribution to research and of some use to practitioners and policy making.

Methods

This retrospective study used secondary data on HIV-patients who enrolled in the Armed Forces General Teaching Hospital (AFGTH), Addis Ababa, Ethiopia. The hospital serves as a tertiary level teaching and referral hospital delivering health services to the defense forces, civilians in the Ministry of National Defense and their dependants, as well as public patients referred by other specialized hospitals. The ART clinic had its own separate facilities that include: pharmacy, dermatology, and ART laboratory units. A total of 734 patients who started ART between September 2003 and August 2007, were included for the study. These patients were followed up until August 2010.

Patients were eligible for ART on the basis of the 2002 World Health Organization (WHO) guidelines (WHO stage IV or CD4 cell count of lower than 200 cells/μL). Patients older than 15 years of age who never received any ART, and who started ART between September 2003 and August 2007 at the ART clinic of AFGTH were considered. The investigators submitted the proposal to the Institutional Review Board Committee (IRBC) of AFGTH and obtained approval from the same. The hospital top management, upon receiving the recommendation of IRBC, gave its full consent for the study.

The study was based on a review of the intake forms and follow-up cards of HIV patients on ART at AFGTH ART clinic. The forms were designed by the Federal Ministry of Health for uniformity for use in the country to document almost all relevant clinical and laboratory variables. Patients' intake and follow up forms (cards) were cross examined for inconsistencies so that data quality issue could be ensured. The data were collected by a statistician and a public health officer, then coded, cleaned and analyzed using SPSS, SAS, and STATA software.

The response variable "survival time" of HIV patients taking ART was defined as the length of time from ART start date until the date of death, measured in months. The predictor (covariates) variables included in the study were: age (in years), gender (male, female), marital status (never married, married, others), level of education (no education, primary, secondary and above), religion

(Muslim, Ethiopian orthodox, others), employment status (employed, not employed), opportunistic infections (no, yes), TB co-infection (no, yes), household size (one, two or more), number of rooms of residence (one, two or more), risk behavior (regular sexual partner, casual or both regular and casual sexual partner), substance (tobacco, alcohol, soft drugs) use (no, yes), functional status (working, ambulatory, bedridden), WHO clinical stages (stage I, II, III and IV), CD4 cells count, body weight (kg) and types of regimen (D4T-based, AZT-based).

The statistical methods employed in this study were two: a non-parametric method called the Kaplan-Meier method (13) and a semi-parametric method known as Cox-proportional hazards regression model (14). For the theory and applications of these methods the interested reader can consult, among other sources (15) and (16).

The Kaplan-Meier method is employed to estimate survival, and the associated log-rank is used for comparing estimated survival curves. The survivor function and hazard function are the two functions of central interest in describing and summarizing survival data. The basic quantity employed to describe time-to-event phenomena is the survival function; that is, the probability of an individual surviving or being event-free beyond some plausible point in time. The hazard function describes the risk of an outcome (e.g., death, failure, hospitalization) in an interval after a specified time, conditional on the subject having survived to that specified time. The Cox model is a regression model that describes survival as a function of potential predictor variables. The parameters in the model were estimated by the partial maximum likelihood technique. Tests about the validity of the proportional hazards assumption of the model and overall goodness of fit have to be done to see if an adopted model is appropriate before it could be used as final. The proportional hazards assumption, which asserts that the hazard ratios should remain constant overtime, is vital to the interpretation and use of a fitted proportional hazards model. Plots of Cox-Snell and Schoenfeld residuals were used for the purpose of verifying the proportionality assumption. The likelihood ratio, score and Wald tests were used to test the goodness of fit of a Cox regression model.

Results

***General*:**

This study included 734 ART patients for whom data for the variables of interest (introduced above) were complete. The patients were followed up for a median of 38.5 months. Of these 88.3% were censored and 11.7% death cases. The majority of patients were males (548); 268 were never married; 381 had at least secondary school education; 632 were Ethiopian orthodox; 530 were employed; 413 had a single room of residence; 479 had at least two members in the household; 515 were naïve to substance use; 196 had bedridden functional status; 28 had regular sexual partners. The regimen d4T was frequently prescribed for 403 patients; 210 were in clinical stage IV. TB and opportunistic infections (OIs) were prevalent among 403 and 648 patients, respectively. The median age, CD4 count and weight of patients at start of ART were 34 years (inter-quartile range 29-40 years), 83 cells/mm^3 (inter-quartile range 36-139.25 cells/mm^3) and 53 kg (inter-quartile range 48-59 kg), respectively. The socio-economic and clinical characteristics of the patients are given in Table 1.

***Results of the Descriptive Analysis*:**

Among the total of 734 study subjects, 86 (11.7%) died during the first 12 months. Of these 28 (32.6%) deaths occurred within the first three months after initiation of ART; another 15 died in the following three months of follow up; that is, a total of 43 (50%) deaths occurred within six months. In the last six months, 43 patients died; that makes the remaining 50% of the total.

The log-rank test was conducted 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 in Table 2 manifest no significant differences among the categories of gender, marital status, religion, level of education, number of rooms within residence, risk behavior, ART regimen and substance use. On the other hand, the test confirmed significant differences in survival situation among different categories of employment status, household size, functional status, OIs, TB co-infection and WHO clinical stages.

***Results of the Proportional Hazards Cox Regression Analysis*:**

The bivariate analysis indicated that not all predictors/variables were important to be included in the multivariable analysis stage on the basis of the selection/elimination process of the lax criterion at 25% level of significance. The covariates that were found to be statistically significant in the bivariate analysis were excluded successively in order of the magnitude in which they increase the log-likelihood. This process gave rise to a multiple proportional hazards Cox regression model that included only six covariates, namely employment status, functional status, WHO clinical stage, OIs, TB co-infection, and CD4 cell count which were significant at 5% level (Table 3).

The Cox model of Table 3 shows that no covariates showed a trend/pattern with time, confirming that the hazard ratios remained constant over the study time. Also, the plots of the scaled Schoenfeld residuals of each covariate against log-time (not shown in the paper) were used to check if the assumption of proportional hazards was violated. The eight plots showed randomness; the smoothed plots approximated the horizontal line through zero reaffirming the fulfillment of proportional hazards assumption.

The overall goodness of fit of the provisional/ preliminary model adopted so far (with the covariates in Table 3) was tested using the Cox-Snell residuals plot;

this test gave results that speak for the quality of model fit. In addition to these, the results of the likelihood ratio score and Wald tests for model goodness of fit confirmed that the model fit was significant at 5% level. Hence, the Cox model with those predictors/variables given in Table 3 becomes the final model.

Having established all the above statistical facts about the model we now provide the results based on the final model. It is worthwhile pointing out that the remaining covariates in the model had been controlled while presenting results about a single predictor variable.

CD4 cell count: The estimated hazards ratio (HR) for a 50 cells/mm^3 increase in the baseline CD4 cell count was 0.779 (with 95% CI:0.640 - 0.947) showing that the hazard rate for patients, whose CD4 cell count was higher by 50 cells/mm^3 was about 22.1% lower than for patients in the next lower category.

TB co-infection: The estimated HR for TB co-infected patients in relation to those who were not infected with TB was 1.734 (95% CI: 1.039 - 2.893). It means that the patients infected with TB had about 1.734 (or 73.4%) higher mortality than patients without TB infection.

Opportunistic Infections: This study indicated that patients who suffered from OIs had nearly a 9-fold (or 885%) risk of dying than those who were free of OIs (estimated HR 8.985 with 95% CI: 1.240-65.085).

Employment status: The estimated HR for employed patients was 2.310 (95% CI: 1.248-4.275). This implies that employed HIV patients were 2.3-times more likely to die than their unemployed counterparts.

Table 1: Socio**-demographic and clinical characteristics of HIV patients under ART in the Armed Forces General Teaching Hospital, Addis Ababa, 2011(*n*=734).**

Covariates	**Category**	**Censored (%)**	**Dead**	**Total**
Gender	Female	164 (88.2%)	22	186
	Male	484 (88.3%)	64	548
	Never married	233 (86.9%)	35	268
Marital status	Married	317 (88.3%)	42	359
	Others	97 (91.5%)	9	106
Religion	Muslim	38 (82.6%)	8	46
	Coptic orthodox	560 (88.6%)	72	632
	Others	50 (89.3%)	6	56
	No education	38 (88.4%)	5	43
Education level	Primary	267 (86.1%)	43	310
	Secondary and above	343 (90.0%)	38	381
Employment status	Employed	456 (86.0%)	74	530
	Not employed	192 (94.1%)	12	204
No of Rooms	Only one	360 (87.2%)	53	413
	2 rooms and more	288 (89.7%)	33	321
Household size	Only one	217 (85.1%)	38	255
	two and more	431 (90.0%)	48	479
Substance use	No	452 (87.8%)	63	515
	Yes	196 (89.5%)	23	219
	Working	261 (95.6%)	12	273
Functional status	Ambulatory	237 (89.4%)	28	265
	Bedridden	150 (76.5%)	46	196
	Regular	24 (85.7%)	4	28
Risk behavior	Casual or both regular and casual	624 (88.4%)	82	706
TB co-infection	No	311 (94.0%)	20	331
	Yes	337 (83.6%)	66	403
ART regimen	D4T-based	352 (87.3%)	51	403
	AZT-based	296 (89.4%)	35	331
OIs	No	85 (98.8%)	1	86
	Yes	563 (86.9%)	85	648
WHO clinical stage	Stage I and II	199 (99.0%)	2	201
	Stage III	286 (88.5%)	37	323
	Stage IV	163 (77.6%)	47	210

Table 2: **Results of the bivariate Cox regression analysis - HIV patients under ART in the Armed Forces General Teaching Hospital, Addis Ababa, 2011(n=734).**

Covariates	Sig.	Hazard ratio
Gender	0.921	1.025
Marital status	0.285	
Married	0.122	1.782
Never married	0.297	1.466
Religion	0.364	
Muslim	0.213	1.963
Coptic orthodox	0.662	1.205
Education	0.100	
Primary	0.698	1.201
Secondary and above secondary	0.535	0.744
Employment status	0.003	2.499
Room	0.153	1.373
Household size	0.017	1.684
Risk	0.628	1.282
Substance	0.559	1.153
Functional status	0.000	
Ambulatory	0.005	2.650
Bedridden	0.000	6.952
WHO clinical stage	0.000	
Stage III	0.000	12.688
Stage IV	0.000	27.217
OIs	0.014	11.740
TB co-infection	0.000	2.932
Regimen	0.206	1.321
Age	0.129	1.020
Weight	0.001	0.959
CD4 Count	0.000	0.989

Table 3: **Summary statistics - HIV patients under ART in the Armed Forces General Teaching Hospital, Addis Ababa, 2011(*n*=734).**

Covariates	P-value	Estimated hazard ratio	Estimated 95% CI for the hazard Ratio	
			Lower	Upper
Employment status	0.008	2.310	1.248	4.275
Functional Status	0.001			
Ambulatory	0.044	2.011	1.018	3.973
Bedridden	0.000	3.358	1.734	6.500
WHO Stage	0.000			
Stage III	0.008	7.052	1.677	29.658
Stage IV	0.001	12.640	3.003	53.199
OIs	0.030	8.985	1.240	65.085
TB co-infection	0.035	1.734	1.039	2.893
CD4 count	0.017	0.779	0.640	0.947

WHO clinical stages: The estimated HRs and CIs for WHO levels III and IV, respectively, were 7.052 (95% CI: 1.677-29.658) and 12.640 (95% CI: 3.003-53.199). The interpretation is that: patients in stage III and IV were, respectively, 7-fold and 12.64-times at risk of dying than patients in stages I and II.

Functional status: The estimated HRs and CIs of HRs for ambulatory and bedridden patients were 2.011 (95% CI: 1.018-3.973) and 3.358 (95% CI: 1.734-6.500), respectively. The implication is that ambulatory and bedridden patients, respectively, were twice and 3.36-times at higher risks of death than patients who were actively engaged in work.

Discussion

In this study, baseline CD4 cell count, TB co-infection, employment status, opportunistic infections, functional status and WHO clinical stage were found to be statistically significant determinants of survival longevity of the patients on ART. The remaining part of this section relates the results of the current study with the findings of similar research undertakings.

It is to be expected that baseline CD4 cell count would have an impact on health status, and therefore, mortality of patients on ART. In this connection we point out the research findings of six studies done in sub-Saharan countries. Of these, the findings in (17, 18, 19) identified low CD4 cell count as a determining factor of death while (20, 21, 22, 23) showed that CD4 count was a laboratory predictor of mortality in the sense that higher CD4 count is associated with longer survival experience. Our findings concur with the findings of the above sources.

The impact of TB-confection on the survival longevity of HIV-positive people could only be negative. According to (24) and (25), TB co-infection was found to be a cause of high mortality of HIV patients. This study arrived at the same conclusion.

Three studies in sub-Saharan Africa showed that OIs were found to be common causes of death among patients under ART (18, 26, 27). The current study established a similar finding.

In the two studies (28, 29) unemployment was found to be a risk factor contributing to mortality of HIV patients; being employed contributed to longer survival among HIV-patients taking ART. Contrary to the above our results concluded the opposite.

It is a known fact that WHO clinical stages have direct association with the health status of HIV patients. Our finding showed that that the two advanced WHO clinical stages III and IV were found to be independent markers of mortality among HIV-patients on ART. This conclusion was in agreement with the findings in (18, 19, 30).

Functional status (remaining active, inactive or being ambulatory) has an association with the wellbeing an individual, whether healthy or not healthy. In the case of HIV patients on ART the findings, according to (31, 32), showed that reduced ability to perform activities of daily living (ADL) led to shorter survival. The findings in (21) showed that ambulatory and bedridden patients, respectively, were 82.5% and nearly four-and-half times more likely to die compared to those engaged in active working. The current study revealed that ambulatory and bedridden patients were twice and nearly three-and-half times, respectively, at higher risks of death than active patients.

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This study revealed gender, marital status, religion, level of education, number of rooms in a residence, risk behavior, ART regimen and substance use as being statistically non-significant covariates of survival of HIV infected patients under ART. The paramount justification for the non-significance of these covariates may be due to the respective small number of cases in addition to the prevailing bias in the secondary data.

Conclusion and Recommendations:

This retrospective study gave an insight into survival and its determinants in an army hospital setting in Ethiopia. It revealed that the estimated mean survival time of patients under the study was 72 months. High mortality occurred in the earlier months of treatment. Advanced WHO clinical stages (III and IV), lower CD4 cell count (<50 cells/mm^3), TB co-infection, history of OIs, patients in bedridden and ambulatory functional status were found to be strongly related to the mortality of HIV-infected patients that were included in this study.

The results suggested that, since lower CD4 cell count, being bedridden and WHO clinical stages are markers of the progression of the disease, patients should be informed about their health status related to the medical diagnostic results. Such information could give patients time to make their minds and get prepared to receive ART. The high rate of early mortality had to be addressed by increasing the availability of early HIV diagnosis and treatment services. Since employed patients experienced a high level of mortality due attention must be given to create favorable conditions at their work places. It could be that the employment brought with it stress and exhaustion thereby contributing to shortening of their survival status.

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