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ORIGINAL ARTICLE

GENDER DIFFERENCES IN DEATH AND LOSS TO FOLLOW-UP AMONG HIV-POSITIVE PATIENTS ON ANTIRETROVIRAL THERAPY IN TIGRAY, ETHIOPIA

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ABSTRACT

Background: *In Ethiopia data concerning the influence of gender on death associated with HIV/AIDS and loss to follow-up in care and treatment are controversial.*
Objective: *Our study intended to further investigate gender-related differences in antiretroviral therapy outcomes in Tigray (Ethiopia).*
Methods: *We used data from the "Cohort of African People Starting Antiretroviral therapy' project, a prospective study of a cohort of HIV-positive patients who started ART in Tigray. The study population included HIV-positive patients starting antiretroviral therapy between January 2013 and December 2015. We compared baseline characteristics between men and women using Kruskal Wallis t-test and Chi-squared test. We employed Kaplan-Meier method to estimate the probability of mortality and loss to follow-up for men and women and univariate and multivariate Cox Proportional Hazards models to compare differences in antiretroviral therapy outcomes by gender.*
Results: *The study population included 1,622 patients, 1,003 (61.8%) women and 619 (38.2%) men. Median follow -up time was 2.6 years and 2.1 years, respectively for women and men. In the multivariate analysis men had a significantly higher risk of loss to follow-up than women (aHR 2.8, 95% CI: 2.00-4.01); but no significant sex differences in mortality was observed (aHR 1.2, 95% CI: 0.76-1.84).*
Conclusions: *Findings showed gender-related differences in loss to follow-up, not in mortality. Several structural and social factors may influence the gender difference in loss to follow-up. However, specific investigations are needed to get a better understanding of the reasons why men are more likely to be lost to follow-up than women and programmes with a gender-oriented approach should be implemented.*
Keywords*: antiretroviral treatment; HIV/AIDS, loss-to follow-up; gender; mortality.*

INTRODUCTION

In spite of remarkable progress over the past two decades, the AIDS epidemic is still far from ending. Rates of mortality and loss to follow-up remain unacceptably high in low-income countries (LICs), where nearly three quarters of people living with HIV (PLHIV) reside (1,2). Several studies have investigated how demographic, social, immuno-virological and clinical factors influence prognosis of PLHIV. In particular, the role of gender has been widely analyzed. Extensive literature from LICs shows that men are more likely to be diagnosed with advanced HIV disease (3-5) compared to women, thus being at high risk of poor immunological recovery and adverse clinical outcomes. However, the impact of gender on HIV/AIDS mortality and loss to follow-up is widely debated: some studies found higher rates of mortality and loss to follow-up among men compared to women (6,7), while others did not (8-10).

According to 2016 Joint United Nations Programme on HIV/AIDS (UNAIDS) data, Ethiopia is a sub-Saharan country hosting about 710,000 (570,000–880,000) PLHIV with a 1.1 (0.8-1.3) HIV prevalence in adults (11).

Since 2005, Ethiopia experienced a rapid increase in antiretroviral therapy (ART) coverage, which in 2016 reached 59% [47-53] of PLHIV ([1). Nevertheless, in the same year 20,000 (10,000-31,000) AIDS-related deaths were recorded (1) and long-term attrition from care, mainly due to loss to follow-up, remains high (12. Besides, also in Ethiopia data regarding the influence of gender on outcomes are controversial [13-1)9]. This makes it urgent to establish gender difference in HIV outcomes in order to address direct interventions and policy change. Hence, the objective of this study was to investigate gender-related differences in mortality and loss to follow-up in a cohort of patients starting ART in Tigray, Ethiopia.

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METHODS

Study design and setting: We used data from the "Cohort of African people Starting Antiretroviral therapy (CASA)" project, a prospective, ongoing, multisite study of a cohort of HIV-positive patients who started ART in seven health facilities (HFs), including two health centers and five hospitals, located in Tigray, the northeastern region of Ethiopia.

Participants: HIV-positive patients over 14 who initiated ART between January 01, 2013 and December 31, 2015 and who agreed to provide their contacts were included in this study. Follow-up data was available until December 2016.

Data source: Baseline and follow-up visits were performed according to the standard of care of the participating HFs. Data was systematically collected by ART nurses using forms designed for this study and a software developed for the purpose of this study was used to enter data of participating patients.

Variables: The following baseline information was included in this analysis: type of HF, gender, age, educational status, marital status, body mass index [(BMI, weight/height^2: <=18.5= underweight, 18.6-25=normal, >25 overweight)], WHO clinical stage (stage I to stage IV), CD4+ cell counts (defined as the value available at any time in the six months before starting HIV treatment) and the presence of active tuberculosis (TB). The outcomes of interest were mortality and loss to follow-up. Patients were considered dead if they had been recorded as dead in the patient's exit-form. Patients were considered lost to follow-up (LTFU) if they had missed the last scheduled visit for more than three months and had never returned till the censorship date (December 31, 2016) of the cohort.

Data analysis: Baseline characteristics were compared between men and women using Kruskal Wallis t -test and Chi-squared test for continuous and categorical variables, respectively. The Kaplan-Meier method was used to estimate the probability of mortality and loss to follow-up for men and women at different time -points. Univariate and multivariate Cox Proportional Hazards models were used to compare differences in ART outcomes (mortality and loss to follow-up) by gender. Type of HF, gender, age (14-24, 25-34, 35-44, >=45), educational status (no education, primary, secondary, tertiary education), marital status (never married, married, separated/divorced, widow/widower), BMI (underweight, normal, overweight), WHO clinical stage (I/II or III/IV), CD4 cell count (<200 or >= 200) and active TB were considered in the univariate model. Predictor variables which resulted in having statistical significance in the univariate analysis (p-value <0.2) were included in the multivariate analysis. The final models retained all variables with a p-value of < 0.05 (statistically significant). The end of follow-up was defined as the date of death, last date of a clinic visit or December 31, 2016. Time to death was censored at the date of recorded death. Follow-up of LTFU patients was censored at the date of the last clinic visit at the HF. Statistical analyses were performed using both the SPSS software, version 21.0 (SPSS Inc, Chicago, IL, USA) and the SAS statistical package, version 9.2 (SAS Institute, Inc., Cary, NC).

Ethical consideration

Ethical approval was obtained from Health Research Ethics Review Committee of Mekelle University College of Health Science (Reference number: ERC 0129/2012). All patients provided written informed consent. For patients aged 14 to 18 the informed consent was signed by adult relatives acting as guardians (immediate families e.g. father or mother or next of kin) and not by the patients themselves.

RESULTS

Participants' characteristics at ART initiation: The study population included 1,622 patients 1,003 (61.8%) women and 619 (38.2%) men (Table 1). At ART initiation, men were older than women (36 versus 31 years). More men than women were underweight (44.7% versus 38.9%) whereas more women than men were overweight (5.7% versus 2.6%). More than half of the women (51.3%) did not have a primary education level. Men had a lower median CD4 count (182 cells/microLitre versus 257 cells/microLitre) and the majority (54.6%) were clinically symptomatic. Men more than women were co-infected with active TB (12.1% versus 9.0%).

Gender and death: Eight seven (44 women and 43 men) patients died during the study period. Estimated proportion of death among women and men was 3.4% and 5.0% at 12 months; 4.2% and 7.0% at 24 months; 5.3% and 8.8% both at 36 and 48 months, respectively. The majority of deaths occurred in the first 12 months after ART initiation both for women and men (Table 2). In the univariate analysis, men had a higher risk of mortality than women (HR 1.72, 95% CI: 1.13-2.61). In the multivariate analysis, no statistically significant difference was observed (aHR 0.71, 95% CI: 0.50-1.03). Baseline factors associated with a higher risk of death were WHO III-IV stage, lower CD4 cell count, and being overweight or underweight (Table 3).

Table 1: Baseline demographic and clinical characteristics by gender

	Total 1622	Women 1003 (61.84%)	Men 619 (38.16%)	p-value*
Health Facility, n (%)				
Hospital	1101 (67.9)	652 (65.0)	449 (72.5)	0.002
Health Center .	521 (32.1)	351 (35.0)	170 (27.5)	
Age at start of ART (years), (n, range), median	(1622,16-82),33	(1003,17-82),31	(619,16-71),36	<0.001
14-24 n (%)	189 (11.7)	147 (14.7)	42 (6.8)	
25-34	703 (43.3)	483 (48.2)	220 (35.5)	
35-44	464 (28.6)	248 (24.7)	216 (34.9)	
>=45	266 (16.4)	125 (12.5)	141 (22.8)	
Educational status, n (%)				
No education	726 (44.8)	515 (51.3)	211 (34.1)	<0.001
Primary	463 (28.5)	257 (25.6)	206 (33.3)	
Secondary	284 (17.5)	166 (16.6)	118 (19.1)	
Tertiary	149 (9.2)	65 (6.5)	84 (13.6)	
Marital status, n (%)				
Never married	282 (17.4)	131 (13.1)	151 (24.4)	<0.001
Married	762 (47.0)	421 (42.0)	341 (55.1)	
Separated/Divorced	450 (27.7)	338 (33.7)	112 (18.1)	
Widow/Widower	128 (7.9)	113 (11.3)	15 (2.4)	
BMI (kg/m^2), n (%)				
Underweight	666 (41.1)	390 (38.9)	276 (44.7)	0.003
Normal	881 (54.4)	556 (55.4)	325 (52.7)	
Overweight	73 (4.5)	57 (5.7)	16 (2.6)	
Clinical stage, n (%)				
WHO I-II	796 (49.1)	458 (45.7)	338 (54.6)	<0.001
WHO III-IV	826 (50.9)	545 (54.3)	281 (45.4)	
CD4+ count (cells/microLitre), (n, range), median	(1585, 2-1777), 235	(980, 3-1777), 257	(605, 2-1121), 182	<0.001
<200 n (%)	726 (45.8)	895 (40.3)	331 (54.7)	<0.001
>=200	859 (54.2)	585 (59.7)	274 (45.3)	
Active TB, n (%)				
Yes	147 (9.1)	72 (7.2)	75 (12.1)	0.001
No	1475 (90.9)	931 (92.8)	544 (87.9)	
Median-person-years of follow-up median (range)	2.4 (1-4)	2.6 (1-4)	2.2 (1-4)	<0.001

Table 2: Kaplan-Meier estimate of mortality and loss to follow up after ART initiation by gender

Months of follow-up	Mortality (Women) cumulative events; mortality estimate (95% CI)	Mortality (Men) cumulative events; mortality estimate (95% CI)	Loss to follow up (Women) cumulative events; mortality estimate (95% CI)	Loss to follow up (Men) cumulative events; mortality estimate (95% CI)
12 months	33; 3.4 (2.2-4.6)	29; 5.0 (3.2-6.8)	32; 3.4 (2.2-4.6)	48; 8.4 (6.1-10.8)
24 months	39; 4.2 (2.8-5.6)	38; 7.0 (4.8-9.2)	55; 6.2 (4.6-7.8)	69; 13.0 (10.1-15.9)
36 months	44; 5.3 (4.5-6.1)	43; 8.8 (7.5-10.1)	63; 7.8 (5.8-9.8)	82; 16.9 (13.4-20.4)
48 months	44; 5.3 (4.5-6.1)	43; 8.8 (7.5-10.1)	67; 9.1 (6.8-11.5)	84; 18.1 (14.2-22.0)

Table 3: Gender-related differences in mortality and loss to follow up

	Mortality ^HR (95%)	Mortality ^^aHR (95%)	Loss to follow-up ^ HR (95%)	Loss to follow-up ^^aHR (95%)
Health Facility				
Hospital	Reference	-	Reference	-
Health Center	0.72 (0.45-1.16)		0.71 (0.50-1.03)	
Gender				
Women	Reference	Reference	Reference	Reference
Men	1.72 (1.13-2.61)*	1.19 (0.76-1.84)	2.26 (1.64-3.12)*	2.83 (2.00-4.01)**
Age				
14-24	Reference	-	Reference	Reference
25-34	2.18 (0.77-6.15)	1.99 (0.70-5.66)	0.82 (0.51-1.31)	0.72 (0.45-1.17)
35-44	2.78 (0,97-7,96)	2.13 (0.74-6.17)	0.77 (0,46-1.28)	0.57 (0.33-0.97)
>=45	4.16 (1.44-2.04)	3.07 (1.05-9.00)	0.41 (0.21-0.81)*	0.30 (0.15-0.62)**
Educational status				
No education	Reference	-	Reference	-
Primary	0.74 (0.43-1.28)		1.12 (0.77-1.61)	
Secondary	1.09 (0.62-1.93)		0.96 (0.61-1.51)	
Tertiary	1.33 (0.68-2.60)		0.64 (0.32-1.29)	
Marital status				
Never married	Reference	-	Reference	Reference
Married	0.68 (0.38-1.19)		0.57 (0.37-0.86)*	0.72 (0.46-1.11)
Separated/Divorced	0.80 (0.43-1.47)		0.91 (0.59-1.40)	1.40 (0.88-2.21)
Widow/Widower	1.06 (0.48-2.35)		0.37 (0.15-0.87)*	0.79 (0.32-1.94)
BMI (kg/m^2)				
Normal	Reference	Reference	Reference	-
Underweight	3.41 (2.12-5.50)*	2.69 (1.64-4.42)**	1.20 (0.87-1.67)	
Overweight	2.52 (0.96-6.61)*	2.84 (1.07-7.56)**	0.75 (0.31-1.86)	
Clinical stage				
WHO I-II	Reference	Reference	Reference	-
WHO III-IV	2.80 (1.75-4.48)*	1.91 (1.16 -3.17)**	1.27 (0.92-1.74)	
Active TB				
No	Reference	Reference	Reference	-
Yes	2.50 (1.46-4.31)*	1.37 (0.77- 2.45)	1.18 (0.68-2.05)	
CD4 count (cells/ microLitre)				
>= 200	Reference	Reference	Reference	-
<200	3.06 (1.92 - 4.89)*	2.25 (1.38-3.68) **	1.29 (0.93-1.80)	

^ Crude Hazard Ratio ^^ adjusted Hazard Ratio * p value < 0.2; ** p value < 0.05

Gender and Loss to Follow-up: A total of 151 patients (67 women and 84 men) were LTFU. The probability of loss to follow-up of women versus men was 3.4% and 8.4% at 12 months; 6.2% and 13.0% at 24 months; 7.8% and 16.9% at 36 months; 9.1% and 18.1% at 48 months (Table 2). Both in the univariate and multivariate analysis, gender was independently associated with loss to follow-up (aHR 2.83, 95% CI: 2.00-4.01). In the multivariate analysis also the age group older than 45 at baseline was associated with loss to follow-up (aHR 0.30, 95% CI: 0.15-0.62) (Table 3).

DISCUSSION

In this study, we found gender-related difference in loss to follow-up but not in mortality in a cohort of Ethiopian PLHIV on ART. Some studies conducted in Ethiopia showed no association between gender and survival (20-22). However, other studies from Ethiopia and sub-Saharan Africa found that mortality seems to be higher in men than in women (13, 27). Besides, a systematic review from both developed and developing countries also showed that women have a slightly higher survival compared to men (28).

In our study BMI value, WHO clinical stage and CD4 cell count were the factors associated with mortality. Underweight or overweight patients had a higher risk of death compared to those with normal BMI. In a systematic review including 50 studies from resource-limited settings, Gupta *et al.* found low BMI values to be independently associated with early mortality (29,31). Low CD4 counts (< 200 cells/microliter) at ART initiation was also an independent factor associated with a higher mortality, as also shown in other studies conducted in Ethiopia and other sub-Saharan countries (32-36).

In the same way, consistent with studies from sub-Saharan Africa, advanced WHO clinical stage at ART initiation was a statistically significant predictor of mortality (37). The low average value of CD4 and the presence of opportunistic infections in the study population could suggest that patients have delayed ARV therapy. Patients may have received a late diagnosis, for having performed the test long after contracting HIV infection, when the disease was already in an advanced stage. This result suggests that innovative strategies are needed to diagnose HIV infection at an earlier stage, before the onset of advanced disease (38).

In our study, men were more likely to become LTFU than women. This result is consistent with that of other studies conducted in Ethiopia as well as in other sub-Saharan Africa countries (39-41). Several structural and social factors may influence the gender difference in loss to follow-up. Firstly, as already reported in other African countries, Ethiopian men have high occupational mobility, which favors loss to follow-up (42). Secondly, men often experience alcohol and drug abuse, which notoriously decreases care adherence (43, 44). Thirdly, male sex is usually associated with ideals of strength and well-being; this model may reinforce HIV-related stigma and may hinder men's access to healthcare services (45). This study has both strengths and limitations. As a limitation, the reported death could be an underestimate of true mortality as we were unable to accurately ascertain patients' deaths. We expect that some of the patients classified as LTFU might have died.

Moreover, although the hazard of death between genders was not significantly different in this analysis, men had a higher rate of mortality. It is possible that the sample of this study was not large enough to detect a significant difference. The strengths of this study are its multi-site and prospective design. In conclusion, we found gender difference in loss to follow-up but not in mortality within PLHIV receiving ART in Ethiopia. Specific investigations are needed to get a better understanding of the reasons why men are more likely to be LTFU than women and programmes with a gender-oriented approach should be implemented.

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Competing interests

The authors have declared that no competing interests exist.

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