Survival and Predictors of Mortality among Adult Patients on Highly Active Antiretroviral Therapy at Debre-Markos Referral Hospital, North West Ethiopia; A Retrospective Cohort Study

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Abstract

Background: The number of annual acquired immune deficiency syndrome (AIDS)-related deaths worldwide is steadily decreasing. In resource-poor settings, like Ethiopia the treatment was started recently. The survival and factors contributing to mortality are not yet well established.

Objective: To analyze the survival and predictors of mortality among adult patients started highly active antiretroviral treatment from September, 2005 to August, 2010 at Debre Markos Hospital, Ethiopia.

Methods: This was a retrospective cohort study among 930 adults who started HAART between September 2005 and August 2010 at Debre-Markos Hospital. Data was extracted from paper based medical records data base and the survival of patients was estimated by Kaplan-Meier Predictors of mortality were identified by Cox proportional hazards models.

Results: The survival patients were 57.0% (95% CI [53-60]) at 72 months. The significant predictors of mortality were advanced WHO stage (AHR=1.6, 95% CI [1.118-2.371]), mild anemia (AHR=2.6, 95% CI [1.886-3.640]), moderate to severe anemia (AHR=4.3, 95% CI [2.998-6.131]), poor adherence (AHR=3.1, 95% CI [2.341-4.129]), CD4 50-99 cells/l (AHR=2.0, 95% CI [1.058-3.889]), CD4<50 cells/l (AHR=2.2, 95% CI [1.140-4.182]) and not taking cotrimoxazole prophylaxis (AHR=1.7, 95% CI [1.272-2.172]).

Conclusion: The study has shown an overall high mortality. The advanced WHO stage, anemia, not taking cotrimoxazole prophylaxis, poor adherence and low CD4 cell count plays an important role in the mortality of patients. A careful monitoring of patients particularly during the first 3 months of HAART is necessary.

Keywords: HAART; Survival; Mortality; Ethiopia

Introduction

Acquired immune deficiency syndrome (AIDS) is one of the most destructive epidemics the world has ever witnessed. Globally an estimated 34 million people were living with HIV. About 2.7 million people were newly infected and 1.8 million were died in 2010 [1]. The problem is worse in Sub-Saharan Africa, in 2010, an estimated 22.9 million people in the region were living with HIV/AIDS and 1.2 million AIDS-related deaths, representing 67% of global AIDS deaths [1].

Antiretroviral drugs introduced in 1996 are a turning point for hundreds of thousands of people with access to health care systems [2,3]. Until the end of December 2010, more than 6.6 million people were receiving HIV treatment from 14.2 million eligible people living with HIV in low and middle income countries. This 47% coverage of HAART averted 2.5 million deaths in low- and middle-income countries since 1995 [1]. In these countries the estimated mortality after initiation of HAART was ranged from 5% to 40.7%, majority of these deaths occur soon after initiation of HAART as a result of advanced illness or immune reconstitution syndrome [4-7].

In Ethiopia HAART was started recently in 2005. At the end of June 2010, 550 health facilities were providing ART program (148 hospitals and 402 health centers). More than 473 thousand patients were enrolled to HIV/AIDS care and 268,934 patients were started on highly active antiretroviral therapy (HAART). The treatment coverage of HAART has reached to 80% [8]. Although the relationship between survival and its predictors such as low CD4 count, anemia, and advanced disease stage has been described elsewhere [9-13], the independent predictors of survival as well as the interaction of these identifiers in the general HIV-infected population after the advent of HAART remain poorly characterized in Ethiopia.

A better knowledge of prognostic factors would allow closer follow-up of and more targeted interventions in high-risk patients, thus reducing excess mortality. Therefore, the main aim of this study was to determine the survival and predictors of survival of patients after the initiation of HAART at Debre Markos Hospital. The finding will provide empirical evidence for program planner, decision makers to design a new and/or strengthen the existing intervention that improves the survival and reduce the high probability of death in HIV patients, for ART program implemen ter at the different level by enabling them to access a base line data on predictors of survival of patients on HAART.

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Methods

Study design, area and period

A retrospective cohort study was conducted at Debere Markos Referral Hospital (300 Km North West of Addis Ababa) from December, 2011 to May, 2012. Adult patients who started HAART from September, 2005 to August, 2010 were included in the study except incomplete medical records of WHO clinical stage, CD4 cell count and transferred in patients from other health facilities.

Sample size determination

The sample size was estimated by using Cox proportional hazards model \( \text{stower } \text{cox} \) in STATA 11 menu (Stata Corp, College Station, Texas USA). Calculation was based on the assumption that \( \alpha=5\% \), power=80% and standard deviation=0.5. The significant predictors assessed from the different study were used to calculate the largest sample size. Data incompleteness was anticipated to be 10%, and then the total sample size for this study was 930.

Data collection and quality control

The data was collected by using standard checklist, developed based on ART intake and follow up forms employed in ART clinic. Three experienced nurses who were trained for comprehensive HIV care were data collectors and investigators were supervising for consistency, completeness and accuracy every day. The most recent laboratory results before starting ART were generally used as baseline values. However, if there is no pre-treatment laboratory test, results obtained within one month of ART initiation will be used. Every incomplete questionnaire has been sent back to the corresponding data collector for check up under supervision. Ten percent of the collected data was randomly selected and re-entered and compared with the already entered to check the correct entry of the data.

Study variable and endpoints of the study

Time to event in months was the outcome variable. The independent variables were age, sex, educational level, marital status, occupation, residence, functional status, WHO clinical stage, anemia, drug regimen, CD4 count, cotrimoxazole prophylaxis, past opportunistic infection. Anemia classification was normal if hemoglobin level \( \geq 12 \) g/dL for women and \( 10-12.9 \) g/dL for men), moderate to severe anemia \( 9-11.9 \) g/dL for women and \( 10-12.9 \) g/dL for men), moderate to severe anemia \( (\text{hemoglobin}<10 \text{ g/dL}). \)

The endpoint in this study was death from all causes. HAART initiated patients were followed until the date of death, lost to follow-up, transfer out or until the end of the study. Individuals on HAART, lost to follow-up, transfer out at the end of the study period were censored; that is they were considered as alive for the time period they had been under follow up. The survival time was calculated in months using the time between dates of treatment initiation and to date of event (death) or date of censored. Finally, individuals alive and on HAART were censored at August, 2007, 31, 2011.

Statistical analysis

Data analysis was conducted by STATA version 11.0 (Stata Corp, USA). Kaplan-Meier survival analysis was applied to estimate the survival of different groups of patients on HAART; Log-rank (Cox Mantel) test was used to compare the KM curves for two or more categories of patients on HAART \([15-20]\). The hazard ratio and predictors of mortality of patients on HAART over a period of time \( t \), was analyzed by Cox proportional hazards model. Multicollinearity was excluded using Spearman’s correlation coefficient with a cutoff at 0.5. Every independent variables were tested with dependent variable and baseline variables significant at \( P<0.2 \) level in bivariate analysis were included in the multivariable Cox regression model. All tests were two-sided and level of significance was set at \( P<0.05 \). The assumptions of Cox proportional hazard was assessed by scaled Schoenfeld residuals. The influential observations on the parameter estimate in this survival analysis were assessed by DFBETA plots. Overall summary measures of goodness of fit of the model were assessed by Cox-Snell residuals and Hosmer and Lemeshow \( R^2 \).

Ethical considerations

Ethical clearance was obtained from institutional review board of Mekelle University and Debre-Markos hospital officials was communicated using support letter from Department of Public Health. No personal identification was registered and confidentiality was maintained by using data collectors from the service providers. No raw data was given to other parties.

Results

Cohort basic characteristics at the initiation of HAART

A total of 930 records were included in the study. The median age of patients was 34 (IQR, 28-40). Five hundred twelve (55.1%) of the patients were females. Thirty one point two percent (290) of the patients were illiterate and 41.6% were married. At the initiation of HAART, the median weight was 50.0 (IQR, 44-55) Kg. Six hundred ninety nine (75.0%) of the cohort were on WHO stage III. The median CD4 count was 116 (IQR, 59-167) cells/µL. The median hemoglobin value was 12.4 (IQR, 10.6-14.0) g/dL. Fifty two per cent (484) of the clients had three or more opportunistic illness. Approximately 64.0% (593) and 41.0% (381) of patients had fever (>1 month, unexplained) and recurrent upper respiratory tract infection, respectively. About 20% (182) of study participant had TB co-infection. Twenty point five (191) percent of the clients were poorly adhered (Table 1).

Cohort’s survival pattern

The total person-years follow up was 1597.6 with a cumulative incidence of 1.9 deaths per 100 person-years. The mean survival time of patients on HAART was 20.6 (SD=19.8) months. The estimated mortality was 18.6, 20.5, 21.8 and 22.9 per 100 person-years at 6, 12, 24 and 72 months respectively. The survival probability of patients who initiated HAART was 68%, 64% and 61% at 6, 12 and 24, respectively. The overall survival of patients on HAART was 57% at 72 months of follow up (Figure 1).

The lowest survival probabilities was observed for patients with CD4<50 cells/µL 32.0%, WHO stage IV 33.0%, moderate to severe anemia 20.0%, poor adherence 26% and not taking cotrimoxazole prophylaxis category 50% and male 52.0%.

Predictors of Survival of Patients on HAART

After applying bivariate and multivariable analysis five variables were found to be significant predictors of mortality among adult HIV patients using HAART. These were advanced WHO stage (AHR=1.63, 95% CI [1.118-2.371]), mild anemia (AHR=2.62, 95% CI [1.886-3.640]) and moderate to severe anemia (AHR=4.29, 95% CI [2.998-6.131]).
poor adherence (AHR=3.11, 95% CI [2.341-4.129]), CD4 50-99 cells/µl (AHR=2.03, 95% CI [1.058-3.889]), CD4<50 cells/µl (AHR=2.18, 95% CI [1.140-4.182]) and not taking cotrimoxazole prophylaxis (AHR=1.66, 95% CI [1.272-2.172]) (Table 2).

**Discussion**

The result of our study revealed that the overall survival of patients on HAART was 57.0% at 72 months of follow up. Low CD4 cell count, WHO clinical stage IV, anemia, poor adherence and cotrimoxazole prophylaxis were independent predictors of mortality among patients on HAART (p<0.05).

The overall survival of patients on HAART in this study was 57.0% after 5 years (95% CI: 52.9%-60.2%) which was in line with study conducted in Cameroon [6] where the survival probability was 47% (95% CI: 40.0%-55.0%) at 5 years which still was very low. Mortality was high in this cohort, and two thirds of it occurs in the first three months after initiation of HAART. This was higher than the previous studies conducted in other African countries [21-24] but less than to the study conducted in Tanzania (40.7%) [5]. This higher deaths probably might be due to late initiation of treatment as a study conducted in Ethiopia earlier indicated that the mortality of patients who initiated HAART early was 11.3% [13] which might strengthen the recommendations over the need to initiate ART at the early stage of the disease. The presence of advanced disease at baseline in most cases requires closer attention and frequent follow up by clinicians in order to prevent and treat conditions in early follow up periods.

Advanced WHO stage IV at baseline was an independent predictor of survival. This is in line with previous studies [5,6,21,24,25] which shows that advanced stage of the disease was associated with more than a doubling in the hazard of death. This might be associated with immune reconstitution syndrome and worsening of drug toxicity with these particular patients.

The prevalence of base line hemoglobin level ≤ 10 g/dl at the initiation of HAART in this study is 18.0% which is lower than other studies conducted in other part of Ethiopia, 39.8%, and Tanzania where half of the patients had hemoglobin level<10 g/dl [5,26]. Since majority of the study participants were in the WHO stage III, CD4<200 cells/l and more than half of them had three or more opportunistic infection, hence the incidence of anemia might increased with progression of HIV infection which probably had contributed to increase the risk of death [27]. Anemia was a strong predictor of mortality in this study. Studies from developing countries such as Zambia, Tanzania, Cameroon and Senegal also showed that hemoglobin level less than 10 g/dl was independently associated with mortality [6,27]. This might be because of worsening the condition by using HAART.

In this study, the risk of mortality was increased when the baseline CD4 cell count was decreasing which was in line with studies conducted in Sub-Saharan Africa which indicates that CD4 count less than 50 cells/µl (versus CD4>50 cells/µl) was a risk factor for mortality of patients on HAART [10,11,21,24,25]. Researches revealed patients are more prone to opportunistic infections, like tuberculosis, when HAART is initiated at lower CD4 count [28]. So this might indicate the importance of initiating HAART earlier.

Being put on cotrimoxazole prophylaxis was found to improve the survival probability of the patients on HAART significantly. This finding was supported by studies conducted in Hawassa Hospital, Ethiopia, Guadeloupe and South Africa [11,29,30]. This could be due to the benefit from cotrimoxazole in prevention of the classic

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**Table 1**: Baseline characteristics and associated mortality among 930 HIV-infected patients starting ART at Debre Markos Hospital, 2012.
opportunistic infections; *Pneumocystis pneumonia*, toxoplasmosis, bacterial pneumonia sepsis and diarrhea [30].

Poor adherence at the initiation of HAART had significant association with mortality in this study which was congruent with previous study conducted in Addis Ababa [10] and Malawi [22]. Researchers also revealed that good adherence was significantly correlated with high general health perception scores, and overall quality of life component scores [31].

In this retrospective study socio-demographic character such as being male, older age did not show an association with mortality of patients initiated on HAART. However; different studies showed that being male and older age were significant predictors of survival [5,10,11,13,32]. Various studies [5,21,22,28,33] found no association between sex and survival which support this study. Systematic review study also indicated paradox findings with regard to the relationship of socio-demographic characteristics and survival of patients on HAART [34].

**Limitations of the study**

The data were collected retrospectively from patient files in a context of routine care and hence there might be a certain degree of under reporting of events. Strict assumptions to exclude those records do not have CD4 count and WHO clinical stage may create under or over estimation of the health outcome and the survival rate. Baseline weight, height, hemoglobin and other socio-demographic variables have faced data incompleteness. All deaths were considered as HIV/AIDS related due to the lack of records on the cause of death.

**Conclusion**

The probability of survival of patient on HAART was 57% at 72 months and high mortality was observed in the first 3 months after initiation of treatment. The independent factors of mortality were being advanced WHO stage, low hemoglobin level, not taking cotrimoxazole prophylaxis, low CD4 count (<50 cells/µl) and poor adherence.

**Acknowledgements**

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**References**


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**Table 2:** Multivariate Cox’s proportional hazards regression model showing significant independent predictors of mortality of patients started HAART from September, 2005 to August, 2010 at Debre Markos Hospital, 2012.

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