Original article

Survival analysis of patients under chronic HIV-care and antiretroviral treatment at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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Abstract

Background: Health care planning depends upon good knowledge of prevalence that requires a clear understanding of survival patterns of patients who receive medication, treatment and care. Survival analysis can bring to light the effect that some demographic, social, medical and clinical characteristics have on the mortality rate of HIV-patients.

Objectives: The objective of this research undertaking was to estimate mortality rate and identify predictors that have significant impact on the survival status of a sample of patients who received antiretroviral treatment and care in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Methods: The data for this research were collected during the follow-up time from 2005 to 2008. Out of a population of HIV-patients who were taking antiretroviral therapy in the hospital in that period, data on 1,000 patients were used for this study. The study subjects were people in the age range from 15 to 75 years. The Kaplan-Meier Method was employed to estimate mortality; the Cox Proportional Hazards Regression Method was used to identify determinants of mortality.

Results: After initiation of the antiretroviral treatment, HIV-positive patients lived for an average of 5.65 years (CI: 3.69-7.61 years); the median survival age was found to be 3.98 years (CI: 2.98-4.97 years). The number of medications, baseline functional status, CD4 count, antiretroviral treatment, age, gender and weight impact the survival experience of the patients.

Conclusions: Antiretroviral therapy treatment reduced death among AIDS patients by 50 percent. Providing treatment at health facilities outside big towns and in the country should be given due attention. Similar studies in the future need to consider predictors in addition to those considered in this study. [*Ethiop. J. Health Dev.* 2012;26(1):22-29]

Introduction

Studying the history of disease progression due to HIV/AIDS and the treatments are useful for the purpose of developing treatment guidelines, modeling the epidemic and prioritizing and allocating resources. Health care planning depends on good knowledge of prevalence, which requires an accurate understanding of survival patterns. Monitoring the length of survival after diagnosis is, therefore, an important component of the surveillance of AIDS. It provides a basis for evaluating individual prognostic factors. In addition, differences in survival may also reflect differences in access to health care (e.g. access to testing, counseling, preventive treatment). The survival of patients with AIDS may depend on a variety of factors including host factors, the patterns of diseases present, access to health care, diagnostic routines and therapeutic interventions (1).

Long-term sustainable treatment is one choice for people living with HIV. Not only can medications slow the progression of the infection, but can also markedly suppress the virus, thereby restoring the body's immune function and permitting many HIV-infected individuals to lead a normal life. People living with HIV take a number of medications like cotrimoxazole, fluconazole, INH and other medications depending on the type of the opportunistic illness they have.

Even though AIDS drugs have become cheaper and more available because of a variety government and private programs, millions of others still do not have access to the drugs. WHO recommends that in resource-limited settings HIV infected adolescents and adults should start

ART when the following conditions are met: WHO stage 4 regardless of CD4 count, stage 3 disease with consideration of CD4 count below 350/mm^3 in assisting decision making, stages 1 or 2 diseases with CD4 cell count below 200/mm^3. In a setting where CD4 count is not available, the total lymphocyte count (TLC) can be used, and treatment is recommended for WHO stages 3 or 4 (clinical AIDS) irrespective of the TLC and stage 2 with TLC not exceeding 1200/mm^3.

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 (2).

Survival patterns following HIV infection in African populations in the era before antiretroviral therapy (ART) form an important baseline for measuring future successes of treatment programs (3). According to (4)

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

Knowledge of the survival times of patients with AIDS and variables that influence survival are important both for increasing understanding of the patho-physiology of the disease, clinical decision making and planning health service interventions (5). The main challenge here is the sustainability of providing ART and other medications at district hospitals. About one million people were living with HIV in Ethiopia in the year 2008 (6).

A lot of effort has been made to improve the health quality of HIV-positive patients in Ethiopia and extend the time interval from HIV-infection/AIDS-diagnosis to death. For instance, activities like prevention of the disease through effective use of prophylaxis, intervention strategies and awareness raising such as mass media campaigns, peer education about HIV transmission, treatment of other sexually transmitted infections, safe blood transfusion provision, and prevention from mother to child treatment have been taken.

Despite the availability of a large body of research evidence that addresses issues about AIDS in Ethiopia, the level of understanding about predictor variables associated with mortality rate as a result of HIV infection is low. This study was undertaken with objectives to estimate mortality and identify predictors that have impact on the survival of HIV-positive patients with the hope that the results would contribute to existing knowledge.

Methods

The survival data for this study were obtained from Tikur Anbessa Specialized Hospital, a teaching hospital in Addis Ababa associated with the School of Medicine of the Addis Ababa University. The ART unit in the Hospital provides general voluntary counseling and testing services, follow up, pre-antiretroviral and ARV service for people living with HIV/AIDS. At the Hospital's ART clinic the data were recorded using the standardized data collection formats and registers prepared by the Ministry of Health. Data recording was done by health officers and nurses working in the clinic. The examining medical doctors also recorded follow up information about their patients.

Data recording starts from the date patients started HIV-regular care in the clinic till it was confirmed that patients have experienced one of the events - "death", "lost to follow-up", "dropped from the clinic", "stopped", and "transferred out to other health centers". Information on patients who had been transferred to the clinic were also recorded after reviewing their past history from the referring hospitals or heath centers. In this process the names of patients, initials or hospital initials had been removed adhering to national and international ethical standards.

The database for this study included patients of age from 15 to 75 years who had come to the clinic from the year 2005 to 2008. Even though the number of patients who took the treatment during this time period was large, complete information on the clinical variables chosen for this study could not be obtained for all; this is particularly true in the early years of introduction of the treatment. Hence, a decision was reached to base this study on 1000 patients for whom complete information was available; this size was desirable to obtain reliable results in survival analysis. In addition to that, time constraint and the cost of data collection dictated this research to consider the above-mentioned sample size. In this connection, it is important to point out that some important clinical variables were poorly documented in the ART unit at the time when data collection for this study was done.

The process of data collection for the research involved Distributing data collection formats to the experts in the clinic; checking whether the formats were filled correctly, and entering the correct data into computer. The data were stored in Excel, and then imported to SPSS, SAS and Stata for further analysis. Most of the Descriptive Analysis was done using SPSS software; the proportional hazards regression analysis was performed using SAS and STATA software.

Variables of the study: The response variable in this research that was the "survival time" was defined as the number of days from the date of enrollment of a patient in the HIV-care till one of the events "death", "lost to follow up", "dropped out", "stopped", "transferred out to other health centers or hospitals" occurred. This meant that the survival data studied here were "right-censored". The predictor variables relate to the social, demographic, medical and clinical background of the patients having these respective classifications; age (in full years), gender (male, female), marital status (never married, married, separated, divorced, widowed), religion (Muslim, Coptic Orthodox, Protestant, Catholic, others), weight (in kilograms), functional status (working, ambulatory, bedridden), WHO clinical stages (stage 1, stage 2, stage 3, stage 4), number of medications taken (0,1, 2, 3, 4), CD4 cell count (in mm^3), and highly active antiretroviral therapy (HAART) (yes, no).

The statistical analytic method used in this study is known as Survival Analysis. Survival data analysis involves the modeling and analyses of data that have a principal end point - the time until an event occurs (time-

to-event data). Survival Analysis considers conditional information on the remaining time of a subject's survival given current survival time. Survival data were censored in the sense that they did not provide complete information since, for a variety of reasons, subjects of the study may not have experienced the event of interest. The existence of variables that change over time is also a distinguishing feature in survival analysis.

Descriptive analysis of survival data utilizes non-parametric methods to compare the survival functions of two or more groups. The Kaplan-Meier estimator (product-limit-estimator) of the survival function (7) was employed for this purpose. The log-rank test was utilized to test whether observed differences in survival experience between/among the groups was significant or not.

The multivariable model used was the semi-parametric regression model known as the proportional hazards regression (PHR) model (8). When a study involves multiple characteristics, appropriate statistical techniques must be used to select variables that have significant effects on survival and which are judged to be clinically meaningful for inclusion in a PHR model. Hence, the model development process identifies the relevant variables following model scrutiny as discussed in (9).

Results

Results of the descriptive analysis: This study used observations on 1000 HIV-positive people that were followed during 2005 to 2008. Of those, about 90% were right-censored and the remaining uncensored. HIV-positive patients lived for an average of 5.65 years (CI: 3.69-7.61 years); the median survival age was found to be 3.98 years (CI: 2.98-4.97 years).

A summary of the data for each level of variables is provided in Table 1. Table 2 gives results based on the log-rank test. The *p*-values in Table 2 show differences in survival experience between two or more levels of predictors. All predictors with the exception of marital status, religion and age manifest differences in levels of survival functions. A résumé emanating from descriptive analysis with reference to the seven predictors (leaving out marital status, religion and age) that manifest differences in survival are provided as follows.

Males live for an average of four years longer than females. Patients who were working lived on average one year and two years longer than those in ambulatory and bedridden conditions, respectively. The number of medications had direct or indirect association with the existence of the number of opportunistic infections (OIs). Patients, who took one medication, had longer survival time than others living on average: four years longer than patients who took *no* or *two* medications; five years longer than those who took three and four medications. Taking four medications was associated with the lowest survival time. HIV-positive patients, with WHO clinical stage 1 had an average of two years longer survival time than those in stages 2, 3 and 4. Those patients in clinical stages 2, 3 and 4 had (more or less the same) three years survival time. Patients, who were eligible for ART, but had not taken the therapy, had a shorter survival time; which was on average five years shorter than those receiving ART. Patients having weights 45 to 54 kilograms lived four years longer on average than those having weight in the range of 55 and 80 kilograms. Patients, who weighed 20 to 34 kilograms and 35 to 44 kilograms, respectively, lived five and six year shorter on average compared with those people who had weights in the range 45 to 54 kilograms. Those having CD4 cell count above 200/mm^3 lived three years longer on average than patients with CD4 cell count below 200/mm^3.

Results of the PHR model: The Cox model procedure that includes model selection, tests, diagnosis and fit confirmed that there were no problems with regard to interactions of main effects and confounding. Therefore, the results in Tables 3 and 4 are based on the main effects; the model is sometimes called the crude (unadjusted) model. Because age is such a demographic variable that could influence survival status, it was brought into the multivariable model, and was found to be significant. The following elaboration details survival experience based on estimated crude hazard ratios (HR) in Table 4. It should be pointed out that variables with *p*-values below 0.05 were considered as statistically significant.

Table 1: **Socio-demographic and clinical characteristics of HIV-positive patients at ART initiation in Tikur Anbessa Specialized Hospital, Addis Ababa, 2005-2008, (*n* =1000).**

Characteristics	Category	Total	Failed	Censored	Percent Censored
Age	15-29	273	20	253	93
	30-44	399	46	353	88
	45-59	298	30	268	90
	60-75	30	4	26	87
Gender	Female	472	56	416	88
	Male	528	44	484	92
Marital Status	Never married	310	37	273	88
	Married	371	39	332	89
	Separated	26	3	23	88
	Divorced	135	9	126	93
	Widowed	158	12	146	92
Religion	Muslim	86	11	75	87
	Orthodox	808	78	730	90
	Protestant	95	11	84	88
	Catholic	2	0	2	100
	Others	9	0	9	100
Number of medications	0	265	34	231	87
	1	485	37	448	92
	2	110	17	93	85
	3	120	4	116	97
	4	20	8	12	60
Functional Status	Working Ambulatory	423	33	390	92
	Bedridden	343	35	308	90
		234	32	202	86
WHO clinical stages	Stage 1	29	2	27	93
	Stage 2	102	3	99	97
	Stage 3	474	53	421	89
	Stage 4	395	42	353	89
ART	Yes	428	53	375	88
	No	572	47	525	92
Weight	20-34	45	6	39	87
	35-44	220	26	194	88
	45-54	372	41	331	89
	55-80	363	27	336	93
CD4 count/mm^3	CD4 $\leq$200/mm^3	170	13	157	92
	DC4>200/mm^3	830	87	743	90

Table 2: **Log-rank test *p*-values based on socio-demographic and clinical characteristics data of HIV-positive patients at ART initiation in Tikur Anbessa Specialized Hospital, Addis Ababa, 2005-2008, (*n* =1000).**

Variable	Df	Chi-sq	Log-Rank Test *p*-Value
Gender	1	3.80	0.04
Marital Status	4	8.26	0.08
Religion	4	2.57	0.63
Functional status	2	16.69	<0.0001
Number of medication	4	32.87	<0.0001
WHO clinical stages	3	9.69	0.02
ART	1	11.14	0.001
Age	3	3.48	0.32
Weight	3	15.58	0.001
CD4 count/mm^3	1	7.85	0.04

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Table 3: **Estimated parameters for the *preliminary* Proportional Hazards Regression Model Containing variable significant at 20% level in the bivariate analysis for the data from Tikur Anbessa Specialized Hospital, Addis Ababa, 2005-2008, (*n* =1000).**

Variable	df	Parameter Estimate	Std. Er.	Chi-Sq	Pr>Chsq
Gender	1	-0.435	0.230	3.567	0.059
Age2	1	0.799	0.289	7.609	0.006
Age 3	1	0.459	0.336	1.864	0.172
Age 4	1	1.473	0.595	6.137	0.013
Marital 0	1	0.148	0.263	0.316	0.574
Marital 2	1	0.665	0.616	1.166	0.280
Marital 3	1	-0.661	0.382	2.994	0.084
Marital 4	1	-0.360	0.345	1.088	0.297
Function 1	1	0.274	0.258	1.132	0.287
Function 2	1	1.153	0.294	15.374	<.0001
Nummedic 1	1	-0.987	0.250	15.532	<.0001
Nummedic 2	1	-0.389	0.317	1.504	0.220
Nummedic 3	1	-1.788	0.533	11.242	0.001
Nummedic 4	1	1.078	0.415	6.758	0.009
WHO1	1	0.388	0.754	0.265	0.607
WHO2	1	-0.904	0.614	2.170	0.141
WHO3	1	0.288	0.224	1.643	0.200
ART	1	-0.662	0.219	9.098	0.003
CD4	1	-0.002	0.001	3.519	0.061
Weight	1	-0.042	0.011	13.791	0.000

Socio-demographic characteristics: The estimated HR for females was 0.55 (CI: 0.365-0.843), meaning that males were dying at a rate of 45% lower than females. The referent category for age was the age group from 15 to 29 years. The estimated HRs for the age groups (30-44] and (60-75] were 1.65 (CI: 1.080-2.514) and 2.86 (CI: 1.006-8.140), respectively. As age the group (45-59] was insignificant (see Table 3 at 0.05 level) it was excluded. For bedridden patients, the estimated HR was 2.67 (CI: 1.661-4.305) as compared to the referent category "working". The status of being ambulatory did not have a significant contribution at 0.05 level (see Table 3). That is why it is not included in the final model. A 5 kilogram increase in weight resulted in an estimated HR of 096 (CI: 0.994-0.984).

Clinical characteristics: The referent category pertaining to the number of medications was the group not taking any medications. The estimated HRs for those taking one, three and four medications, respectively, are 0.46 (CI: 0.301-0.715), 0.21 (CI: 0.075-0.580) and 4.06 (CI: 1.869-8.823). The category of the two medications was not included according to the 0.05 level exclusion rule (see Table 3). The estimated hazard ratio for ART was 0.50 (CI: 0.328-0.757) relative to the category not taking ART. A 10/mm^3 increase in CD4 count was associated with a HR 0.98 (CI: 0.996-0.999).

Table 4: **Estimated parameters for the *final* Proportional Hazards Regression Model for the data from Tikur Anbessa Specialized Hospital, Addis Ababa, 2005-2008, (*n* =1000).**

Variable	df	Parameter Estimate	Std. Er.	Chi-Sq	Pr>Chi-Sq	HR Estimate	95% CIE for HR	
Gender	1	-0.589	0.214	7.616	0.006	0.55	0.365	0.843
Age2	1	0.500	0.215	5.378	0.020	1.65	1.080	2.514
Age4	1	1.051	0.533	3.888	0.039	2.86	1.006	8.140
Function 2	1	0.984	0.243	16.385	<.0001	2.67	1.661	4.305
Nummedic 1	1	-0.768	0.221	12.100	0.001	0.46	0.301	0.715
Nummedic 3	1	-1.569	0.523	9.005	0.003	0.21	0.075	0.580
Nummedic 4	1	1.401	0.396	12.529	0.000	4.06	1.869	8.823
ART	1	-0.697	0.214	10.627	0.001	0.50	0.328	0.757
CD4	1	-0.002	0.001	4.278	0.039	0.98	0.996	0.999
Weight	1	-.037	0.011	12.368	0.000	0.96	0.944	0.984

Note: The categories and status of some of the predictors are as follows: age 1(15-29 years), age 2 (30-44 years), age 3 (45-59 years), age 4 (60-75 years); function 1 (working), function 2 (ambulatory), function 3 (bedridden); nummedic 0 (no medication), nummedic 1 (taking one medication), nummedic 2 (taking two medications), nummedic 3 (three medications) nummedic 4 (four medications).

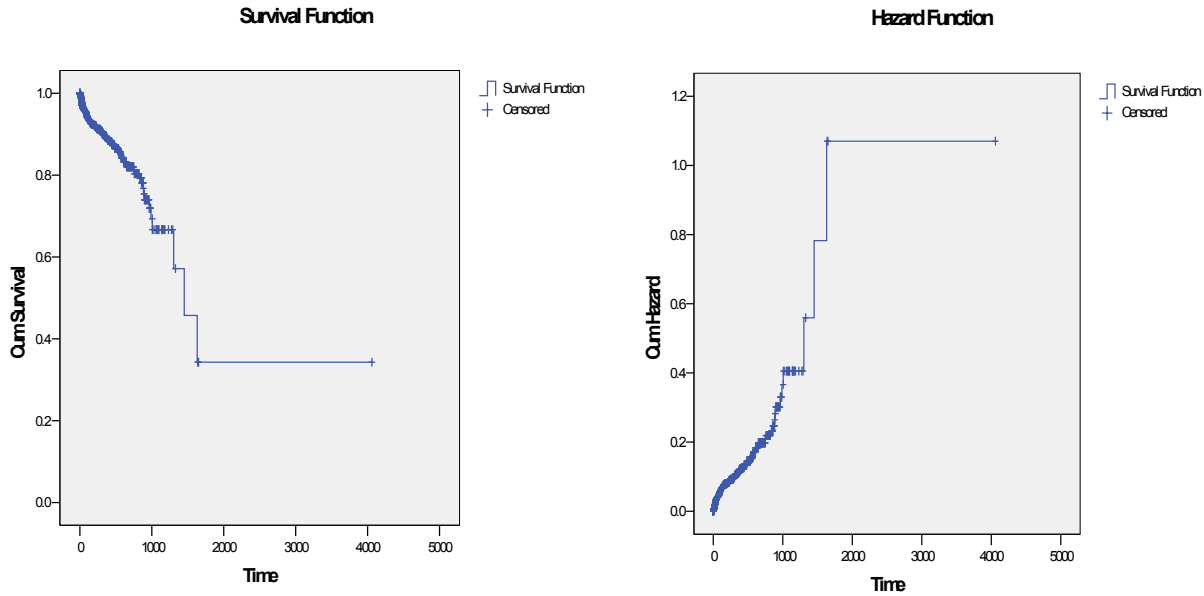

Figure 1: **Overall Survival and hazard functions (in days)**

Discussion

Female HIV-positive patients had shorter survival on average compared to males. It was observed that the survival time of patients under ART varied along differences in functional status. Bedridden patients had the least survival time. Patients, who took one medication lived longer on average than those who took two, three and four medications. Patients who took four medications had the least survival time. Those weighting in between 45 kg and 54 kg lived longer on average than those weighting between 35 and 44 kg. Those weighting between 20 kg and 34 kg had on average better survival experience than patients in the weight group 35 kg and 44 kg. People living with HIV/AIDS under ART had better survival time on average than patients who were eligible for ART, but did not take the treatment. CD4 cells counts showed a strong influence on the survival status; patients with counts of more than 200/mm^3 had higher survival experience than those with counts below 200/mm^3. Increasing in CD4 count is achieved through ART. Comparison of survival estimates by treatment groups suggested that there were significant differences in the survival status with regard to the number of medications taken.

Gender has a significant influence on survival (10). The association of gender with survival is found not to be significant (3, 11, 12). Contrary to (13), the situation where it was showed that males are in a higher risk of death compared to females, this study shows that females experienced higher mortality rate than males.

Results in (3, 12) showed that survival is strongly related to age. The results of (13) suggest that survival is independent of age. This study has also come up with similar conclusions as in (3, 12).

Low ability to attain self-sufficiency in the requirements of daily living (ADLs) related to shorter survival (14, 15). The findings of this study showed (13) ambulatory and bedridden patients, respectively, were 82.5% and nearly four-and-half times more likely to die compared to those working. The study also showed that bedridden patients were more than two-and-half times likely to die than those patients engaged in work.

People living with HIV take a number of medications depending upon the number of opportunistic infections that exist in their body. In this connection (16) the study showed that mortality increased because of stopping one of the medications, namely Cotrimoxazole (CTX). The study indicated that HIV-positive people taking no medication were at higher risk of dying. Those who were taking four medications were likely to die at a rate which was about 4.06 times higher than patients who took no medications; this rate could be as much as 8.82-fold or as little as a 1.87-fold.

The findings of the study (13, 17, 18, 19) showed that patients taking HAART lived longer. HAART reduced mortality by 65% (19). A mortality decline of 49.3% was observed (13). This study reached the same conclusion as others mentioned here, and showed that the rate of reducing of mortality was 50%. Taking ART could increase longevity by

months (18). According to this study, the median survival time was 3.98 years was almost 48 months.

The studies (12, 13, 20, 21) showed that CD4 count is a laboratory predictor of mortality in the sense that higher CD4 counts are associated with longer survival time. The current study concurs with conclusions above.

Weight loss is a cause for reduced longevity (22, 23). This study agrees with the foregoing conclusion; it also shows that a 5kg weight gain reduces mortality by 7 percent.

Conclusions and Recommendations

The study revealed that after initiation of the treatment, HIV-positive people lived on average 5.65 years with median survival time estimated to be nearly 4 years. From among the variables included in the study, three of them (religion, marital status and WHO clinical stages) did not have significant impact on survival. The number of medications, baseline functional status, CD4 count, antiretroviral treatment, age, gender and weight had significant impact on the survival experience of patients. Females lived shorter than males. Patients, who were working lived longer compared to ambulatory or bedridden patients. The number of medications had significant influence on the length of survival; taking four medications was strongly associated with shortest survival, while higher body weight did not indicate longer survival, whereas low weight was not necessarily associated with shorter survival. Older age was associated with higher risk of death. ART improved the quality of life of HIV-positive people. Higher CD4 cell counts (>200/mm^3) were observed to have an association with better survival experience. Antiretroviral treatment had changed the health status of the HIV-positive people by prolonging the survival time of victims. The treatment reduced deaths among AIDS patients by 50%.

The Ethiopian Health Policy should focus on thorough and integrated primary health care with emphasis on community-based services. The Health Service Extension Program introduced in 2004 is intended to bring the health services closer to the people. According to the package, health centers and district hospitals have the duties to provide HIV care, medications and treatment including ART. It is therefore, encouraging to observe that the Integrated Management of Adolescent and Adult Illness (IMAI) developed by WHO providing practical guidance on decentralized and integrated delivery of HIV care is being used. In this regard, the main challenge remains to be the sustainability of providing ART and a number of the medications at district hospitals.

As the literature on survival and mortality of AIDS patients points out, predictors related to nutrition, body exercise, levels of income and social condition are associated with survival. Similar future research undertakings should seek to identify additional characteristics (social, economic, behavioral, nutritional, environmental, and the like) that may affect the mortality rate of HIV-positive patients receiving ART service.

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