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Predictors of mortality among HIV positive adults on antiretroviral therapy in Debremarkos Referral Hospital, Northwest Ethiopia

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Globally, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) reduces life expectancy by seven years. Mortality is high among non-treated patients in Ethiopia with about 58.1/100 person years of observation. However, the predictors of mortality have not been adequately studied. Hence, the main objective of the study was to determine predictors of mortality among HIV positive adults on antiretroviral treatment in Debremarkos Referral Hospital, Northwest Ethiopia. A facility-based retrospective cohort study design was conducted from September to February, 2013. Data were collected from 640 patients who were enrolled for treatment in Debremarkos Referral Hospital from 2005 to 2013. Proportional hazards Cox model was used to show the independent predictors of the risk of mortality. A total of 261 patients died during the follow up period. Baseline hemoglobin level of < 10 g/mm^3 (Adjusted Hazard Ratio (AHR) = 1.86, 95% CI: 1.39 to 2.64), baseline ambulatory functional status (AHR = 2.72, 95% CI: 1.90 to 3.90), bedridden functional status (AHR = 2.38, 95% CI: 1.32 to 4.27), baseline World Health Organization (WHO) staging III and IV (AHR = 2.16, 95% CI: 1.10 to 4.25), recent antiretroviral therapy (ART) adherence (AHR: 2.16, 95% CI: 1.03 to 4.56) and fair adherence (AHR = 1.88, 95%CI: 1.08-3.29) were associated with increased mortality. The risk rate of patients with unexplained chronic diarrhea and without prophylaxis for tuberculosis was increased by 1.53 and 3.98 times compared to patients without diarrhea and treated with tuberculosis prophylaxis, respectively. The mortality rate was high during early phase of treatment especially within the first 6 and 12 months. Baseline hemoglobin < 10 g/mm^3, baseline functional status-ambulatory and bedridden functional status, baseline WHO staging (stage III and IV), poor recent antiretroviral therapy adherence, chronic diarrhea and absence of tuberculosis prophylaxis were all significant predictors of mortality. Therefore, patients with the aforementioned predictors should be followed closely and frequently.

Key words: Predictors, mortality, HIV positive adults, antiretroviral therapy, Ethiopia.

INTRODUCTION

Expanding access of treatment had been contributing by 19% decline of deaths among people who are living with human immunodeficiency virus (HIV) between 2004 and 2009 (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010). A review of 14 cohort studies in high income countries showed that there is still a large discrepancy between the life expectancy of the general population and an HIV-infected individual. The death rates remain higher in HIV-infected individuals than in un-infected individuals, even when successfully treated, and that

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both AIDS and several serious non-AIDS events are more common in those with a lower CD4 cell count (WHO, 2002; Hogg et al., 2008).

Life expectancy at age 20 is decreased to 18.3 and 11.4 year for men and women who are infected by HIV, respectively (Biadgilign et al., 2012). The overall estimated mortality rate in 12 months post-antiretroviral treatment (ART) initiation is 14%. In sub-Saharan Africa (SSA), most causes of death are tuberculosis (TB), acute sepsis, cryptococca meningitis, malignancies (especially Kaposi's sarcoma and chronic diarrhea or wasting syndrome (Gupta et al., 2011; Stephen et al., 2008; Johannessen et al., 2008).

In developed countries, there is early initiation of ART with well monitoring and evaluation of the drug effects as well as patient response. Although, in Ethiopia free based ART is practiced for eight years, there is no enough data on mortality predictors once they are enrolled to treatment. The effectiveness of highly-active antiretroviral therapy (HAART) could vary from region to region because of the difference in background disease burden (such as tuberculosis or intestinal parasites), viral subtypes and possible genetic differences in drug metabolism (Massaquoi et al., 2009).

In the Debremarkos hospital, there has not been a study on mortality predictors of HIV patients on ART since the commencement of the service. Therefore, this study was designed to identify predictors of mortality among HIV positive adults who were on ART in Debremarkos Referral Hospital, Northwest Ethiopia.

METHODOLOGY

Study design, area and period

A facility-based retrospective cohort study design was conducted in Debremarkos Referral Hospital from 30th September, 2013 to 30th February, 2013.

Study population

All HIV positive adults' record in Debre Markos Referral Hospital who were on antiretroviral therapy enrolled to treatment from 30th September, 2005 to 30th February, 2013 were the source population and selected HIV positive adults' record on care and support follow up who had started ART at the hospital within the same period were included in the study. All HIV positive adults' record who were on antiretroviral therapy enrolled for treatment from 30th September, 2005 to 30th February, 2013 in Debre Markos Referral Hospital were used for source population, and selected HIV positive adults' record on care and support follow up who had started ART at the hospital within the same period were included in the study.

Eligibility criteria

All adult (≥ 15 years old) HIV positive individuals on care and support follow up who had started ART and had at least one visit in Debre Markos Referral Hospital were included. Adults with incomplete registration cards during the review who started ART from other healthcare institutions, drop outs, lost and transfer were excluded from the study.

Sample size determination

As the investigation was a cohort study, the sample size required for achieving statistically significant results was determined using two population proportion formula. Therefore, sample size was calculated by taking into account the major exposure variables and using open epi version 3.04.04 statistical package (Biadgilign et al., 2012). Among exposure variables, WHO staging is chosen as the main exposure variable of non-accidental mortality during the 6 years of follow up since it was considered to give the optimal sample size and most significant result. In this regard, a 5% level of significance (two-sided), a power of 80% and a ratio of unexposed to exposed of 1:1, estimated proportion of mortality in Ethiopia was taken as 4.1% for non-exposed group (WHO stage I and II) and 10.1% for exposed group (WHO stage III and IV) (Tsegaye and Worku, 2011; Worku and San Sebastian, 2009; Jerene and Lindtjørn, 2005) (Table 1). However, in practice, getting 320 patients in their WHO stage I and II was difficult and the rest were from stage III and IV. Thus, the total sample size was 640.

Sampling technique

Simple random sampling technique was used to recruit predetermined sample size from the clinic computerized register. First registration number was identified and computer generated number was used to select study subjects among the eligible cards. In Debremarkos Referral hospital, there were a total of 8,412 HIV patients enrolled for care and treatment between the year 2005 and 2013. To follow the patient for at least a minimum of 6 years, we included patents enrolled between September, 2005 and January, 2008 which was a total of 5,122 patients. From these patients, 273 transfer in, 24 incomplete registration, 45 lost, 259 drop, 1 stop and 76 children less than 15 years were excluded from the study, resulting in 1,646 eligible patients. The samples of 640 patient registration cards were selected randomly.

Variables of the study

The dependent variable of this study was occurrence of death and independent variables included demographic factors and clinical conditions such as WHO staging, baseline CD^{+}_{4} counts, Hgb status, opportunistic infections, concomitant illness, diagnosis/functional status, cotrimoxazole prophylaxis and base line body weight.

Operational definition

1. Incomplete card: When one of the independent variable is not registered namely, CD_4^+ cells, Hgb, WHO stage, functional status and TB status
2. Lost to follow up: Not seen since ≥ 1 month < 3 months (Worku and San Sebastian, 2009; Jerene and Lindtjørn, 2005).
3. Drop: Lost to follow up for > 3 months.
4. Transfer out: A patient referred to another health facility for care evidenced by his/her document.
5. Transfer in: A patient who started treatment I in another health institution and continued in Debremarkos hospital as evidenced by his/her registration card.

Functional status

1. Working: Able to perform usual work in or out of the house;
2. Ambulatory: Able to perform activities of daily living;

Table 1. Sample size calculation of retrospective cohort study HIV patients on ART in Debremarkos referral hospital, Northwest Ethiopia, 2005 to 2013.

Assumption	Major exposure variable	Sample size by Fleiss with CC Formula	Total number of sample size
Two-sided significance level: 0.05 Power: 80 Ratio of sample size: 1:1 Percent of Unexposed with Outcome: 4.1 Percent of Exposed with Outcome: 10.1 Odds Ratio: 0.38 Relative risk: 0.41	WHO clinical HIV staging grouped (I, II non exposed; III, IV exposed)	Number of exposed=320 Number of non-exposed=320	640

3. Bedridden: not able to perform activities of daily living (Jerene and Lindtjorn, 2005).
4. Baseline: Start of ART initiation;
5. ART regimen: Types of first line, second line, change in regimen;
6. Follow up outcomes: Lost to follow up, transfer out, adherence;
7. Mortality: if patient was known to be dead as reported by treating clinicians or community health agents, neighbor and/or relatives other than accidental causes while on ART;
8. Adherence: adherence is defined as good if adherence is > 95% (< 2 doses of 30 doses or < 3 dose of 60 dose is missed) as documented by ART physician; fair if adherence is between 85 to 94% (3 to 5 doses of 30 doses or 3 to 9 dose of 60 dose is missed) as documented by ART physician; and poor if adherence is < 85% (> 6 doses of 30 doses or > 9 dose of 60 dose is missed) as documented by ART physician;
9. Side effect: As recorded by ART physician/nurse on the patient card.

Data collection procedure

Data collecting checklist was prepared based on routine data registration protocol using the standardized ART entry and follow up form employed by the ART clinic. The data collecting checklist was used by data collectors for recording information from patients' cards.

Data quality control

To ensure quality, data were collected by ART staff nurses working in the hospital after one day training on the techniques of data collection. The completeness of data was checked by two trained supervisors so as to provide feedback in registration process and to correct when necessary. Furthermore, every night, data collectors, supervisors and principal investigators used to discuss about documenting the findings and exchange of the information. Moreover, pre-test was done on registrations that were not included in the final study.

Data processing and analysis

The data were entered in Epi data version 3.1 computer program. Prior to the analysis, the whole data were cleaned and 20% of the data was double-entered. The completeness of the data was checked. Errors related to inconsistency were verified using cross tabulation and other data exploration methods. The data was exported to statistical package for social sciences (SPSS) version 16.0. Then recorded, categorized and sorted to facilitate analysis. Then analysis done using SPSS version 16.0. Univariate Cox-proportional Hazards model was used to assess the relationship between baseline variables and mortality and calculate hazard ratios. Those variables showed statistical significance in univariate analysis with p-value of < 0.25 (David Jr., 1999) were selected for multivariable analysis and declared as statistically significant when p-value < 0.05.

Ethical consideration

Ethical clearance was obtained from the Ethical Review Board of Debremarkos University, College of Health Sciences, Department of Public Health. Permission was obtained from Debremarkos Referral Hospital and ART clinic. Verbal informed consent was obtained from responsible bodies of the hospital and ART clinic prior to the review. Confidentiality and privacy of the information were assured and maintained.

RESULTS

Between 19th September, 2005 to 30th January, 2008, 5,122 HIV patients were enrolled in Debremarkos Referral Hospital, from which 2,604 were on ART. Eventhough, 5,122 HIV patients were enrolled between 19th September, 2005 to 30th January, 2008 in Debremarkos Referral Hospital, only 2604 patients were on ART.

Basic characteristics of the cohort

Cards of six hundred and forty (379 alive and 261 death) adult HIV infected individuals were included in the present study. Among the cohort, 53.10% were females and the mean age was 35.40 years (standard deviation (SD) ± 9.62). Five hundred ninety five (93.00%) of the study participants were followers of orthodox religion and 260 (40.80%) were married. Two hundred and thirty four (36.60%) of the study participants had primary education. The median weight at base line was 50.00 kg (Inter Quartile Range (IQR) = 44.00 to 55.00 kg). Base line mean hemoglobin was 12.23 (IQR = 10.60 to 14.00). The base line median CD4 count was 115.00 cells/µl (IQR = 63.25 to 164.75). About 399 (62.30%) were at WHO clinical stage III during the initiation of ART. Moreover, 415 (64.80%) of the participants were in working functional

Table 2. Socio-demographic characteristics of patients initiated ART at Debremarkos Referral Hospital, 2005-2013 (N=640).

Variable	Alive (n=379, %)	Death (n=261, %)
Sex		
Male	176 (46.40)	124 (47.50)
Female	203 (53.60)	137 (52.50)
Age (years)		
15-29	107 (16.70)	82 (12.80)
30-44	214 (33.40)	118 (18.40)
45-59	52 (8.10)	55 (8.60)
≥ 60	6 (0.90)	6 (0.90)
Residence		
Urban	275 (43.00)	181 (28.30)
Rural	104 (16.20)	80 (12.50)
Ethnicity		
Amhara	369 (57.70)	258 (40.30)
Oromo	5 (0.80)	1 (0.20)
Tigray	5 (0.80)	2 (0.30)
Marital status		
Married	168 (26.20)	93 (14.50)
Widowed	77 (12.00)	47 (7.30)
Never married	41 (6.40)	32 (5.00)
Divorced	77 (12.00)	71 (11.10)
Separated	16 (2.50)	18 (2.80)
Educational status		
Not educated	89 (13.90)	78 (12.20)
Primary	149 (23.30)	85 (13.30)
Secondary	94 (14.70)	66 (10.30)
Tertiary	47 (7.30)	32 (5.00)
Occupation status		
Merchant	87 (13.60)	38 (5.90)
NGO employee	10 (1.60)	7 (1.10)
Gov't employee	82 (12.80)	63 (9.80)
Day laborer	69 (10.80)	48 (7.50)
"Jobless"	27 (4.20)	13 (2.00)
Farmer	53 (8.3)	47 (7.30)
Others	51 (8.0)	45 (7.00)

functional status and 196 (30.60%) were ambulatory in the time of ART initiation (Tables 2 and 3).

Baseline opportunistic infections were recorded in the patient registration; 92 (14.38%), 6 (0.94%), 234 (36.56%), 203 (31.79%) and 381 (59.53%) had esophageal candidacies, Kaposi's sarcoma, oral recurrent candidacies, unexplained persistent diarrhea and fever, respectively. Twenty four patients (3.75%) had presumed diagnosis of pneumocystic carnii pneumonia (PCP). Patients with unexplained weight loss > 10% were 103 (16.09%) and with recurrent severe bacterial pneumonia, active TB, herpes simplex, recurrent upper respiratory tract infections and herpes zoster were 197 (30.78%), 89 (13.91%), 94 (1.68%), 192 (30%) and 101 (15.75%), respectively (Figure 1).

Predictors of mortality

This study tried to identify the predictors of mortality among adult HIV positive patients on ART. Accordingly, baseline hemoglobin level of < 10 g/mm^3 (AHR = 1.88, 95% CI: 1.39 to 2.64), baseline ambulatory functional status (AHR = 2.72, 95% CI: 1.90 to 3.90), bedridden functional status (AHR = 2.38, 95% CI: 1.32 to 4.27), baseline WHO stages III and IV (AHR = 2.16, 95% CI: 1.10 to 4.25), side effects of drug (AHR = 7.81, 95% CI: 4.58 to 13.31), recent ART adherence (AHR = 2.16, 95% CI: 1.03 to 4.56), fair adherence (AHR = 1.88, 95% CI: 1.08 to 3.29), unexplained persistent chronic diarrhea (AHR = 1.53, 95% CI: 1.09 to 2.15) and absence of TB prophylaxis (AHR = 3.98, 95% CI = 1.87, 8.44) were significant predictor of mortality among patients on ART (Tables 4 and 5).

DISCUSSION

In this retrospective cohort study, 261 patients died resulting in seven years overall mortality rate of 10.74/100 person-year observation (PYO). Meanwhile, the independent predictors of death were base line hemoglobin < 10 g/mm^3, ambulatory and bedridden functional status, advanced WHO clinical stage, patients with no recorded side effect of the drug, poor adherence for ART drug, presence of unexplained persistent diarrhea and absence of TB prophylaxis recently.

In this study, after initiation of the antiretroviral treatment, the incidence of mortality was 10.74/100 PYO. Many studies showed that mortality incidence among patients taking ART is decreasing since the discovery of the drug (Jerene and Lindtjørn, 2005; Jerene and Næss et al., 2006; Jerene et al., 2006; Ergete, 2011). Estimated mortality rate in ART+ group was 15.40/100 PYO and most of the death occurred during the first three months (Jerene and Lindtjørn, 2005). Mortality incidence in pre-HAART and HAART group was 58.1/100 PYO (Jerene et al., 2006) and 25.90/100 PYO (Tsegaye and Worku, 2011). In this regard, previous studies showed that mortality is declined by 65.00% in patients on HAART. This study revealed that mortality was decreased compared to the previous studies. This might be due to the relatively longer study period covering both early and recent phases of treatment. People's awareness has been increased so that they sought treatment in relatively less advanced disease stage. Moreover, treatment guidelines become more familiar to health professionals

Table 3. Baseline clinical and laboratory information of 640 patients initiated ART at Debremarkos Referral Hospital, 2005 to 2013.

Variable	Alive (n=379, %)	Death (n=261, %)
Base line prophylaxis		
Not given	35 (9.20)	38 (14.60)
Cotrmoxazole	338 (89.20)	212 (81.20)
INH	4 (1.10)	7 (2.70)
Fluconazole	2 (0.50)	4 (1.50)
Base line weight (kg)		
<60	333 (87.90)	237 (90.80)
≥60	46 (12.10)	24 (9.20)
Base line CD^{4+} (cells/µl)		
<50	55 (14.50)	66 (25.40)
50-99	74 (19.50)	64 (24.60)
100-200	205 (54.10)	108 (41.50)
201-350	44 (11.60)	22 (8.50)
>350	1 (0.30)	0 (0.00)
Baseline Hgb (g/dl)		
<10	34 (11.30)	69 (33.20)
≥10	268 (88.70)	139 (66.80)
Not recorded	77 (12.00)	53 (8.28)
Functional Status		
Working	299 (78.90)	125 (47.90)
Ambulatory	116 (44.40)	9 (2.40)
Bedridden	71 (18.70)	20 (7.70)
WHO staging		
Stage I and II	109 (17.03)	35 (5.47)
Stage III and IV	270 (42.20)	226 (35.31)
ART eligibility criteria		
WHO staging	40 (10.60)	17 (6.50)
Immunologic	108 (28.50)	48 (18.40)
Both	231 (60.90)	196 (75.10)
Side effect		
Yes	212 (55.90)	25 (9.60)
No	167 (44.10)	236 (90.40)
ART adherence		
Good	369 (97.40)	215 (82.40)
Fair	4 (1.10)	17 (6.50)
Poor	6 (1.60)	29 (11.10)

and the care given to patients has been improving. Prior free- ART treatment, no adequate voluntary counseling and testing (VCT) services and high prevalence of HIV related stigma all lead to advanced presentation of patients to clinical care.

This study showed that high mortality of patients during early phase of treatment in line with different studies (Jerene et al., 2006; Amuron et al., 2011; Assefa et al., 2011; Mulissa et al., 2010; Dean et. al, 2011; Dupont, 1990; Schoenfeld and Richter, 1982; Mageda et al., 2012) even though, none of the observational studies indicated the exact cause of high mortality at initial phases of treatment.

In the present study, patients with hemoglobin < 10 g/dl at baseline were at high risk of death. Study on cause-specific mortality indicators study from low and middle income countries (LMIC) (Sabin et al., 2009) in Tanzania rural hospital (Jerene et al., 2006), studies in Ethiopia (Amuron et al., 2011; Abose and Enkusilassie, 2012; Tsehaineh, 2010) indicated that patients with anemia were at high risk of death after ART initiation. The possible explanation for this phenomenon could be 234 of the patients took zidovudine (ZDV) which is responsible for persistent anemia as indicated in other study (Kebebew, 2011). Functional status during ART initiation was significant predictor of mortality. Patients in ambulatory functional status and bedridden were at increased hazard rate of death by 2.72 and 2.38 times than patients in working functional status, respectively. This finding is consistent with many studies done in Ethiopia; for example, study done in eastern Ethiopia showed a 4.09 time of mortality risk for patients in bedridden functional status than working ones (Solomon, 2011).

As stated in southern Ethiopia, the risk of death among working patients is lowered by 55% than bedridden patients during ART initiation (Amuron et al., 2011). The mortality risk of patients in ambulatory and bedridden functional status is 2.11 and 3.35 times compared to working patients in Military Hospital in Addis Ababa, Ethiopia (David Jr., 1999). Ambulatory and bedridden functional status is 2.87 and 6.90 times at risk of death than the working status (Mageda et al., 2012). The risk of mortality was increased in ambulatory and bedridden patients by 1.53 and 2.99 times than working patients (Jerene and Lindtjorn, 2005). Therefore, patients who are of ambulatory and bedridden functional status should get due attention in order to reduce their mortality rate.

In this study, patients with fair and poor ART adherence were at high risk of death (2.16 and 1.88) times than those with good adherence. In line with this, patients who have poor adherence were at risk of death by 3.92 than with those who have good adherence patients in Addis Ababa (Kebebew, 2011). Eventhough adherence assessment technique was not as such reliable in the current study (self reported), it was a significant predictor of death. This could be an alarm for further study of the reasons for adherence and also to increase the survivals of patients by establishing ways to good adherence. So, patients with poor ART adherence should be followed more frequently to decrease risk of death.

Late presentation of patients for clinical care was seen in this study in which majority of patients were at WHO clinical stages III and IV. This resulted in increased risk of

Table 4. Bivariate and multivariable Cox-regression analysis of clinical characteristics of the cohort studied (n=640 patients) in Debremarkos referral hospital, 2005-2013.

Variables	Frequency		CHR (95% CI)	AHR (95% CI)	P- value
Baseline prophylaxis	**Alive**	**Dead**			
Not given	35	38	1	-	-
Cotrmoxazole	338	212	1.23 (0.74-0.94)	1.75 (0.61-5.06)	0.29
INH	4	7	0.66 (0.55-2.76)	0.83 (0.52-1.39)	0.45
Fluconazole	2	4	1.24 (0.44-3.49)	2.94 (0.49-17.48)	0.23
Base line weight (kg)					
<60	333	237	1.37 (0.90-2.09)	1.02 (0.57-1.83)	0.92
≥60	46	24	1	1	
Hemoglobin (g/dl)					
<10	34	69	2.76 (2.06-3.69)	1.86 (1.31-2.64)	0.0001*
≥10	268	139	1	1	
Functional Status					
Working	299	125	1	1	-
Ambulatory	116	9	3.24 (2.51-4.18)	2.72 (1.90-3.90)	0.0001*
Bedridden	71	20	4.18 (2.59-6.74)	2.38 (1.32-4.27)	0.004*
Baseline CD^{4+} (cells/µl)					
<50	100	21	1	1	-
50-99	130	8	0.75 (0.53-1.05)	1.02 (0.63-1.64)	0.93
100-200	301	12	0.51 (0.37-0.69)	1.11 (0.71-1.73)	0.64
≥201	60	7	0.47 (0.29-0.77)	0.70 (0.34-1.45)	0.34
WHO staging					
Stage I and II	109	35	1	1	0.02*
Stage III and IV	270	226	2.23 (1.56-3.19)	2.16 (1.10-4.25)	
ART eligibility criteria					
WHO staging	40	17	1	1	-
Immunologic	108	48	1.04 (0.60-1.81)	1.50 (0.67-3.34)	0.31
Both	231	196	1.81 (1.10-2.98)	1.28 (0.69-2.39)	0.42
Side effect					
Yes	212	25	1	1	0.0001*
No	167	236	8.02 (5.31-12.14)	7.81 (4.58-13.31)	
ART adherence					
Good	369	215	1	1	-
Fair	4	17	3.49 (2.12-5.74)	2.16 (1.03-4.56)	0.04*
Poor	6	29	4.10 (2.76-6.08)	1.88 (1.08-3.29)	0.02*

*Significant at p<0.05, CI= confidence interval, ** marginally significant at p<0.05, AHR =Adjusted Hazard Ratio; CHR=Crude Hazard Ratio

death among patients by 2.16 times than patients at stages I and II. This is similar with studies in Tanzania which was 4.16 times risk of death in advanced WHO stage (Johannessen et al., 2008). But the difference in magnitude may be due to many subjects (201) in stage IV in Tanzanian study. Also, studies in Ethiopia supported this finding (Worku and San Sebastian, 2009; David Jr., 1999). Moreover patients in advanced clinical stages are prone for TB infection (Mageda et al., 2012; Tsehaineh, 2010; David Jr., 1999). This was evidenced that absence

Table 5. Bivariate and multivariate Cox regression analysis of base line opportunistic infection among ART follow up patients (n=640) in Debremarkos referral hospital, 2005-2013.

Opportunistic infections	Frequency		CHR (95%CI)	AHR (95% CI)	p-value
Esophageal candidacies	**Alive**	**Dead**			
Yes	3	31	1	1	0.58
No	30	184	0.68 (0.46-1.00)	0.89 (0.60-1.33)	
Oral recurrent candidacies					
Yes	9	73	1	1	0.06
No	24	142	0.48 (0.37-0.68)	1.35 (0.98-1.87)	
Unexplained chronic diarrhea (> 1 month)					
Yes	4	68	1.43 (1.07-1.92)	1.53 (1.09-2.15)	0.01*
No	29	147	1	1	
Unexplained wt loss >10%					
Yes	2	23	1	1	0.15
No	31	193	0.59 (0.44-0.79)	0.76 (0.52-1.11)	
Severe bacterial pneumonia					
Yes	55	45	1	1	0.13
No	28	170	0.55 (0.32-0.95)	0.54 (0.24-1.21)	
Recurrent URTI					
Yes	4	27	1	1	0.67
No	30	189	0.82 (0.63-1.06)	0.93 (0.67-1.28)	
Herpes zoster					
Yes	61	39	1.01 (0.72-14.22)	1.32 (0.86-2.03)	0.19
No	318	221	1	1	
TB screened during ART start					
On treatment	5	41	3.90 (2.77-5.48)	2.33 (0.82-6.60)	-
Positive	8	26	3.46 (2.30-5.19)	2.07 (0.73-5.82)	0.27
Negative	366	193	1	1	0.11
TB prophylaxis given					
Yes	97	11	1	1	0.0001*
No	282	249	5.85 (3.20-10.70)	3.98 (1.87-8.44)	
TB treatment recently					
Yes	18	67	3.18 (2.41-4.21)	1.12 (0.41-3.08)	0.81
No	361	193	1	1	

*Significant at $p < 0.05$, CI= confidence interval, AHR =Adjusted Hazard Ratio; CHR = crude hazard ratio.

of TB prophylaxis is risk for death by 3.98 times than those with TB prophylaxis. Therefore, patients in advanced clinical stage were highly at risk of death and may be because of high prevalence of opportunistic infections (OI) including TB that calls an attention for routine screening and provision of prophylaxis as per the guideline. Patients with side effect survive more than those patients with no recorded side effects. Probably this is due to high mortality rate in early periods of treatment in which side effects are not commonly seen. Unexplained chronic diarrhea increased risk of death by 1.53 times. Studies in LMIC on cause-specific mortality predictors among adult on ART patients show that chronic diarrhea contributes (10.00 to 25.00%) to death compared to other causes of

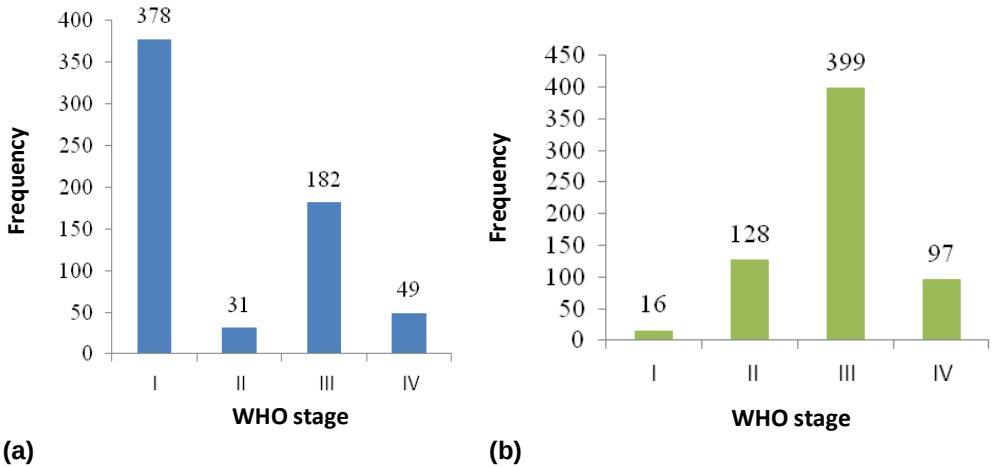

Figure 1. Baseline and recent WHO clinical stages of patients on ART in Debremarkos referral hospital, 2005-2013. (a) Recent WHO staging, (b) Baseline WHO staging.

death (Sabin et al., 2009). Therefore, patients with unexplained diarrhea should be treated accordingly and to be closely followed to decrease risk of death.

Conclusion

High mortality rate was observed during early phase of ART especially within the first 6 and 12 months. The independent predictors of mortality were lower baseline hemoglobin, being in ambulatory and bedridden functional statuses, advanced WHO clinical stage, poor ART adherence, non-recognition of side effects of drugs, non-provision of TB prophylaxis and unexplained persistent diarrhea.

RECOMMENDATIONS

For clinical practitioners

1. Patients being on ambulatory and bedridden functional status should be assessed for other possible concomitant disease conditions and treated with closer follow up so as to minimize the risk of death.
2. Hemoglobin should be measured at every visit and re-adjust medications that aggravate anemia since it is main predictor of death.
3. Patients with unexplained chronic diarrhea, oral candidacies, and herpes zoster should be followed with special attention and these symptoms should be treated promptly.
4. Since poor adherence to ART is significant predictor of mortality, every patient has to be counseled intensively than what is done previously.
5. Important clinical characteristics of patients like WHO staging, CD4 count, Hgb and other OIs should be documented correctly and regularly.

For adherence supporters, case managers and counselors

1. These groups of the health team should access health status information of patients particularly on advanced age, being in ambulatory and bedridden functional status.
2. Adherence preparation, supporting and assessment mechanisms must be employed.

For researchers

The cause for early mortality should be studied further.

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