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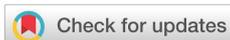
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Research Article

Predictors of mortality among adult patients enrolled on Antiretroviral Therapy in Hiwotfana specialized University Hospital, Eastern Ethiopia: Retrospective Cohort study

Abstract

Objective: Mortality of HumanImmunodeficiency Virus (HIV)- infected patients have been reduced substantially since the introduction of Antiretroviral Therapy (ART). However, many studies have shown high mortality. But the factors associated with this high mortality are poorly characterized. So this retrospective cohort study aims to determine mortality and identify predictors of it among patients on ART at Hiwotfana specialized university Hospital (HFSUH).

Result: A total of 61 (11.9%) deaths were observed giving an overall mortality rate of 2.8 per 100 person years. Advanced WHO stages (hazard ratio (HR) =3.44, 95% CI: 1.73 - 6.85), baseline CD4 count less than 200cells/mm3 (HR=3.18, 955 CI: 1.671- 6.06), regimen changed (HR=23.62, 95% CI: 9.95 - 56.05), and being anemic (HR=3.23, 95% CI: 1.71 - 6.11) were the independent predictors of mortality. Patients who started AZT based initial regimen had a lower risk of mortality (HR=0.29, 95% CI=0.13 - 0.64) when compared with the D4T based regimen.

Introduction

Globally, the number of people living with human immunodeficiency virus (HIV) reached 38.8 million in 2015(1). Ethiopia is one of the sub-Saharan African countries hardest hit by the HIV epidemic. In Ethiopia, there were 786,040 HIV-infected people, 39,140 new HIV infections and 28,650 HIV/AIDS deaths in 2015 [1].

There has been a dramatic decline in morbidity and mortality in patients with HIV disease in all demographic sub-populations with the advent of highly active antiretroviral therapy (HAART) [2-4]. Global mortality peaked in 2005 at 1.8 million and subsequently fell by 5·5% per year to 1.2 million in 2015 [1]. According to UNAIDS/Ethiopia report, approximately 20,000 HIV related deaths [5]. Despite the increased availability of ART and promising efficacy, early mortality has been high after initiating ART [6,7]. Factors contributing to the high fatality rate and reduced quality of life in poor countries are poorly peederstood.

Multiples of factors have been associated with mortality among clients on ART [7-10]. However, those factors which contribute to the deaths of HIV-infected patients while on ART are not well explored particularly in eastern Ethiopia. Therefore, this study aimed to investigate the predictors of mortality among adult ART users in HFSUH, eastern Ethiopia.

Methods

Study period, setting and participants

The present study was conducted from January to June 2016 in HFSUH located eastern part of Ethiopia. The hospital starts ART service in 2005 and since then it has been providing, free of charge ART to eligible HIV-infected patients.

The treatment protocol for Ethiopia is implemented using World Health Organization (WHO) ART treatment guideline for HIV infection in adults and adolescents [11] and national guidelines for HIV prevention, care and treatment: Federal Democratic Republic of Ethiopia [12]. According to the current treatment guidelines, HIV infected adults are eligible to start ART if their CD4cell count is < 500cells/mm3 irrespective of CD4 count or WHO clinical stage 3 or 4 irrespective CD4 cell count. Breast feeding women, pregnant women, and sero-discordant

couples can start ART irrespective of CD4 cell count. For all HIV-infected children below 15 years of age, ART is recommended irrespective of WHO clinical stage and CD4 cell count.

Study design

A retrospective cohort study was conducted from January to June 2016 on treatment-naïve adult patients who enrolled on ART from 2005 to December 2015. Sample size calculation was done based on the assumption that the type I error of 5%, power by 80% and the exposure variable is CD4 count less than 200cells/mm³ (HR =5.4) which gives the maximum sample size among significant predictors collected from relevant literatures. Based on this, random sample of 513 patient's medical records was drawn for data collection. Regarding the sampling technique, patients' medical card numbers were generated from the computer database according to their entry time and adult patients were filtered using eligibility criteria, then we give a unique number for the remaining records and select each record for our study using systematic random sampling. Pregnant women started ART for prevention of mother to child transmission (PMCT), regimen change, and transfer in were excluded from the study.

Data collection and quality control

A Standard checklist containing study variables were developed from the patient registry card which was developed by the Ethiopian Federal Ministry of Health (FMOH). During data collection, the most recent laboratory results before starting ART were generally used as baseline values. If there is no pre-treatment laboratory test, however, the results obtained within one month of ART initiation were used. The data collection/extraction process was supervised by the principal investigator. Two trained data collectors were involved in the study; both were nurses working in the ART clinic. All completed data were examined for clarity and consistency on a daily basis.

Study variables and measurements

Patients' survival time (time to death) was the outcome variables of this study. In some patients who lacked the time of death, the last follow up time was used. Mortality/death was defined as any recorded AIDS-related deaths, including deaths due to opportunistic infections secondary to delayed ART initiation, treatment failure and poor adherence to both ART regimen and prophylactic antibiotics

The independent variables include: age, sex, marital status, past opportunistic infection (OI), baseline WHO clinical stages, baseline CD4 counts, nutritional status (measured by body mass index (BMI)), baseline opportunistic infection, IPT status, initial HAART, Hemoglobin level (Patients were called anemic if the hemoglobin level is (<12mg/dl)), HIV/TB co-infection, Isoniazed prophylaxis therapy (IPT) status, and regimen change. Regimen change excludes transfer-out and defaulters.

Statistical analysis

The collected data were cleaned, categorized, coded, entered and analyzed by using STATA 12. Kaplan-Meier survival analysis was used to estimate survival probability. We applied Cox-proportional hazards regression to identify risk factors associated with outcome variable (time of regimen change). Variables found to be associated with the outcome in the univariate analysis assuming a significance threshold of 20% were included in the multivariate analysis. The multivariate analysis results showed a significant effect on the outcome considering the significance thresholds of 5% were described.

Ethical consideration

Ethical clearance was obtained from Ethical clearance board of Haramaya University, college of Health and Medical science (reference number sop 792/1/2016) and data access permission was obtained from the medical director of HFSUH. We simply extracted anonymized data from the patient's medical registry and no participant was involved in the study.

Results

Characteristics of study participants

A total of 513 patients medical records were used to extract the information. The socio-demographic characteristics of the cohort are summarized in table 1. The mean age of the patients was 34.75 +7.19 years. Up on enrolment, 48.34% of the patients were in WHO clinical stage III or IV and the mean CD4 count were

Table 1: Baseline factors of HIV-infected patients on initial HAART at Hiwotfana Specialized University Hospital from 2005 to June 2016, eastern Ethiopia.

Variables	Alive (n)	Dead (n)	Total (N)
Mean Age, years ± SD			34.75± 7.19
Sex			
Female	267	34	301
Male	185	27	212
BMI			
Underweight (<18.5)	195	41	236
Normal (18.5 - 25)	236	17	253
Above weight(>=25 -30)	16	2	18
Obese (>=30)	4	1	5
WHO stages			
Stage I &II	251	14	265
Stage III&IV	201	47	248
CD4 count(cells/mm3)			
<200	170	48	218
≥200	282	13	295
IPT status			
Not took	177	49	226
Took	274	12	286
Active HIV/TB co-infection			
No	397	43	440
Yes	55	18	73
Regimen change			
No	212	50	262
Yes	240	11	251
HAART regimen			
D4T-based	176	20	196
AZT-based	122	13	135
TDF-based	153	28	181
Anemic status			
Non-anaemic	206	48	254
Anemic	208	12	220

221 cells /mm³ (+111.32). The initial HAART regimens were changed for 251(48.93%) of the patients during the follow up period.

[i]IPT, Isoniazid prophylaxis therapy, WHO clinical stage I indicates asymptomatic and persistent generalized lymphadenopathy; WHO clinical Stage 3 was defined if one of the following is present: weight loss of >10% body weight, chronic diarrhea for >1 month, fever for >1 month, oral candidiasis, or pulmonary Tb within the previous year, or severe bacterial infections; WHO clinical Stage 4 was defined if one of the following is present in an HIV diagnosed patient: HIV wasting syndrome, PCP, toxoplasmosis of the brain, cryptosporidiosis with diarrhea for >1 month, cytomegalovirus disease, herpes simplex virus infection, progressive multifocal leukoencephalopathy, candidiasis, extra-pulmonary Tb, lymphoma, kaposi's sarcoma.

Prevalence and trends of mortality

Patients were followed for a total of 2123.9 person years (PY) with a median follow up of 48.48 months. The overall mortality rate was 2.8 per 100 PY of follow-up (95% CI=2.22 - 3.69). In this cohort, 11.9% (n=61) of the patients were died, most of the deaths, 27 (44.26%), occurring within the first six months. The estimated survival probability at 6, 12, 18 and 24 months were 94.6%, 93.5%, 92.3% and 89.7%, respectively.

Predictors of mortality

The results from the multivariable Cox proportional hazards regression analysis found patients who were on WHO clinical stage III or IV (HR=3.44, 95% CI: 1.73 - 6.85), regimen changed (HR=23.62, 95% CI: 9.95 - 56.05), baseline CD4 count less than 200 cells/mm³ (HR=3.18, 955 CI: 1.671- 6.06) and anemic patients (HR=3.23, 95% CI=1.71 - 6.11) had higher odds of death compared with their respective counterparts shown in table 2. Patients who started AZT based initial regimen had 71% less risk of mortality (HR=0.29, 95% CI=0.13 - 0.64) when compared with the D4T based regimen.

Discussion

This 10-year retrospective cohort study of HIV/AIDS patients on HAART gives an insight into survival and its predictors in hospital settings in Ethiopia. In this cohort, 1/10th (11.9%) of the patients died and the majority of the deaths (44.26%) occurred within the first six months. Studies from other parts of Ethiopia, Shashamane referral hospital, Jinka hospital and Ethiopian Somali region reported comparable results, 10.3%, 10%, 11.1% respectively [13-15]. In contrary, studies from other regions of Ethiopia, Nekemte Referral Hospital (7.2%) and Aksum Hospital (8.85%) reported lower mortality [9,16].

The estimated survival probability of our cohort at 6, 12, 18 and 24 months were 94.6%, 93.5%, 92.3% and 89.7%, respectively. This shows a better survival compared with Ethiopian Somali [13] and Malawi studies [20]. This better survival in our cohort group may be due to majority of this cohort started HAART at WHO stage I or II (51.66%) and at a CD4 count > 200 cells/mm³ (57.5%).

Previous studies done in Ethiopia show that advanced WHO clinical stage was one of the major predictors of mortality for patients enrolled on ART [17-19]. This study was consistent with those findings. A Cohort study from Cameroon [20], indicated patients with stage III (2 times) and stage IV (3.79 times) more likely to die than patients with stage I or II. Previous studies in Africa, Tanzania, South Africa and Senegal [7,21,22] also showed that advanced stage of the disease was associated with more than doubling in the hazard of death.

In this cohort study, clients with baseline CD4 count < 200 cells/mm³ had higher hazard of mortality than patients with CD4 count >200 cells/mm³. Cohort study in university of Gondar indicated patients presented with CD4 count < 200cells/mm³ had 5 times higher risk of mortality than those with >200cells/mm³[23]. In line with the present study, different studies found twice or more risk of mortality among patients with CD4 count of < 200 cells/mm³ (7,8,24). Advanced immunodeficiency was associated with opportunistic infection, thereby increasing the likelihood of death

Patients who were anaemic at baseline were 3 fold higher risk of mortality than those who doesn't have. Previous studies done across many parts of Africa and in industrialized countries reported that anaemia at baseline was independently associated with higher mortality among patients enrolled on ART [7,20,25]. A Similar study from Ethiopia by Tadesse and colleagues [15], mortality was higher among patients with anaemia than their comparator. Although there is no concrete evidence on causal association between anaemia and mortality,

Table 2: Hazard ratios of mortality according to baseline variables in HIV-infected patients starting HAART in Hiwotfana Specialized University Hospital from 2005 to June 2016, eastern Ethiopia.

Variables	Unadjusted HR	p-value	Adjusted HR	P-value
WHO clinical stages (vs. I &II)				
Stage III & IV	3.16 (1.74 − 5.75)	0.000	3.44(1.73 - 6.85)	**0.000**
CD4 count (cells/mm3)(vs.≥200)				
<200	4.47(2.42 - 8.28)	0.000	3.18(1.671- 6.06)	**0.000**
TB status (vs. Negative)				
Positive	2.44 (1.41- 4.24)	0.001	0.88(0.48 - 1.62)	**0.683**
Regimen changed(vs. No)				
Yes	8.87(4.46 - 17.67)	0.000	23.62(9.95-56.05)	**0.000**
Initial HAART (vs. D4T-based)				
AZT- based	1.29(0.63 - 2.62)	0.489	0.29(0.13 - 0.64)	**0.002**
TDF-based	3.31 (1.77 − 6.19)	0.000	0.55(0.27 - 1.13)	**0.103**
Anaemic status(vs. non-anaemic)				
Anemic	3.73(1.98 - 7.02)	0.000	3.23(1.71 - 6.11)	**0.000**

the incidence of anemia, increased with the progression of HIV disease [7,26,27].

The initial regimen change was a significant predictor of mortality in this cohort study. Different studies confirm that ART regimen change causes diminishing the clinical and immunological benefit of treatment [28,29] failing virological suppression, increase drug resistance [30] and thereby increase morbidity and mortality due to HIV/AIDS [30,31]. This cohort also showed that patients on Zidovudine based regimens were shown to have less risk of mortality (HR: 0.34; 95% CI: 0.16 – 0.76) than D4T based regimen.

Conclusion

This study has revealed an overall low mortality rate, but the high mortality rate in the first six months of HAART initiation. Advanced WHO stages, lower CD4 count, ART regimen changed, D4T based regimen and anemia were the independent predictors of mortality. For this reason, early enrolment of patients on HIV care service and treatment is very crucial to improve patients' survival.

Limitations of the study

We acknowledge the limitations of the current study, including: 1) This study includes only patients' medical records with complete baseline information, so this might have made a selection bias; 2) all deaths documented were considered as HIV/AIDS related deaths due to lack of available records on the cause of death; 3) it also shares limitations of retrospective studies.

Acknowledgments

Authors' contributions

EM: conceived, designed and participated in data collection, conducted the data analysis and interpretation, developed the first draft and revised subsequent drafts. MH: participated on data collection, data analysis and interpretation. TF: reviewed and commented on successive drafts. AB: commented on successive drafts.

Ethics approval

Ethical clearance board of Haramay University, College of Health and Medical science, ethically approved all the study methods and protocols and responded with a letter reference number sop792/1/2015. Informed consent was not taken from the patients, as the information was extracted from anonymized data.

Availability of data and material

All relevant data are within the paper. The STATA data of individual patients are not permitted to be provided to other bodies, as indicated on ethical clearance. However, researchers who need further clarification can obtain anonymised data from the corresponding author on reasonable request.

References

1. GBD 2015 HIV Collaborators (2016) Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. Lancet HIV 3: e361-e87. **Link:** https://goo.gl/GknZY4

2. Chan KC, Wong KH, Lee SS (2002) Universal decline in mortality in patients with advanced HIV-1 disease in various demographic subpopulations after the introduction of HAART in Hong Kong, from 1993 to 2002. HIV Med 7: 186-192. **Link:** https://goo.gl/CouFTm

3. May M, Boulle A, Phiri S, Messou E, Myer L, et al. (2010) Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet 376: 449-457. **Link:** https://goo.gl/y7xL5a

4. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, et al. (2006) Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA 296: 782-793. **Link:** https://goo.gl/TPkCgw

5. UNAIDS (2016) global-AIDS-update-2016. **Link:** https://goo.gl/u7HMk9

6. Ivers LC, Kendrick D, Doucette K (2005) Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. Clin Infect Dis 41: 217-224. **Link:** https://goo.gl/N9d18z

7. Johannessen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, et al. (2008) Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infect Dis. 8: 52. **Link:** https://goo.gl/h4H6qe

8. Biadgilign S, Reda AA, Digaffe T (2012) Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. AIDS Res Ther 9: 15. **Link:**

9. Tadesse K, Haile F, Hiruy N (2014) Predictors of mortality among patients enrolled on antiretroviral therapy in Aksum hospital, northern Ethiopia: a retrospective cohort study. PLoS One 9: e87392. **Link:** https://goo.gl/Y4nUQ1

10. Poka-Mayap V, Pefura-Yone EW, Kengne AP, Kuaban C (2013) Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study. BMJ Open 3. **Link:** https://goo.gl/ddVCQx

11. WHO (2010) Antiretroviral therapy for HIV infection in adults and adolescents. Geneva: WHO, 2010. **Link:** https://goo.gl/dosaQo

12. FHAPCO (2014). Country Progress Report on HIV / AIDS: Federal Democratic Republic of Ethiopia. Addis Ababa, Ethiopia 2014 **Link:** https://goo.gl/MNmUah

13. Alemu AW, Sebastian MS (2010) Determinants of survival in adult HIV patients on antiretroviral therapy in Oromiyaa, Ethiopia. Glob Health Action 3. **Link:** https://goo.gl/eXSkfZ

14. Damtew B, Mengistie B, Alemayehu T (2015) Survival and determinants of mortality in adult HIV/Aids patients initiating antiretroviral therapy in Somali Region, Eastern Ethiopia. Pan Afr Med J 22: 138. **Link:** https://goo.gl/YkRFe6

15. Tachbele E, Ameni G (2016) Survival and predictors of mortality among human immunodeficiency virus patients on anti-retroviral treatment at Jinka Hospital, South Omo, Ethiopia: a six years retrospective cohort study. Epidemiol Health 38: e2016049. **Link:** https://goo.gl/tNKZEr

16. Hambisa MT, Ali A, Dessie Y (2013) Determinants of Mortality among HIV Positives after Initiating Antiretroviral Therapy in Western Ethiopia: A Hospital-Based Retrospective Cohort Study. ISRN AIDS 2013: 491601. **Link:** https://goo.gl/NvwusR

17. Tadele A, Shumey A, Hiruy N (2014) 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. J AIDS Clin Res 5: 280. **Link:** https://goo.gl/vuisvX

18. Mulissa Z, Jerene D, Lindtjorn B (2010) Patients present earlier and survival has improved, but pre-ART attrition is high in a six-year HIV cohort data from Ethiopia. PLoS One 5: e13268. **Link:** https://goo.gl/vtFRvZ

19. Setegn T, Takele A, Gizaw T, Nigatu D, Haile D (2015) Predictors of Mortality among Adult Antiretroviral Therapy Users in Southeastern Ethiopia: Retrospective Cohort Study. AIDS Res Treat 2015:148769. **Link:** https://goo.gl/2fbDFz

20. Sieleunou I, Souleymanou M, Schonenberger AM, Menten J, Boelaert M (2009) Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon. Trop Med Int Health 14: 36-43. **Link:** https://goo.gl/o3WF54

21. Etard JF, Ndiaye I, Thierry-Mieg M, Gueye NF, Gueye PM, et al. (2006) Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. AIDS 20: 1181-1189. **Link:** https://goo.gl/w9mftC

22. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R (2005) Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. AIDS 19: 2141-2148. **Link:** https://goo.gl/tkk4fb

23. Wubshet M, Berhane Y, Worku A, Kebede Y, Diro E (2012) High loss to followup and early mortality create substantial reduction in patient retention at antiretroviral treatment program in north-west Ethiopia. ISRN AIDS 2012: 721720. **Link:** https://goo.gl/szFfYK

24. Johansson KA, Robberstad B, Norheim OF. Further benefits by early start of HIV treatment in low income countries: survival estimates of early versus deferred antiretroviral therapy. AIDS Res Ther 7: 3. **Link:** https://goo.gl/FAk4rf

25. Harris RJ, Sterne JA, Abgrall S, Dabis F, Reiss P, et al. (2008) Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. Antivir Ther 13: 959-967. **Link:** https://goo.gl/Pke9oF

26. Masaisa F, Gahutu JB, Mukiibi J, Delanghe J, Philippe J (2011) Anemia in human immunodeficiency virus-infected and uninfected women in Rwanda. Am J Trop Med Hyg 84: 456-460. **Link:** https://goo.gl/2tESQM

27. Obirikorang C, Issahaku RG, Osakunor DN, Osei-Yeboah J (2016) Anaemia and Iron Homeostasis in a Cohort of HIV-Infected Patients: A Cross-Sectional Study in Ghana. AIDS Res Treat 2016: 1623094. **Link:** https://goo.gl/5V5oSR

28. Assefa Y, Lynen L, Wouters E, Rasschaert F, Peeters K, et al. (2014) How to improve patient retention in an antiretroviral treatment program in Ethiopia: a mixed-methods study. BMC Health Serv Res 14: 45. **Link:** https://goo.gl/QHTdPy

29. Gesesew HA, Ward P, Woldemichael K, Mwanri L (2017) Prevalence, trend and risk factors for antiretroviral therapy discontinuation among HIV-infected adults in Ethiopia in 2003-2015. PLoS One 12: e0179533. **Link:** https://goo.gl/mDMNmg

30. Li X, Margolick JB, Conover CS, Badri S, Riddler SA, et al. (2005) Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 38: 320-328. **Link:** https://goo.gl/YMiG95

31. **Rosen S, Fox MP (2011) Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med 8: e1001056. Link:** https://goo.gl/w68XTD