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Determinant of mortality in HIV infected people on antiretroviral therapy in Southwest Ethiopia

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The introduction of antiretroviral drug has considerably reformed the course of HIV/AIDS from life threatening epidemic to a chronic manageable health problem. Mortality and morbidity associated with HIV/AIDS are changing. The main aim of this study was to assess the potential determinant of death among people infected with HIV and initiated anti-retroviral therapy (ART). A general retrospective cohort method was used on 2655 people undertaking ART at Mizan Hospital from 7 January, 2005 to 8 May, 2013 in Southern Ethiopia. The three age groups: Pediatrics (age under 10 years), teens (age between 11 and 19 years), and elderly (age older than 20 years) was used to stratify the cohort. The usual clinical follow-up registry of the ART clinic was the main data for the study. Kaplan-Meier (KM) method was used to compare the survival experience of patients after initiation of ART. Cox proportional regression model was used to assess determinant of mortality. A total of 2655 patients, consisting of 6.3% pediatrics, 3.3% teenagers and 90.4% elderly were included in the study. The survival probability at the sixth month after initiation of the treatment was 96, 94, 96 and 96% for pediatrics, teenagers and adults, respectively. A low initial CD4 (P=0.001), advanced WHO clinical disease stage (P=0.01), receiving ISONIAZID preventive prophylaxis (P=0.02), tuberculosis coinfection (P < 0.001) and being bedridden (P < 0.002) was an independent determinant of death. The cumulative incidence of mortality rate for HIV patients has been low in this study hence early initiation of the treatment is highly recommended.

Key words: Anti-retroviral therapy, mortality, South Ethiopia.

INTRODUCTION

Occurrence of the Human Immunodeficiency Virus (HIV) epidemic is one of the major challenges that the world has seen in recent past. Millions of individuals have died of HIV in the last thirty years. The large proportion of deaths reportedly occurred in sub-Sahara African countries where antiretroviral treatment was announced recently (Federal Democratic Republic of Ethiopia, 2012). Highly active antiretroviral therapy (HAART)

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pharmacological intervention has inhibitory effects on HIV replication which has revealed positive results on the HIV epidemic. The suppression of viral copying is mainly related to the steady rise in the CD4 count and results in medical stabilization (AIDS Institute, 2013; Organization, 2012b). The antiretroviral therapy (ART) interventions have yielded considerable results. The 2012 World AIDS Day report revealed that there were 700,000 fewer new infections in the world in the year 2011 than a decade ago, with much of the progress supposedly attributed to the ARV therapy (WHO World AIDS Day, 2012).

Evidence showed that untreated HIV infection can lead to higher morbidity and mortality from conditions other than HIV, even at high CD4 counts (AIDS Institute, 2013; Zaidi et al., 2013; Johnson et al., 2013; Andreychyn and Zhyvytsia, 2013). Researchers currently recommend that all patients living with HIV be treated with ART to decrease transmission of HIV from one another (AIDS Institute, 2013; Organization, 2012b). This is due to increasing evidence that patients with well-known HIV infection have benefited from ART at all stages of the disease (Cohen et al., 2011; Organization, 2012a). Decreased viral load which should have reduced transmission risk from ART is now part of the established strategy aimed at dropping HIV transmission (AIDS Institute, 2013; Organization, 2012a).

In Ethiopia, HIV epidemic has remained a major public health problem mainly affecting people of productive and reproductive age (CSA-Ethiopia, 2011). Since HIV cases reported in the mid-1980s in Ethiopia (MOH Guidelines, 2003), both government and non-governmental organizations have shown commitment to prevent its spread and alleviate its impact from the early days of the epidemic. That included expansion of ART provision to health facilities located closer to the communities has improved access to ART for vulnerable groups. In Ethiopia, around two hundred and fifty thousand people living with HIV initiated treatment and nearly two hundred thousands are currently on ART (WHO, 2005). In spite of the courage shown regarding universal access to the treatment, there is a critical shortage of figures about the results of the therapy in the country. Thus, the objective of this study is to examine the survival status and associated factors.

METHODOLOGY

An open retrospective cohort study design was carried out at one ART clinic in Mizan Hospital, on people living with HIV/AIDS (PLWHA) who attend ART follow-up clinic.

Study setting

Mizan Hospital is a general hospital found in Southern Ethiopia, 565 km in southwest Addis Ababa. ART service was introduced in 2003 in the hospital. A total of 2682 patients who started ART was selected using distinctive identification serial number from the ART database and studied.

Data processing and analysis

A secondary data routinely collected for clinical monitoring and evaluation purpose in the hospital was used. The data were fed into an ART register database by a trained data clerk during the follow-up time. Data recording and entry usually starts when patients engaged in HIV- follow-up care in the hospital. The accessed database was retrieved using Microsoft Excel; data were transported to Epi-Info 7 for windows; and the imported data were checked for completeness, cleaned and edited. Twenty-seven data with inadequate information was omitted from the analysis. The data was analyzed using SPSS version 20 for windows.

The survival time was analyzed in months using the time interval between dates of ART started and date of event (death), date of transfer for transferred out (TO), first date of the first missed appointment for lost cases and the date in which patient completed the end of follow up. The data were categorized into three age groups: pediatrics (age younger than 10 years), teens (age 11 to 19 years), and adults (age older or equal to 20 years). The characteristics of the study participants were designated in terms of quantitative value of descriptive statistics for numerical data and frequencies or proportion for nominal data. The actuarial life table method and/or KM approaches were carried out to compare the survival experience of study participants after initiation of ART. The Log rank test was used to test if the detected variance in survival experience in the groups was significant or not. Proportional Cox-regression hazard model was used in identifying potential predictors of mortality.

Measurement

The outcome of interest for the present study was death from any causes that was confirmed through medical registration in the ART clinic. Individuals alive and on the treatment, lost from follow up care, dropped and/or transferred out were seen as censored at the end of the follow-up time.

The study encompasses all patients who initiated the treatment from 2005, regardless of age. For individual patients, the following starting point information was taken: Age at initiation of ART (years), sex (male, female), entry CD4 cell count, baseline WHO medical stage, baseline functional status, date of last visit for clinical care, and date final event took place.

Ethical considerations

Personal identification data was maintained for confidentiality.

RESULTS AND DISCUSSION

The present study included 2655 patients out of 2682 patients who had initiated ART since 2005, irrespective of age. Of the 2655 patients, there were 6.3% pediatrics, 3.3% teenagers, and majority 90.4% were adults. The median interquartile range (IQR) age in year was 30.5 (IQR: 25.5, 35.6) for the adults and 17.8 (15.5, 19), 3(1, 7),

Table 1. Entry basic demographic and clinical characteristics of the study participant, Mizan Hospital, 2005 to 2013.

Characteristics	Age category n (%)			χ^2 p-value
	Children	Adolescent	Adult	
Sex (N =2655)				
Male	98(58.3)	14(16.1)	1111(46.3)	
Female	70(41.7)	73(83.9)	1289(53.7)	0.001
Age (n=2655, Mean (±SD)	4.1(3.1,3.1)	16.8(2.4 18)	31.5 (8.1)	
Base line CD4 (n=2446) median(IQR)=169(91,257)	336(214.5,569)	215(103.5, 270)	162.5(88, 249)	
CD4 0-49	5(4.9)	6(7.3)	264(11.7)	
50-199	17(16.7)	34(41.5)	1137(50.3)	0.001
≥200	80(78.4)	42(51.2)	861(35.9)	
WHO stage at entry (n= 2655)				
Clinical Stage one	11(6.5)	9(10.3)	246(10.2)	
Clinical Stage two	17(10.1)	10(11.5)	398(16.6)	0.105
Clinical Stage three	113(67.3)	58(66.7)	1443(60.1)	
Clinical Stage four	27(16.1)	10(11.5)	313(13)	
Baseline functional status (n=2655)				
Bedridden	29(17.3)	2(2.3)	145(6)	
Ambulatory	113(67.3)	27(31)	570(23.8)	0.001
Working	26(15.5)	58(66.7)	1685(70.2)	
Tuberculosis status (n=2655				
Yes (+ve)	30(17.9)	17(19.5)	533(22.2)	0.364
No (-ve)	138(82.1)	70(80.5)	1867(77.8)	
Isoniazid (n=2655)				
Yes	5(3)	11(12.6)	206(8.6)	0.014
No	163(97)	76(87.4)	2194(91.4)	
Regimen substitution (n= 2655)				
Yes	22(13.1)	19(21.8)	414(17.2)	0.191
No	146(86.9)	68(78.2)	1986(82.8)	
Cotrimoxazole prophylaxis (n=2655				
Yes	149(88.7)	77(88.5)	2131(88.8)	0.996
No	19(11.3)	10(11.5)	269(11.2)	

for teenagers and pediatrics correspondingly. More than half (54%) of participants were females among which 83.9% were found in the teenagers.

The baseline weight at treatment initiation was 50 (44, 56), 51 (45.5, 57) 42 (34.7, 50) and 13 kg (9, 16) for adult, teenagers and pediatrics, respectively. Cotrimoxazole preventive therapy (CPT) was provided to 89% of pediatrics, 87% teenagers and 89% adults. Tuberculosis co-infection was 18, 20 and 22% of teenagers, adolescents and adults, respectively. Regarding the WHO clinical stage of disease, for tuberculosis, majorities in all the age groups; 67% pediatrics, 67% teenager and 60% adults were in Stage three, while 16% pediatrics, 12% teenagers and 13% adults were in Stage four. The CD4 cell count at the time of entry was meaningfully different across the age groups (P=0.001): Pediatric patients still under the treatment at a median (IQR) cells/ml^3 cell count of 367 (240, 726), teenager patients that started at a median (IQR) cells/ml^3 of 198 (101, 271) and adult participants that started at a median (IQR) cells/ml^3 of 160 (IQR85, 245) (Table 1).

The incidence rate of mortality throughout the follow-up

Table 2. Probability estimates of periodic survival of the study participant using actuarial table, Mizan Hospital, 2005 to 2013

Duration (month)	Probability of event free experience at in age groups		
	Pediatric	Teens	Elderly
6	0.94(0.89, 0.97)	0.96 (0.88, 0.98)	0.96 (0.95, 0.97)
12	0.91 (0.86, 0.95)	0.93 (0.83, 0.97)	0.95 (0.94, 0.96)
24	0.91 (0.86, 0.95)	0.90 (0.80, 0.96)	0.94 (0.93, 0.95)
36	0.91 (0.85, 0.95)	0.90 (0.79, 0.95)	0.93 (0.92, 0.94)
48	0.91 (0.86, 0.95)	0.90 (0.79, 0.95)	0.93 (0.92, 0.94)

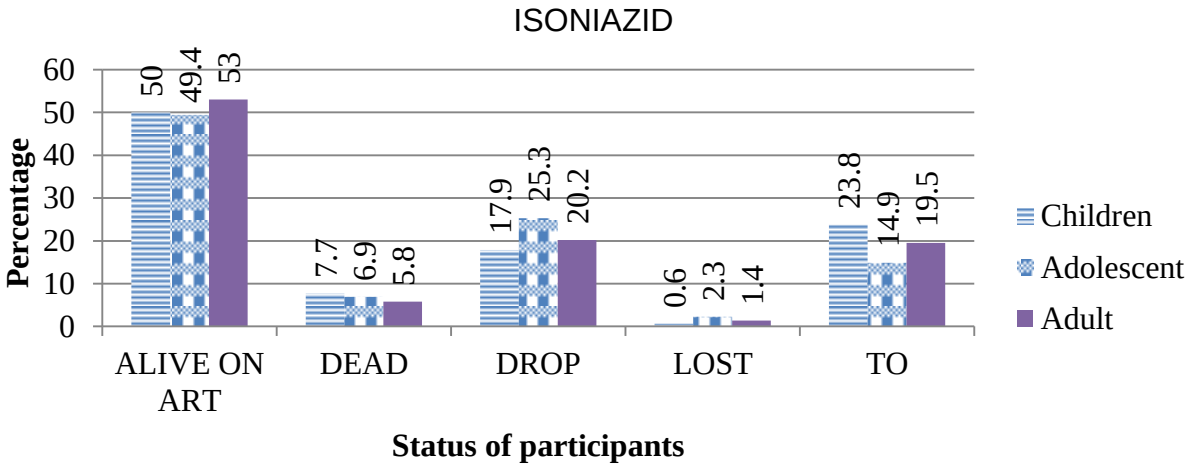

Figure 1. Final events of study participant, Mizan Hospital, 2005 to 2013.

time was 5.8, 6.9 and 7.7% among adult, teenagers and pediatrics, respectively. The failure rate was nearly 18% in children, 20% in adults and 25% in adolescents (Figure 2). The survival probability at the sixth month after the initiation of the treatments was 96 and 94% for pediatrics, 96% for teenagers, and 96% for adults (Table 2).

The trend of clients engaged in ART by the particular year at the study area was shown in Figure 2. The result reveals that children survival rate was 83 months (79, 87), 81 months (75, 86) for adolescent and 89 months (87, 90) for adults. Throughout the follow-up time, there were 159 deaths and 537 dropouts (Figure 1). In Cox regression model, gender, initial CD4 count, functional status and WHO clinical stage at treatment initiation, Isoniazid prophylaxis for tuberculosis co-infection, and age category was considered (Table 3). This model revealed that there is no significant difference between male and female in the risk of death. Progress of participants with advanced disease are as follows: Stage IV had higher risk (HR) (95% CI) 4.5(1.36, 14.88) of death when compared with patient with Stage I; Stage III had HR (95% CI) 3.2 (1.06, 10.23) of dying than Stage I, whereas there are no significant hazard risk differences compared with Stage II. Participants with a history of tuberculosis co-infection had higher risk (HR) (95% CI) 1.25 (1.03, 1.53) of death throughout the follow-up time. Danger of death in patient who did not take Isoniazid prophylaxis lowers by HR (95% CI) 72% on average when compared with taking Isoniazid during the follow-up time.

The HR (95% CI) for bedridden and ambulatory patients were 2.63 (2.05, 3.36) and 1.56 (1.31, 1.86) higher as compared to the working group. Patient ART initiated at CD4 count less than 50 cells/ml^3 were HR (95% CI) 1.977 (1.55, 2.52) when compared with patient ART initiated at CD4 count >200 cells/ml^3.

The result revealed that there was no significant difference in the age groups in crude mortality rate. However, higher proportions of lost to follow-up were seen in adolescent and adult than children. In multivariate analysis, explanatory variables did not reveal significant difference in mortality in all age groups, whereas higher proportion of adolescents was lost to follow up. A study done in Uganda (Bakanda et al., 2011) revealed that

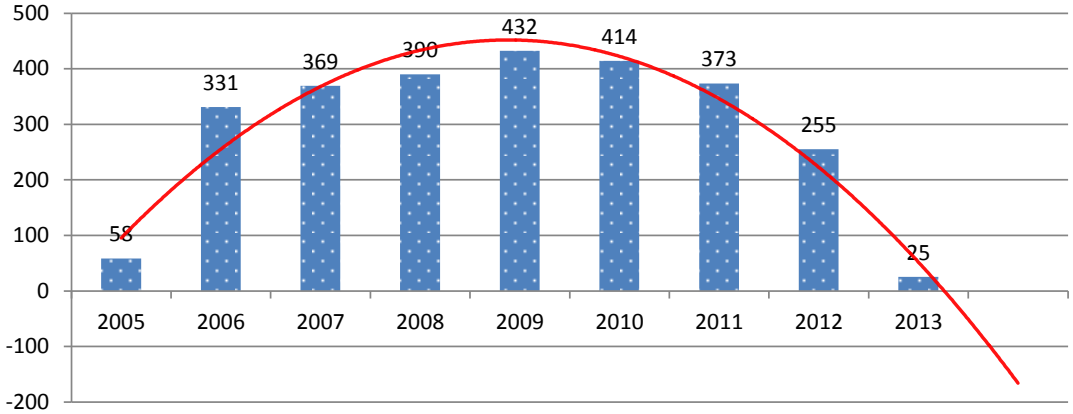

Figure 2. Trends in initiation of ART in study setting (Mizan Hospital, 2005 to May 2013).

Table 3. Cox proportional hazard regression model, predictors of mortality in study participants, Mizan Hospital, 2005 to 2013.

Characteristics	n	AHR (95% CI)	p
Age category	**2655**		
Child ≤10 years)	168	R	
Adolescent (11–19 years)	87	1.879(0.704,5.015)	0.208
Adult (≥20 yrs.)	2400	1.412 (0.789, 2.526)	0.245
Gender	**2655**		
Male	1223	0.987 (0.721, 1.350)	0.333
Female	1432	R	
WHO stage	**2655**		
Clinical Stage one or	266	R	
Clinical Stage two	425	2.142 (0.597, 7.681)	0.242
Clinical Stage three	1614	3.209 (1.060, 10.235)	**0.049**
Clinical Stage four	350	4.506 (1.364, 14.883)	**0.014**
Baseline functional status	**2655**		
Active	1769	R	
Self-helping	710	2.848 (1.939, 4.183)	**0.0001**
Bedridden	176	6.724 (4.253, 10.630)	**0.0001**
Ever ISONIAZID	**2655**		
Yes	222	R	
No	2433	0.205 (0.065, 0.647)	**0.024**
CD4 category	**2446**		
≤50	275	2.262(1.33, 3.82)	**0.003**
50-199	1188	1.414(0.91,2.2)	0.124
≥200	983		
Tuberculosis status	**2655**		
Yes(+ve)	580	1.25(1.027,1.525)	**0.026**
No(-ve)	2075		

there were no significant differences both in mortality and lost to follow-up among the age groups. However, a report from South Africa showed that adolescents had worse outcomes compared to their adult counter parts (Nachega et al., 2009). Likely explanations for this difference may be the sociocultural and other variations in the age groups in different countries.

In this study, risk of death was not related to gender. This is in line with other studies in Ethiopia that revealed gender has no significant effect on mortality (Alemu and Sebastián, 2010; Biadgilign et al., 2012). Contrary to these findings, ample evidences (Bakanda et al., 2011; Tsegaye and Worku, 2011; Assefa and Wencheko, 2012) confirmed male sex as an independent predictor of mortality. These debatable reports may be related to the socio-cultural differences in the study setting.

A patient who initiated ART as bedridden (inability to attain self-care in the daily living) had the shortest survival rate than working (able to perform routine activities). The result is consistent with various reports in Ethiopia (Biadgilign et al., 2012; Tsegaye and Worku, 2011; Assefa and Wencheko, 2012). The study showed that bedridden patients were 6.7 times more likely to die than those patients involved in their everyday activities. CD4 cell counts had a strong influence on the survival experience of patient on ART (Bakanda et al., 2011; Biadgilign et al., 2012; Zachariah et al., 2006). This study draws similar result and conclusion as the above researchers. New findings by other researchers reported that those patients with higher CD4 counts are at low risk for immediate adverse outcomes. There is suggestion in a number of literature that if ART is initiated with higher or normal CD4, both morbidity and mortality will be lessened (Andreychyn and Zhyvytsia, 2013; Kitahata et al., 2009; Hanna et al., 2013). New York report on ART (AIDS Institute, 2013) recommended that all patients with HIV infection be evaluated for initiation of ART regardless of the CD4 count. This is due to growing evidence that HIV patients benefit from ART at all stages of the disease (Cohen et al., 2011; Organization, 2012a). The result is consistent with other study reports from Ethiopia (Alemu and Sebastián, 2010; Biadgilign et al., 2012; Zachariah et al., 2006). WHO staging provides a basis for the development of AIDS defining conditions, characterized by severe clinical manifestation, which leads to gradual deterioration of the immune system. Therefore, it is likely that patients with deteriorating immunity are faced with challenges of survivorship.

This study has shown that patients with history of tuberculosis were 1.3 times at higher risk of mortality than those without a history of tuberculosis during the follow-up period. Similarly, study done by many scholars confirmed that HIV positive tuberculosis patients had shorter survival rate (Shaweno and Worku, 2012; Cavanaugh et al., 2012). The risk of death in patients who did not take Isoniazid preventive therapy lowered by 72% as compared with their counterparts. The result is not consistent with the documents that advocate Isoniazid as being among the preventive therapy which supposedly extends and improves the quality of life for people living with HIV (Vitoria et al., 2010). The possible reason for controversy is that Isoniazid preventive therapy is not universal amongst the cohorts. Only patients suspected for tuberculosis co-infections by health professionals, and in most cases of advanced medical stages are eligible for Isoniazid (FMOH, 2007).

Conclusions

Generally, this study finds out low incidence of mortality though there was high loss to follow-up rate. The likelihood of survival by the sixth month after beginning of ART was highest for adults compared to children and adolescents. Advanced clinical stage, base line functional status, low CD4 cell count, Isoniazid preventive therapy and tuberculosis co-infection were variables that predispose for mortality. HIV infected individual identification and early initiation of ART in the early stage of the disease should be given priority in the treatment modality. Further researches are required to accurately determine the risk factors related to mortality among the HIV patients who are taking ARV therapy.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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