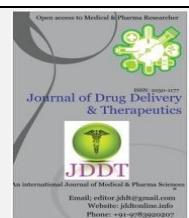


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Research Article

Moderate incidence of lost follow-up and risk factors among adult HIV patients on second-line ART regimens in Amhara region hospitals, Ethiopia

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ABSTRACT

Background and Objectives: Loss to follow-up is a common problem of most patients on antiretroviral therapy in Ethiopia. Second-line antiretroviral therapy is the drug that would be used when the first-line therapy fails. Thus this study intends to determine the incidence and risk factors of time to losses to follow up among Human Immunodeficiency Virus (HIV) patients on second line regimens of Antiretroviral Therapy(ART) in Amhara region Hospitals, Ethiopia.

Methods: Institutional based retrospective cohort study was conducted in the Amhara region hospitals from February to March 2016. A total of 1246 patient from eight hospitals in Amhara region were selected using simple random sampling method and data were extracted from patient charts. The log rank test was used to assess presence of significant difference in time to losses to follow up among levels of categorical variables. Both bi-variate and multivariable Cox proportional hazards models were used to identify factors that affect the time to losses to follow up.

Results: The cumulative incidence of loss to follow up was 5.41% over the entire (eight) years of follow-up. The cumulative incidence rates of death and transfer out were 10.99% and 10.02 %, respectively. In multivariable Cox regression analysis, ambulatory functional status (AHR=0.1967, 95% CI: 0.049- 0.794), male gender (AHR=2.135, 95% CI: 1.053- 4.330), and adherence to ART (AHR=0.442, 95% CI: 0.198-0.989) were significant predictors of time to losses to follow up. The use of 2a, 2e and 2g types of second line regimen reduced the risk of loss to follow up.

Interpretations and Conclusions: The incidence of loss to follow up in Amhara region hospitals was low. Loss to follow up was negatively associated with female gender, ambulatory baseline functional status, adherence, and types of second line regimen types. Further research on the effect of types of drug is recommended by ascertaining whether the reduction in loss to follow up for patients who took drug types of 2a, 2e, and 2g is associated with improved or worsened health outcomes by tracking lost patients closely.

Keywords: loss to follow-up, second line regimens, HIV patients

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INTRODUCTION

Since its introduction, Antiretroviral therapy (ART) has transformed the responses and emphasis that countries gave to HIV/AIDS and resulted in an improvement of health¹. It has also brought a remarkable reduction in the transmission of HIV and HIV-related morbidity and mortality worldwide².

At the end of 2012, 10 million more people were receiving ART in low- and middle-income countries³. In 2015, about 65% (15 million) of the total number of people living with the virus worldwide were receiving treatment for the HIV/AIDS³. However, even though there has been a

continually increasing access to ART, still there are disparities across regions or countries.

When the first-line antiretroviral therapy fails, HIV patient would be recommended to take the second-line therapy⁴. It has been shown that patients loss to follow-up (LTFU) affects the quality of care that patients could get. Loss to follow up is defined as not taking ART refill for a period of 3 months or longer from the last attendance for refill and not yet classified as 'dead' or 'transferred-out' in second line regimens ART. It also affects the evaluation of ART programmes in developing countries⁵. A systematic review done in sub-Saharan Africa about ART programmes showed

that the cumulative incidences of loss to follow-up of patients were 19%, 24% and 31% at 6, 12, and 24 months since the initiation of their treatment, respectively⁵.

Many studies conducted in many parts of the world indicate different results regarding the risk factors of loss to follow up (LTFU). A study done in India showed that the incidence of LTFU is 15.5%⁶. A study conducted in Sub-Saharan African showed that the incidence loss to follow up is 17.7%⁷. The incidences of lost follow-up in ART were 15.6%, 27%, and 36.6% for studies done in southeastern Nigeria⁸, South Africa⁹, and Cameron¹⁰, respectively. Studies done in Ethiopia showed that, the incidence of LTFU were 21.7%, 14.5%, 19.6% in southern Ethiopia hospitals¹¹, Hadiya zone (Southern Nations, Nationalities and Peoples Region)¹², and Ethiopian public hospital clinics¹³, respectively.

In Ethiopia, one of the major problems in ART programme is loss to follow up. A study done in southern Ethiopia¹¹, Rural Ethiopia hospitals¹⁴, and Ethiopian public hospital clinics¹³ showed that the incidence LTFU were 21.7%, 28.4%, and 19.6%, respectively.

A lot of factors were found to be associated with time-to-LTFU including socio demographic factors like educational status, sex, Age, occupational^{6,10,14,16-18} and clinical characteristics like Weight, Height, measures of number of T helper cells (CD4) count, hemoglobin level, Adherence, WHO stage, Functional status, second line regimen drug, Co-trimoxazole preventive therapy, Opportunistic infections, Body mass index^{6,7,9-11,17}. Functional status of a patient was categorized as "working" if their daily activities were not altered due to illness, "ambulatory" if the patient was not fully working but was able to do minor tasks at home, and "bed ridden" when the patient remained in bed most of the time.

A better understanding of the risk factors associated with loss to follow up in Ethiopia could be helpful to design interventions to reduce LTFU in patients who initiate ART. While evidences have proven that ART improves the survival time and quality of life of HIV patients, several clinical characteristics and socio demographic factors contributing to this high loss to follow up are not well understood in Ethiopia.

However, research studies investigating predictors of loss to follow up after ART initiations are scarce in Amhara Region. A better understanding of the risk factors associated with loss to follow up in the region could be helpful to design interventions to reduce Loss to Follow Up in patients who initiate ART.

MATERIALS AND METHODS

Study design and setting

A retrospective follow up study was conducted among adults living with HIV/AIDS and enrolled for second line ART regimens services in Amhara Regional State Hospitals from February 2008 - February 2016. Amhara region is one of the

nine ethnic divisions of Ethiopia. The capital city of Amhara region is Bahir Dar. Report from EDHS showed that there are about 37,637 peoples who are living with HIV in Amhara region and it was 1.6%. According to Health and Health Related Indicators published by Federal Ministry of Health, the region has 17 Hospitals, 520 Health Centers and 2,941 Health Posts. Of the 17 hospitals in the region, eight hospitals were selected by simple random sampling technique that included University of Gondar referral hospital, Felege Hiwot referral hospital, Dessie referral hospital, Woldia general hospital, Debre Markos referral hospital, Debre Tabor general hospital, Finote Salem general hospital, and Debre Birhan referral hospital.

Sample size determination

The sample size for the first objective was calculated by using a single population proportion formula and taking the assumptions of 95% confidence level, margin of error as 5%, incidence of loss to follow up 19.6% which was taken from a study done in Ethiopian public hospital clinic¹³, and a design effect of 2. Finally, we have got a sample size of 484 persons on second line ART.

The sample size for the second objective was calculated by using double population proportion for survival analysis as:

$$n = \frac{(z\sigma/2 + z\beta)^2}{b^2 p_1 p_2 d}$$

$$n = \frac{(1.96 + 0.84)^2}{((\log(2.36))^2(0.603)(0.378)(0.196))} = 1262$$

Where P1 is the proportion of CD4 count greater than or equal to ≥ 100 (60.3%)

P2 the proportion of CD4 count Less than < 100 (37.8%) ; d is that probability of observing the event (19.6%) ; b=2.36 is logarithm of hazard ratio square

Hazard ratio of CD4 count < 100 is 2.36 when CD4 count ≥ 100 is as reference

Sampling procedure

Eight hospitals were selected using simple random sampling from 17 hospitals found in the Amhara region. ART data of HIV patients who initiated the treatment since February 2008 to February 2016 were retrospectively followed. Because, the maximum sample size determined is closer to the total number of ART in the eight Hospitals, we had taken all patients initiated the second line treatment in the specified period and hospitals (Figure 1).

The dependent variable was time LTFU while the following factors were included in the model as independent variables: Socio demographic and anthropometric and clinical factors: Sex, Age, Educational status, occupation, Weight, Height, CD4 count, hemoglobin level, Adherence, WHO stage, Functional status, second line regimen drug, Co-trimoxazole preventive therapy, INH, Opportunistic infections, Body mass index.

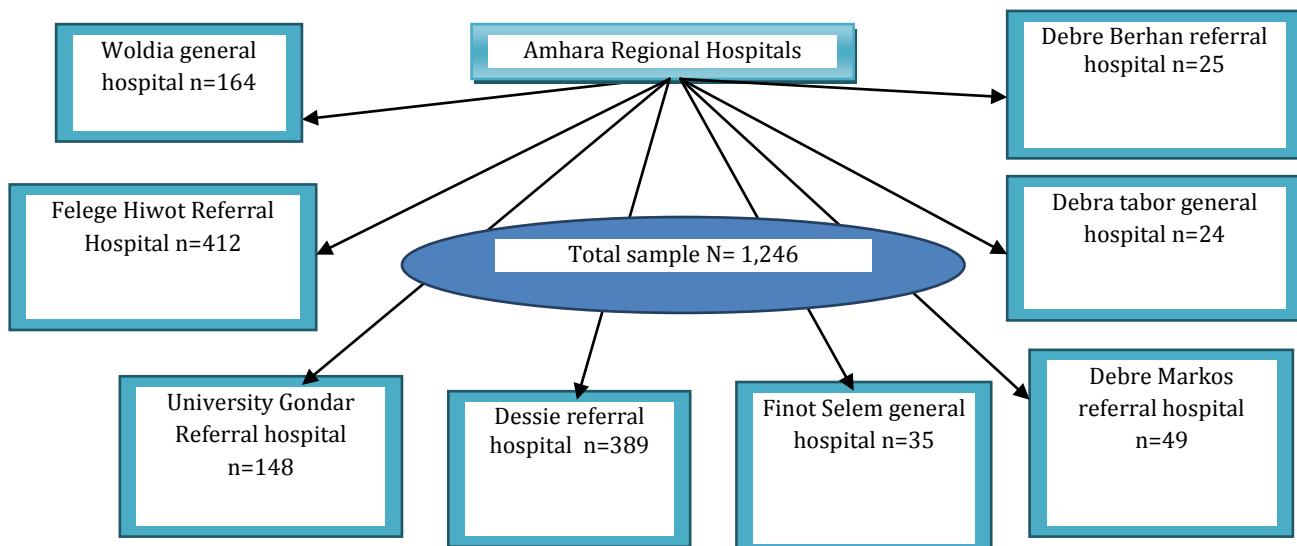


Figure 1: Schematic presentation of sampling procedure of Second line ART users in Amhara region hospitals, Ethiopia, 2016

Data collection procedure and quality control

Data were extracted from standard medical registration books that were already recorded routinely by the data clerk at each hospital. These records were adopted by the National Center for AIDS and STD Control and Ministry of Health and were available at the ART centers. The data were collected by experienced ART programme who were trained on comprehensive HIV care and who were working in the ART clinic at selected hospitals. A supervisor was supervising the process of data collection.

To ensure the quality of data, data collectors who were clinical nurses by profession and were working in ART programs were selected. Moreover, about 5% of questionnaires were pre-tested seven days before the actual data collection was started. During data collection, close supervision was conducted by supervisors and principal investigator, by observing how the data collectors run and the collected data was checked for the completeness, accuracy and clarity. This quality checking was done daily after data collection and correction was made before the next data collection measure. Data clean up and cross-checking was done before analysis. After data collection, data was stored in a secured place to maintain confidentiality and backup of the data was stored in different areas not to lose the data. Each questionnaire was coded separately before analysis.

Data processing and analysis

All returned questionnaires were checked for completeness and consistency of responses visually. The collected data were coded and entered in to EPI INFO version 7 and exported to STATA (version 12) statistical software. Data were cleaned and analyzed using STATA version 12. During descriptive analysis, continuous variables were summarized using mean, median and standard deviation while categorical variables were summarized using proportions and then presented in tables and graphs. Bi-variable

analyses were done to test for associations between the dependent variable (loss to follow up) and independent variables. Before inclusion of predictors to multivariable Cox regression analysis, fulfillment of model assumption was checked using goodness -of- fit test or Schoenfeld residuals (phtest). Multi co-linearity was checked using Variance Inflation Factors (VIF) or tolerance of explanatory variables. Survival analysis using life table and Kaplan-Meier survival curve were used to assess survival status of loss to follow up. The log rank test was used to assess presence of significant difference in survival status of loss to follow up between categorical socio demographic and clinical characteristics. Cox regression model was employed to measure the effect of each variable on the hazard of loss to follow up after adjusting for other variables at 95% confidence level. A variable with P-value < 0.05 in multivariable Cox regression analysis was considered as a factor associated with the loss to follow up at 95% confidence level.

Ethical Consideration

This study was approved by the ethical review committee of University of Gondar. Permission was obtained from the all the eight hospitals and the names of patients were not recorded in our data extraction form and their unique ART numbers were kept locked for better confidentiality.

RESULTS

Socio-demographic characteristics

A total of 1246 adult HIV/AIDS patients participated in the study. The mean age of participants (mean [\pm SD]) was 32.98 (\pm 8.739) years, ranging from 15 to 73 years. Fifty one percent of patients were males, half belonged to less than 32 years of age, one third of them had attended secondary education, and more than one third were unemployed. One third patients were from Felege Hiwot referral hospital (Table 1).

Table 1: Socio-demographic characteristic of HIV patients on second line ART in Amhara region Hospitals, Ethiopia

Variable		Number	Percent
Sex	Female	590	48.72
	Male	621	51.28
Age patients			
	<32	673	54.27
	32-40	369	29.76
	>40	198	15.97
Education			
	No education	378	32.09
	Primary	244	20.71
	Secondary	414	35.14
	Tertiary	142	12.05
Occupation			
	Unemployed	437	37.67
	Government	299	25.78
	Non government	25	2.16
	Private	82	7.07
	Others*	317	27.33
Hospital/ facility			
	Debre Berhan Referral hospital	25	2.01
	Debre Markos Referral hospital	49	3.93
	Debre Tabor general hospital	24	1.93
	Dessie referral hospital	389	31.22
	Felege Hiwote referral hospital	412	33.07
	Finote Salem general hospital	35	2.81
	Gondar University referral hospital	148	11.88
	Woldia general hospital	164	13.16

Baseline Clinical Characteristics

Seven hundred thirty eight (63%) of patients had history of past opportunistic infection; around 666 (55.5%) of the participants have CD4 cell count less than 100 cells/ml at baseline. About 638 (52.7%) of the patients were under WHO stage III. About 391 (41%) of patients were having poor adherence and majority (33.39%) of participants take drug type of 2g=TDF-3TC-LPV/r (Table 2).

Incidence of lost to follow-up

The study participants were assessed retrospectively with a total follow up of 38,956.7 person-months. The overall incidence density of loss to follow up was 1.67 losses to

follow up per 1000 persons-months. The cumulative incidence of losses to follow up was 5.41% over the entire period of follow-up. Others cumulative incidences like death and transfers out were 10.99% and 10.02 %, respectively. The remaining 73.59 % of the participants were actively on treatment when the study ended.

Those who took CPT (blue line) and those who did not take it (red line) were statistically significantly different (p-value = 0.0319) with regard to the incidence of loss to follow up. The graph also showed a constantly diverging pattern except at the end of the follow up period where less emphasis would be given due to the smaller sample size (Figure 2).

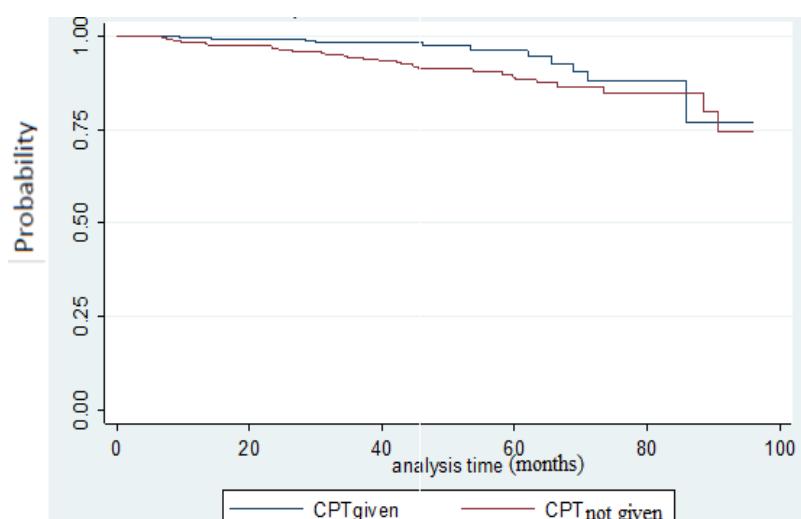


Figure 2: Kaplan-Meier estimate of the survival of patients on second line ART from LTFU grouped by Co-trimoxazole intake status in Amhara region hospitals, North Ethiopia, 2016

Table 2: Clinical characteristics of second line regimens in ART adult living with HIV /AIDS Amhara region hospitals

Variable	Number	Percent
Opportunistic infection		
Yes	738	62.97
No	434	37.03
Baseline functional status		
Working	744	62.16
Ambulatory	394	32.92
Bedridden	59	4.93
WHO stage		
Stage I	129	10.65
Stage II	240	19.82
Stage III	638	52.68
Stage IV	204	16.85
Baseline CD4 count		
<100	666	55.55
>=100	533	44.45
T stage of switch		
T stage I	630	52.72
T stage II	123	10.29
T stage III	360	30.13
T stage IV	82	6.86
Reason of switch		
Clinical failure	338	28.60
Immunologic failure	546	46.19
Virologic failure	253	21.40
Drug toxicity	39	3.30
Others*	6	0.51
Adherence		
Poor	391	41.55
Fair	240	25.50
Good	310	32.94
CPT given		
No	329	27.69
Yes	859	72.31
INH given		
No	885	75.71
Yes	284	24.29
Reason eligible for ART		
Clinical	265	21.88
CD4 count	856	70.69
Viral load	13	1.07
TLC	3	0.25
Transfer in	74	6.11
Baseline weight		
<45	360	29.90
45-60	694	57.64
>60	150	12.46
Second line regimen		
2a=ABC-DDI-LPV/r	203	16.69
2b=ABC-DDI-NFV	4	0.33
2c=TDF-DDI-LPV/r	20	1.64
2d=TDF-DDI-NFV	4	0.33
2e=AZT-3TC-LPV/r	133	10.94
2f=AZT-3TC-ATV/r	112	9.21
2g=TDF-3TC-LPV/r	406	33.39
2h=TDF-3TC-ATV/r	136	11.18
2i=ABC-3TC-LPV/r	87	7.15
2j=ABC-3TC-ATV/r	58	4.77
2k=ABC-DDI-ATV/r	6	0.49
2l=Others**	47	3.87

Factors associated with loss to follow up

To determine the effect of factors on time to lost to follow up, both bi-variable and multi-variable Cox regression was fitted. Covariates having p-values of more than 0.2 in the bi-variable analysis that included occupation, educational level,

history of opportunistic infection, past TB treatment, CPT, and INH given were excluded from the multivariable Cox regression.

In the multi variable Cox regression Age, weight ,CD4 count, T stage at switch and Reason of switch were not estimated to

be independent predictors of time to loss to follow up. In the multi variable Cox regression, male gender was positively and significantly associated with time to loses to follow up. But, ambulatory baseline functional status, good adherence, and drugs other than 2k were inversely associated with time to loss to follow up.

The hazard of loss to follow up for male is 2 times higher when compare to females (AHR= 2.135, 95% CI 1.053-4.330). Ambulatory functional status decreased the hazard of loss to follow up by 80.3 % as compared to those having working functional status (AHR=0.1967, 95% CI 0.049-0

.794). Those who have good adherence decreased the hazard of loss to follow up by 55.8 % as compared to those having poor adherence (AHR=0.442, 95% CI 0.198- 0.989). Patients who took drug type 2a=ABC-DDI-LPV/r (Abacavir-didanosine-Lopinavir/ritonavir)decreased the hazard of loss to follow up by 93.9 % as compared to those who took drug type 2k=ABC-DDI-ATV/r(Atazanavir/ritonavir) (AHR=0.061, 95% CI 0.006-0.594). Those who took drug type 2e=AZT-3TC-LPV/r decreased the hazard of loss to follow up by 93.5 % as compared to those who took 2k=ABC-DDI-ATV/r (AHR= 0.065, 95% CI 0.005-0.825) (Table 3).

Table 3: Bi-variable and multi -variable Cox regression analysis for time to loss to follow up in 8 hospitals in Amhara region of Ethiopia, 2016

Variable	Loss to follow up		CHR(95% CI)	AHR(95% CI)
	Yes	No		
Gender				
Female	28(4.8)	557(95.2)	1	1
Male	33(5.3)	586(94.7)	1.0713(0.6414- 1.7895)	2.135 (1.053- 4.330)
Functional status				
Working	44(5.96)	694(94.0)	1	1
Ambulatory	15 (3.8)	378(96.2)	0.501 (0.274 -0.916)	0.1967(0.049- 0.794)
Bedridden	2(3.4)	57(96.6)	0.696 (0.168 - 2.881)	0.145 (0.0071- 2.956)
Age category				
<32	36 (5.4)	630(94.6)	1	1
32-40	20 (5.43)	348(94.6)	0.887(0.508- 1.547)	1.387 (0.677 - 2.843)
>40	10 (5.05)	188 (94.95)	0.727 (0.350- 1.512)	0.810 (0.318 -2.066)
Reason of switch				
Clinical failure	21 (6.2)	317(93.8)	1	1
Immunological failure	29 (5.4)	511 (94.6)	0.708(0.402 -1.248)	0.733 (0.355-1.511)
Virologic	7 (2.8)	245 (97.2)	0.431(0.174-1.069)	0.353 (0.1198- 1.043)
Drug toxicity	2 (5.1)	37 (94.8)	0.603 (0.140-2.593)	0.321 (0.0356- 2.889)
T stage at switch				
T stage one	31 (5)	593 (95)	1	1
T stage two	10 (8.1)	113(91.9)	1.446 (0.705 -2.969)	1.623 (0.6288- 4.189)
T stage three	17 (4.7)	342(95.3)	0.664(0.361-1.223)	0.7089(0.323- 1.553)
T stage four	61 (5.1)	1,127(94.9	0.537 (0.163 -1.766)	1.109 (0.314-3.912)
Baseline CD4 count				
<100	27(4.1)	636(95.9)	1	1
>=100	30(5.7)	499(94.3)	1.273(0.7482- 2.167)	1.406 (0.718- 2.753)
Adherence level				
Poor	27(7)	360(93)	1	1
Fair	11(4.6)	229(95.4)	0.706(0.348-1.434)	0.717 (0.320-1.604)
Good	9(2.9)	301 (97.1)	0.433(0.2031- 0.9264)	0.442 (0.198- 0.989)
Second regimen				
2a=ABC-DDI-LPV/r	16 (7.9)	186(92.1)	0.087(0.0111- 0.682)	0.061 (0.006-0.594)
2e=AZT-3TC-LPV/r	8(6)	125 (94)	0.144(0.0174- 1.187)	0.065 (0.005-0.825)
2f=AZT-3TC-ATV/r	4(3.67)	105(96.3)	0.208(0.023- 1.878)	0.196 (0.017- 2.263)
2g=TDF-3TC-LPV/r	21(5.2)	385(94.8)	0.069(0.0089-0.527)	0.055(0.006- 0.512)
2h=TDF-3TC-ATV/r	9(6.7)	126 (93.3)	0.358(0.045- 2.847)	0.507(0.051- 5.069)
2i=ABC-3TC-LPV/r	2(2.3)	85(97.7)	0.073(0.006- 0.821)	0.085(0.007- 1.071)
2k=ABC-DDI-ATV/r	5(16.67)	25(83.33)	1	1
2l=Others*	3(6.4)	44(93.6)	0.059(0.0058-0.595)	0.043 (0.003-0 .621)
Baseline weight				
<45	20(5.6)	336 (94.3)	1	1
45-60	31(4.5)	661(95.5)	0.802(0.453-1.419)	0.602 (0.271-1.338)
>60	10(6.7)	139(93.3)	1.07(0.50- 2.287)	0.826 (0.279- 2.445)

The frequencies under the Loss to follow up column are the number of participants used in the bi-variable analyses

In this study, the cumulative incidence rate of LTFU in ART care was 65 (5.41 %). This finding is lower than findings in India⁶, SSA⁷, Nigeria⁸, South Africa⁹, and Cameron¹⁰. It is also lower than studies done in southern Ethiopia hospitals¹¹, Hadiya zone¹², and Ethiopian public hospital clinics¹³. The

differences could be due to variations in study design and patient time follow-ups. However, another study comprising different regions including SSA, Asia, Latin America and Eastern Europe ¹⁵ had got comparable finding with the current study.

Regarding factors, male gender was a positive significant predictor for losses to follow up and good adherence, ambulatory functional status, and second line regimen drug types of 2a, 2e and 2g had an inverse association with the hazard of LTFU. In the current study, the hazard of loss to follow among males was 2.1 times higher as compared to females (AHR = 2.135, 95% CI 1.053- 4.330). A similar finding was reported by a study conducted in India⁶, Cameron¹⁰ and north Ethiopia¹⁶. This could be explain by the fact that men usually travel for work particularly in professions of truck drivers, day working, and due to migrant agricultural works which keeps them away from their home likewise their medication¹⁷.

This study showed that ambulatory functional status decreased the hazard of loss to follow up by 80.3% as compared to those participants whose status was working (AHR=0.1967, 95% CI 0.049-0.794). Similar study done in southern Ethiopia support this study¹¹. The possible justification for this could be due to their routine duty in the working group that could affect negatively their adherence or follow up while it could creat a better condition for those who were ambulatory to attend strictly their treatment.

In this study, those who have good adherence decreased the hazard of loss to follow up by 55.8 % as compared to those having poor adherence. A similar finding was reported by a study conducted in Nigeria¹⁸. Our findings highlight the need for strengthening of treatment adherence by counselors and support groups to minimize LTFU and this could be an indication of the integrity of better adherence and reduced LTFU that may probably work for the synergy of better health.

Age was not a significant risk factor of time loss to follow up in this study. On contrary to this, studies done in south Africa¹⁹, Nigeria¹⁸ and southern Ethiopia¹¹ showed that the younger age was significantly related with higher level of loss to follow up. The contradiction of these studies could be due to the variation in age distribution of those studies^{11,18,19} when comared to the current study .

In this study, CD4 count was not an independent predictor of time to LTFU. However, other studies done in India⁶ and southern Ethiopia²⁰ showed that the lower baseline CD4 cell count was risk factor for LTFU. On the other hand studies conducted in SSA⁷ and Ethiopia rural hospital¹⁴ showed that higher CD4 cell count increased the risk of LTFU. The contradiction in these studies may be due to the difference in confounding variables that were not controlled by the respective studies as it could affect the true effect of CD4 count on LTFU.

In the current study, taking drug types of 2a, 2e and 2g reduced the hazard of LTFU when compared with those who took drug type 2k. This disparity among drugs with regard to the status of LTFU might be associated with the difference in the effectiveness of drugs in improving health which could subject itself to further research.

Limitation

This study included only adults beyond age 15 who were on ART; and this group of participants might not represents individuals whose age was less than 15. The other limitation of the current study is that the possible outcomes of LTFU patients might not have been accurately captured as patients who were classified as LTFU might have actually died or been cared for in other facilities.

CONCLUSION

The incidence of LTFU in Amhara region hospitals was low. Loss to follow up was negatively associated with female gender, ambulatory baseline functional status, adherence, and second line drug types of 2a, 2e, and 2g. Close follow up is recommended to minimize LTFU and improve treatment outcomes of adults on ART with due emphasis for males with working functional status and poor adherence level. We also recommend further research on the effect of drug types by ascertaining whether the reduction in LTFU for patients who took drug types of 2a, 2e, and 2g is associaed with improved or worsened health outcomes by trafcking closely lost patients.

Competing interests

The authors have declared that there was no any competing of interests.

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