Incidence and Predictors of Sever Adverse Drug Reactions Among Patients on Antiretroviral Therapy at Debre Markos Referral Hospital, Northwest Ethiopia

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Abstract

Background: Due to its nature of chronicity and the trend of using more drugs for patients with HIV, antiretroviral toxicity becomes a major challenge of HIV management. Evidences revealed that magnitude of experiencing at least one form of drug toxicity in different setting have been reached up to 90% among patients on antiretroviral therapy. The main aim of this study was to estimate the incidence and predictors of severe adverse drug reactions among People Living with Human Immunodeficiency Virus (PLHIV) at Debre Markos Referral Hospital. Methods: Retrospective follow up study with survival analysis was carried out among people living with Human Immunodeficiency virus. Mean survival time of the cohort was estimated using Kaplan-Meier method. To model the relationship between explanatory variables and the time to adverse drug reaction, Cox-proportional hazard regression model was fitted. Results: Out of the total 485 participants 67 (13.81%; 95% C.I: 10.7%, 16.8%) had experienced sever adverse drug reactions (ADRs). The incidence rate of severe adverse drug reaction development was 3 per 100-person years. Patients residing out of the catchment area to the facility were 73% at higher risk to develop ADR at any time, compared to those living within the catchment area (AHR=1.73; 95% C.I: 1.04, 2.86). The risk of ADRs among patients with baseline WHO clinical stage of III and IV was 2.59 times higher at any time compared to those with WHO stages I and II (95% C.I: 1.54, 4.36). Conclusion: The incidence of adverse drug reactions was relatively lower than reported in different parts of Ethiopia and other African countries. However, the overall burden in the 10 years period was still high. Health professionals working in the ART clinic need to give special attention for patients coming from outside of catchment areas, commercial sex workers and drivers and patients on advanced WHO clinical stages to prevent ADR development among these groups.

Background

HIV infected more than 76.1 million people and claimed 35.0 million lives so far since its epidemic started. By the end of 2016, about 36.7 million people were living with HIV. Ninety-four percent (34.5 million) was the adult population, and 17.7 million were women 15+ years [1]. Sub-Saharan Africa carries the highest burden of HIV and AIDS, with an estimated proportion of 71% of the global total [2]. East and Southern Africa regions are the most affected segment with the HIV pandemic [2].

Global scale-up of antiretroviral therapy coverage increased to 46% at the end of 2015 [3] and it has contributed to a 48% decline in deaths from AIDS-related causes [2]. However, many challenges are hampering the progress still, of which drug toxicity is the main one.

Adverse drug reaction (ADR) is defined as an unpleasant reaction resulting from an intervention related to the use of a medicinal product and predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [4]. Severe reactions may result in death, life-threatening, hospitalization, a regimen change or discontinuation, and further resulting in permanent harm or disability [5].

The world health organization (WHO) launched the test and treat (Treat All) policy for all member Nations [5]. As a result, more people will start ART earlier and remain on treatment for a more extended period on a broader scale. Consequently, it is intuitive to assume how the load of drug toxicity will intensify. WHO also recommended integrating the ARV toxicity surveillance into HIV monitoring and evaluation programs [6].

Recommendations for optimizing ARV toxicity surveillance approaches include “nesting ARV cohort event monitoring in a few centers and strengthening surveillance of hospitalizations due to ARV toxicity at selected hospitals” [7].

Adverse drug reaction is also an obstacle for ART treatment adherence. Evidence indicated that the presence of adverse drug reactions adversely affects ART drug compliance [8].

In realizing the 90-90-90 goals, working against treatment failure and ART drug adherence are essential steps. In this regard, drug toxicity and side effects are the main challenges exhausting follow up, hampering adherence and thereby leading to poor treatment outcomes. ART drug toxicity related distress has been evidenced as one of the detrimental factors against treatment adherence [8]. Especially, achieving the third 90 will be fantasy unless robust efforts are executed.

The WHO technical review meeting on antiretroviral drug toxicity surveillance in 2013 recommended a focus on operational research in order to optimize implementation modalities [6]. Several previous studies regarding adverse drug reactions of ART estimate incidences of all forms of ADRs and did not focus on the severe form, which is the primary determinant for adherence. Therefore, this study aimed to estimate the incidence of severe adverse drug reactions and its predictors among patients on antiretroviral therapy.

Methods

Study Area and Period

The study was conducted at Debre Markos Referral Hospital, Amhara Regional State. Debre Markos Referral Hospital is found in Debre Markos town, the main city of East Gojjam Administrative Zone. It is located 300 km away from Addis Ababa, the capital city of Ethiopia and 264 km from Bahir Dar capital city of Amhara Regional State. In the town, there are four health centers, more than eight private clinics, and one Referral Hospital delivering health care. Debre Markos Referral Hospital serves more than 3.5 million people in its catchment area. It provides comprehensive HIV/AIDS care and support services for more than 3716 adult population on follow up since 2005. Debre Markos town is seventh-ranked by the load of the total population with known HIV status cases as of April 2017 national report [9]. The study used secondary data of patients enrolled from January 2008 to January 2018. The data were retrieved from March 2018 to May 2018.

Study Design and population

A retrospective follow-up study design with survival data analysis was carried out. The target population for this study was all adults who have been on ART follow up from January 2008 to January 2018 at Debre Markos Referral Hospital. Those who had at least one repeated follow-up visit were included and patients with incomplete relevant baseline registries (WHO clinical stage, functional status, regimen type) were excluded from the analysis.

Sampling Technique and Sample Size Determination

The list of all eligible participants on ART follow-up was obtained in soft copy from the ART clinic. A computer-generated simple random sampling method using medical registration numbers was carried out to select patient records.

The sample size was calculated in STATA 14.1 based on sample size determination formula for survival analysis. The total eligible population from which the sample size selected was 3716 adult people on ART follow-up from 2008 to 2018. The final sample size retrieved and analyzed was 485 people on ART follow-up.

Study Variables

The primary outcome of interest for this study is time from ART initiation to the development of severe adverse drug reaction. The explanatory variables include the socio-demographic factors, baseline characteristics, and follow up measurements. The event of interest was severe adverse drug reaction and cases such as loss to follow up, transfer out, and not diagnosed with drug toxicity until the end of the follow-up were considered as censored. Severe adverse drug reaction in this study context was defined as having any one of the following features recorded as drug reaction complaints about seeking care and resulted in either of regimen change, discontinuation and /or in-patient care (including all available laboratory test results): diarrhea, hepatotoxicity, peripheral neuropathy, severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome), anemia, pancreatitis, abdominal pain, jaundice, fat changes, anxiety, depression, vomiting and other rare conditions. Generally, grades 3 and 4 of ARV toxicity according to WHO clinical grading was considered as severe adverse drug reactions as follows: Severe nausea is severe discomfort or reduced intake of a meal for three days or more. Severe vomiting of all foods/fluids in 24 hours, orthostatic hypotension, or necessity for IV therapy was defined as severe vomiting. On the other hand, severe diarrhea was defined as diarrhea with orthostatic hypotension, or necessity for IV therapy.

Data Collection Procedure and Quality Control

A structured data extraction checklist developed based on the ART receiving and follow up guideline was used. Trained health professionals working in the ART clinic were recruited for data collection and supervision.

A pretest was done to check for tool consistency and relevance. Two days of training was given for data collectors and supervisors. Strict follow-up and supervision were carried out during data collection time.

Data processing and analysis

Data were entered using Epi Data version 4.2 and analyzed using R programing statistical software. Kaplan-Meier (KM) survival curve with a Log-rank test was used to compare survival curves for categorical explanatory variables. Median and mean survival times were estimated using the KM method. To model the relationship between explanatory variables and the outcome variable, the Cox-proportional hazard regression model was implemented. For the evaluation of proportional hazards assumption, log-log survival curves, Schoenfeld goodness of fit test and time-dependent covariates approach were used. The goodness of fit of the final model was checked using Cox-Snell residuals with the Nelson-Aalen cumulative hazard function graph.

Results

Baseline and Sociodemographic Characteristics

In this retrospective follow up study, a total of 485 patient cards were retrieved and analyzed. The median age of participants was 33 years (Q1, Q3: 27, 40). Two hundred and seventy-three (44.7%) of the study participants were outside the catchment area, and 59.8% were females (Table 1).

Table 1: Baseline and Socio-demographic characteristics of patients on ART, Debre Markos Referral Hospital, 2008 -2018.

acteristics		Frequency	Percentage
n years	15-24	63	13.0
	25-34	203	41.9
	35-44	146	30.1
	>=45	73	15.1
al status	Not married	82	16.9
	Married	224	46.2
	Divorced	117	24.1
	Widowed	62	12.8
pation	Sex workers	15	3.1
	Drivers	22	4.5
	Contract employee(private)	312	64.3
	Farmer	52	10.7
	Government employee	79	16.3
	Others*	5	1.0
ion	Orthodox	432	89.1
	Muslim	45	9.3
	Other**	8	1.6
ation	No formal education	151	31.1
	Primary education	132	27.2
	Secondary education	202	41.6
	Under weight	167	34.4
	Normal	293	60.4
	Overweight and obese	25	5.2
count	CD4 <=200	291	60.0
	CD4 >200	194	40.0
ine regimen	1a=d4t-3TC-NVP	76	15.7
	1b=d4t-3TC-EFV	68	14.0
	1c=AZT-3TC-NVP	76	15.7
	1d=AZT-3TC-EFV	42	8.7
	1e=TDF-3TC-EFV	208	42.9
	1f=TDF+3TC+NVP	7	1.4
	1g=ABC+3TC+EFV	7	1.4
	1h=ABC+3TC+NVP	1	0.2

*Students, unemployed ** protestant, catholic

Incidence Rates of Adverse Drug Reactions

Out of the total 485 participants, 67 (13.81%; 95% C.I: 10.7%, 16.8%) had experienced severe adverse drug reactions (ADRs). Of the total 67 observed severe adverse drug reaction events, anemia account for the majority 28 (41.79%) of ADRs, followed by peripheral neuropathy 19(28.36%) and serious skin reactions 9(13.43%). The other forms of ADRs were lipodystrophy 4(5.97%), vomiting 4(5.97%), renal failure 2(2.98%), and hepatotoxicity 1(1.49%).

The incidence rate of ADR development was 3 (95% C.I: 2.4, 3.86) per 100-person years, with a total of 2202.7 follow up years. The incidence rates in males and females were 19.3 and 38.5 per 1000-person years of follow up, respectively. The incidence rate of ADR was lower among those who took cotrimoxazole preventive therapy compared to their counterparts (27.8/1000 PY and 40.5/1000PY), respectively. The incidence rate varies at different interval of the cohort (Table 2)

The overall cohort, censoring, and event median follow-up times were 51 (Q1, Q3: 17, 90), 56 (Q1, Q3: 14.75, 96.25), and 47 (Q1, Q3: 31, 56) months respectively. Due to the smaller proportion of the event in the cohort, the median survival time was not estimable. So, we used the survival mean to estimate the mean survival time. In this regard, the survival mean could be estimated better considering the maximum event time, which is reported as restricted mean survival time [10]. The estimated mean survival time using the restricted mean was 73.72 (95% C.I: 71.84, 75.60) months. On the other hand, the estimated median survival time among those who experienced the event of interest (ADR) was 47 (95% C.I: 40.8, 53) months.

The majority of the ADRs were encountered among those whose baseline ART regimen was d4T-3TC-NVP (43.3%) followed by d4T-3TC-EFV (37.3%). The proportion was also higher among those with baseline WHO stage of III and IV (28.4% and 43.3%), respectively.

As the interval incidence rate indicated, as the duration of time follow-up increased the incidence rate also increased. The highest incidence rate was in the interval between years four and five, followed by the interval between three and four (table 2).

Table 2: Person time follow up and incidence rates of ADR among patients on ART, Debre Markos Referral Hospital 2008 to 2018.

Cohort (years)	person-time	failures	Rate per 100 person-time	95% C.I
(0 - 1]	435.25	10	2.29	(1.2, 4.2)
(1 - 2]	364.42	4	1.09	(0.4, 2.9)
(2 - 3]	329.25	10	3.03	(1.6, 5.6)
(3 - 4]	281.58	14	4.97	(2.9, 8.3)
(4 - 5]	230.92	24	10.39	(6.9, 15.5)
> 5	561.25	5	0.89	(0.4, 2.1)

C.I=confidence interval

Survival probability

The majority (92.5%) of the ADRs occurred up to the end of the 5th year of follow up, with more than half the events encountered in the interval between three and five years (Table 3).

Table 3: Cumulative survival probability at different time intervals among patients on ART, Debre Markos Referral Hospital, 2008 -2018.

Time (year)	Beginning Total	Fail	Cumulative Survival probability	95% C. I
1	393	10	0.98	(0.96, 0.99)
3	306	14	0.94	(0.91, 0.96)
5	201	38	0.80	(0.75, 0.84)
7	145	5	0.78	(0.73, 0.82)
10	6	0	0.78	(0.73, 0.82)

Factors Associated with Time to the Development of ADRs in Bivariable Analysis

Variables with p-values of less than 0.25 from the univariable analysis were screened for multivariable analysis in the Cox-proportional hazard model. Variables including gender, residence, baseline WHO

stage, occupation, baseline regimen, regimen change, baseline CD4 cell count, taking cotrimoxazole preventive therapy, baseline BMI, the experience of TB infection and baseline functional status candidate for multivariable analysis. Some of the variables also were significant at a p-value of 0.05.

Females were shorter time ess survivors to develop ADR than males (Log-Rank, p=0.009).

Those from outside of the catchment area to Debre Markos referral hospital were at lower survival compared to those living within the catchment area (Log-Rank, p=0.027).

The goodness of Fit of the Final Model

The goodness of fit of the final Cox regression model was evaluated using the estimate of Cox-Snell residuals drawn against the Nelson-Aalen cumulative hazard function (Figure 4).

The hazard function follows the forty-five-degree line very closely except for large values of the time. It is very common for models with censored data to have some wiggling at large values of time, and it is not something that should cause much concern [11]. Therefore, we would conclude that the final model fits the data well.

Predictors of Time to the Development of Severe ADRs among Patients on ART

After checking for the Cox proportional hazard assumptions using the graphical, statistical and time-dependent methods, the multivariable Cox proportional model was run.

Those with the livelihood of commercial sex work and car driving were 2.78 times at higher risk of developing ADR compared to those with contract employment (95% C.I: 1.31, 5.92). Patients residing out of the catchment area to the facility were 73% at higher risk of developing ADR at any time, compared to those living within the catchment area (AHR=1.73; 95% C.I: 1.04, 2.86). The risk of ADRs among patients with baseline WHO clinical stage of III and IV was 2.59 times higher at any time compared to those with WHO stages I and II (95% C.I: 1.54, 4.36).

Patients who ever took anti-TB prophylaxis were 2.83 times more likely to develop severe adverse drug reactions at any time in the follow up compared to those with no anti-TB prophylaxis (95% C.I: 1.61, 4.96). On the other hand, patients who were on ART regimen groups of d4t-3TC-NVP and d4t-3TC-EFV at baseline and those who experienced regimen change from their baseline for reasons other than ADR were at higher risk of developing ADRs (Table 4).

Table 4: Cox regression analysis of the relationship between explanatory variables and the time to ADR development, Debre Markos Referral Hospital, 2008 – 2018.

Variables	Survival Status		CHR (95% C.I)	AHR (95% C.I)
	Event (ARD)	Censored		
Gender				
Male	18	177	1.00	1.00
Female	49	241	2.01 (1.17, 3.46)	1.62 (0.91, 2.89)
Occupation				
Contract Employee	33	272	1.00	1.00
Sex workers and drivers	10	27	2.14 (1.06, 4.35)	2.78 (1.31, 5.92) **
Merchant	5	4	5.77 (2.24, 14.81)	2.63 (0.81, 8.48)
Farmer	11	41	2.29 (1.16, 4.53)	2.51 (1.22, 5.16) *
Government Employee	8	74	0.75 (0.34, 1.62)	1.19 (0.53, 2.71)
Residence				
Within catchment area	28	245	1.00	1.00
Out of catchment area	39	173	1.72 (1.06, 2.79)	1.73 (1.04, 2.86) *
Baseline WHO stage				
Stage I and II	25	245	1.00	1.00
Stage III and IV	42	173	2.81 (1.71, 4.62)	2.59 (1.54, 4.36) ***
Baseline regimen				
1c+1d+1e+1f	11	322	1.00	1.00
1a +1b	54	90	7.99 (4.18, 15.30)	4.03 (1.98, 8.20) ***
1g+1h	2	6	6.59 (1.46, 29.72)	4.57 (0.79, 26.34)
Baseline CD4				
<=200	52	239		1.00
>200	15	179	0.62 (0.35, 1.09)	1.10 (0.60, 2.05)
Regimen changed				
Yes	62	125	16.63 (6.68, 41.37)	9.99 (3.79, 26.28) ***
No	5	293	1.00	1.00
Ever took CPT				
Yes	49	323	1.00	1.00
No	18	95	1.49 (0.39, 1.15)	1.38 (0.79, 2.43)
Anti TB prophylaxis				
Yes	43	286	1.32 (0.80, 2.18)	2.83(1.61, 4.96) ***
No	24	132	1.00	1.00
Functional status				

Working	43	319	1.00	1.00
Ambulatory	20	86	1.35 (0.79, 2.3)	1.43 (0.77, 2.64)
Bed ridden	4	13	1.61 (0.58, 4.48)	1.38 (0.43, 4.45)

1a= d4t-3TC-NVP, 1b= d4t-3TC-EFV, 1c = AZT-3TC-NVP, 1d= AZT-3TC-EFV, 1e= TDF-3TC-EFV, 1f=TDF+3TC+NVP, 1g=ABC+3TC+EFV, 1h=ABC+3TC+NVP, AHR= adjusted hazard ratio, CHR= crude hazard ratio, CPT=cotrimoxazole preventive therapy, *** significant at p value of 0.001, * significant at p value of 0.05

Discussions

Antiretroviral toxicity is an increasingly important issue in the management of HIV-infected patients. Early start of ART, opportunistic complications decrements and the chronic nature of HIV resulted in more drugs being used in more patients for longer periods, which can increase the likelihood of ADRs development [12].

In this study, we estimated the incidence and identified important predictors of ADR development. The incidence rate of adverse drug reaction was 3 (95% C.I: 2.4, 3.86) per 100-person years of follow up. This finding is lower than findings from Bahir Dar city (4.3/100 PY) [13], finding from seven teaching hospitals in Ethiopia (9/100 PY) [14], two retrospective studies from Nigeria (4.6/100 PY and 4.05/100 PY) [15, 16] and another study in Ethiopia [8]. This lower figure might be related to the difference in follow up duration in which all of these previous studies had a shorter duration than the current study. As the follow-up time increased, the denominator will be larger thereby incidence rate becomes smaller. The interval incidence analysis also revealed supporting results. The incidence rates at some particular time intervals were much higher than the overall rate, which explains the shorter the follow-up duration the higher the incidence be likely. The incidence was higher among females than males 3.85/100 PY and 1.93/100 PY respectively. This finding is in line with a finding of a follow-up study from Nigeria [16]. This might be due to the fact that women are more vulnerable to regimen changes than men probably during pregnancies.

About 13.81% (95% C.I: 10.87%, 17.2%) of the cohort had experienced ADR. This figure is higher than findings from Bahir Dar city (10%) [13], a tertiary hospital in Addis Ababa (7.7%) [17], seven teaching hospitals in Ethiopia (9.5%) [14], Nigeria (1.4%) [15, 16], a tertiary hospital in Ghana (9.4%) [18] and India (2.4%) [19]. The difference might be due to the longer follow up time in the current study which can be explained by the longer the follow-up, the higher the probability of including the ADR incidences. The main reason for ADR development in many works of literature was also switching ART medicines for different reasons and taking concomitant medications, including cotrimoxazole and Isoniazid preventive therapies. In this study, the proportions of regimen switching for reasons other than ADR, taking anti-TB concomitant treatment, and taking cotrimoxazole preventive therapy were 38.6%, 32.2%, and 23.3%, respectively.

About 26.37% of the total cohort experienced regimen change due to adverse drug reactions. This finding is lower than findings from Gondar referral Hospital where side effects were the most frequent (70.45 %) [20] reasons for regimen change, Jimma Southwest Ethiopia where the change due to ADRs accounted for 48.94% of all changes [21] and Kenya where it accounted for 66.3% [22]. This can be explained by the proportion of d4T, which causes the majority of regimen changes is lower (29.7%) in this study than the previous studies in Jimma Southwest Ethiopia and Kenya. On the other hand, it is higher than a finding from Nigeria where the overall prevalence of the regimen change was 73.3% and ADRs attributed to 10% [23], which can be explained by the difference in follow up duration.

Patients with baseline regimen containing stavudine in the combination were at higher risk of developing adverse drug reactions. This is in agreement with previous literature [15, 21, 24], and it might be because stavudine is known for its typical side effects such as abdominal fat distribution, peripheral neuropathy, lipoatrophy or lipodystrophy, lactic acidosis or severe

hepatomegaly with steatosis, and acute pancreatitis [5, 25].

Patients with baseline WHO clinical stages of III and IV were 2.56 times at higher risk of developing adverse drug reactions compared to WHO stages I and II. This finding is in line with findings in Bahir Dar city Northwest Ethiopia [13], Hiwot Fana specialized Hospital Eastern Ethiopia [24], Jos University Teaching Hospital in Nigeria [23], and a study from India [26]. This might also be because patients in the advanced clinical stage of HIV are more vulnerable to increased drug intake for the treatments of opportunistic infections. Subsequently, patients on advanced clinical stages are less resistant to drug side effects and are more likely to change regimens, thereby will find themselves at higher risk of drug reactions [27].

Patients who had ever taken anti-TB medicines were found at higher risk of severe adverse drug reactions development than their counterparts. This is in line with literature revealing HIV-infected patients receiving TB treatment commonly experience drug toxicity [28, 29]; even some findings recommended deferring of ARVs during the intensive phase of TB treatment [29, 30].

Coming from outside of the catchment areas was also another predictor factor for developing adverse drug reactions. It might imply that distance can affect the consistency of drug refiling and might affect getting close follow up and advice from service providers. It can also be related to the lack of social support as patients frequently go far out of their nearby facility due to fear of stigma and discrimination.

The hazard of ADR development among those who had experience of regimen change for reasons other than ADRs was higher compared to those who stayed on a single regimen during their follow up period. This can be because being exposed to multiple ARV drugs even sequentially can increase the risk of adverse drug reactions. It has also an implication of either drug stock out, treatment failure or new TB infection, which are the main reasons for regimen change other than ADRs could contribute to the likelihood of ADR development.

The occupational status of patients also showedstatistically significant association with ADRs, where commercial sex workers and car drivers were at higher risk for ADRs compared to those with contract works. This can be due to the fact that their work nature affects appropriate drug-taking and they are vulnerable to multiple sexual partners which can increase the likelihood of ADR development. They are also more exposed to alcohol intake, and it can cause ADRs. Farmers were also at higher risk than contract workers. This also could be related to their work nature, health facility accessibility and level of awareness, as farmers reside outside of Debre Markos Township.

Limitation of the study

Since this study used secondary data, it has a limitation of including all possible explanatory variables exhaustively. We could not also describe and discuss the detailed profiles of each specific adverse drug reaction.

Conclusion

The incidence of adverse drug reactions was relatively lower than reported in different parts of Ethiopia and other African countries. However, the overall burden in the ten year period was still high. Baseline regimen type, regimen change for different reasons, taking anti-TB prophylaxis or anti-TB treatments, residing outside of the catchment area, and having advanced WHO clinical stages at baseline and working as a commercial sex worker and car driver were found as independent predictors of adverse drug reactions in this retrospective follow up study.

Health professionals working in the ART clinic need to give special attention for commercial sex workers and drivers and patients on advanced WHO clinical stages to prevent ADR development among these groups. Strict follow up of patients taking TB concomitant drugs is essential. Health professionals also should consult patients coming from outside of the catchment area to attend their follow up in the nearby ART center. Further prospective follow up study needs to be conducted to incorporate all possible contributing factors and to have detailed specific ADR profiles.

Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquire Immune-deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral (drugs)
AZT/ZDV	Zidovudine
BMI	Body Mass Index
CD4	Type of T-lymphocyte, white blood cells
CPT	Cotrimoxazole Preventive Therapy
d4T	Stavudine
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency Virus
HR	Hazard Ratio
IPT	Isoniazid Preventive Therapy
LMM	Linear Mixed Model
PLHIV	People living with HIV
PY	Person Year
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the ethical review committee of the University of Gondar College of Medicine and health sciences. A letter of cooperation was sought for Debre Markos referral Hospital. Furthermore, confidentiality was maintained for all forms of information using anonymous medical registration numbers as identification.

Consent for publication

Not applicable

Availability of data and material

All the data supporting the study findings have been included in the manuscript. Additional detailed information and raw data will be shared upon reasonable request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GDK wrote the proposal, did the analysis and prepared the manuscript.

TAA and AT revised the proposal and the manuscript. All the authors have read and approved the manuscript.

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Figures

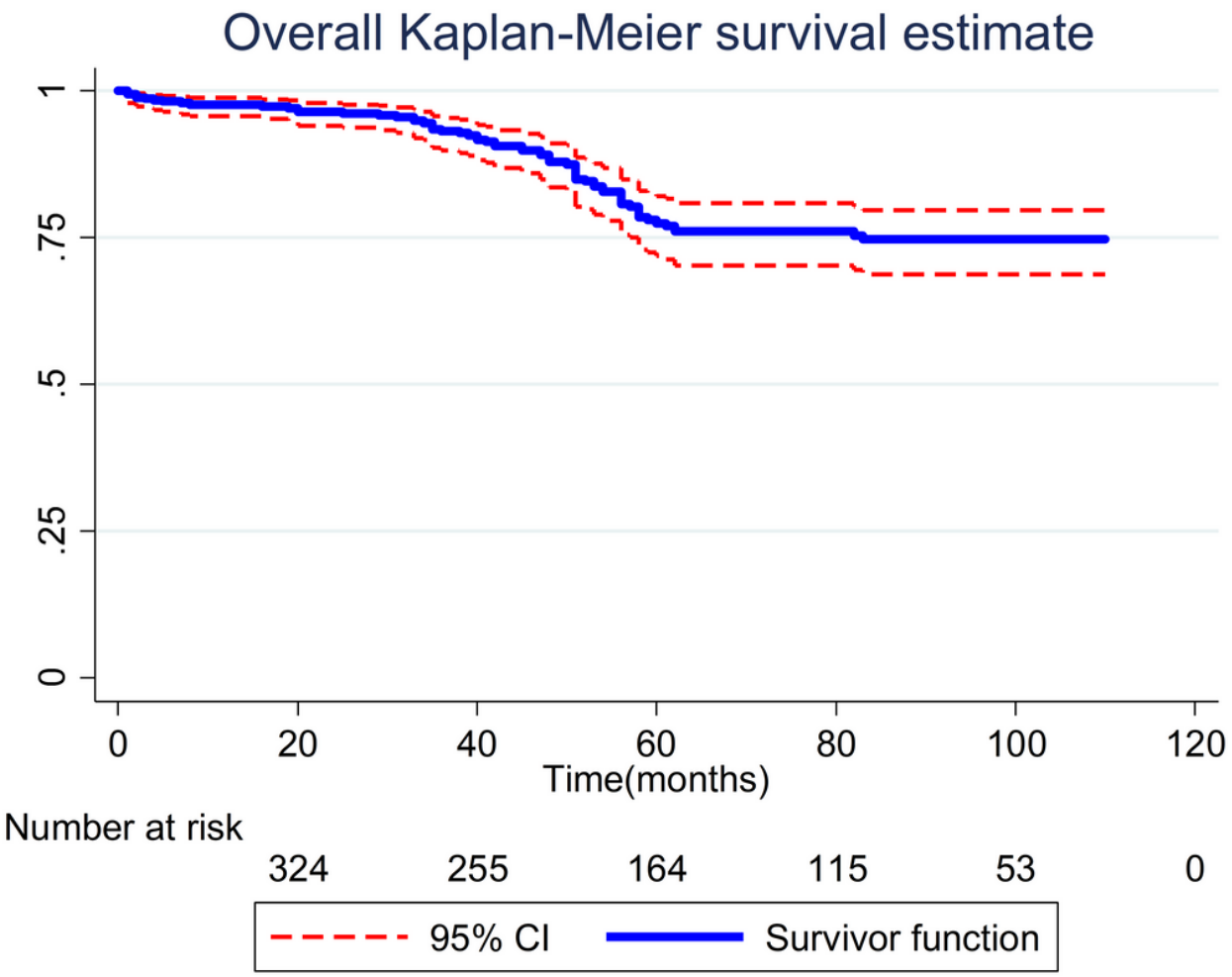

Figure 1

Cumulative survival Kaplan Meier curve for time to the development of ADRs among HIV patients on ART, Debre Markos Referral Hospital.

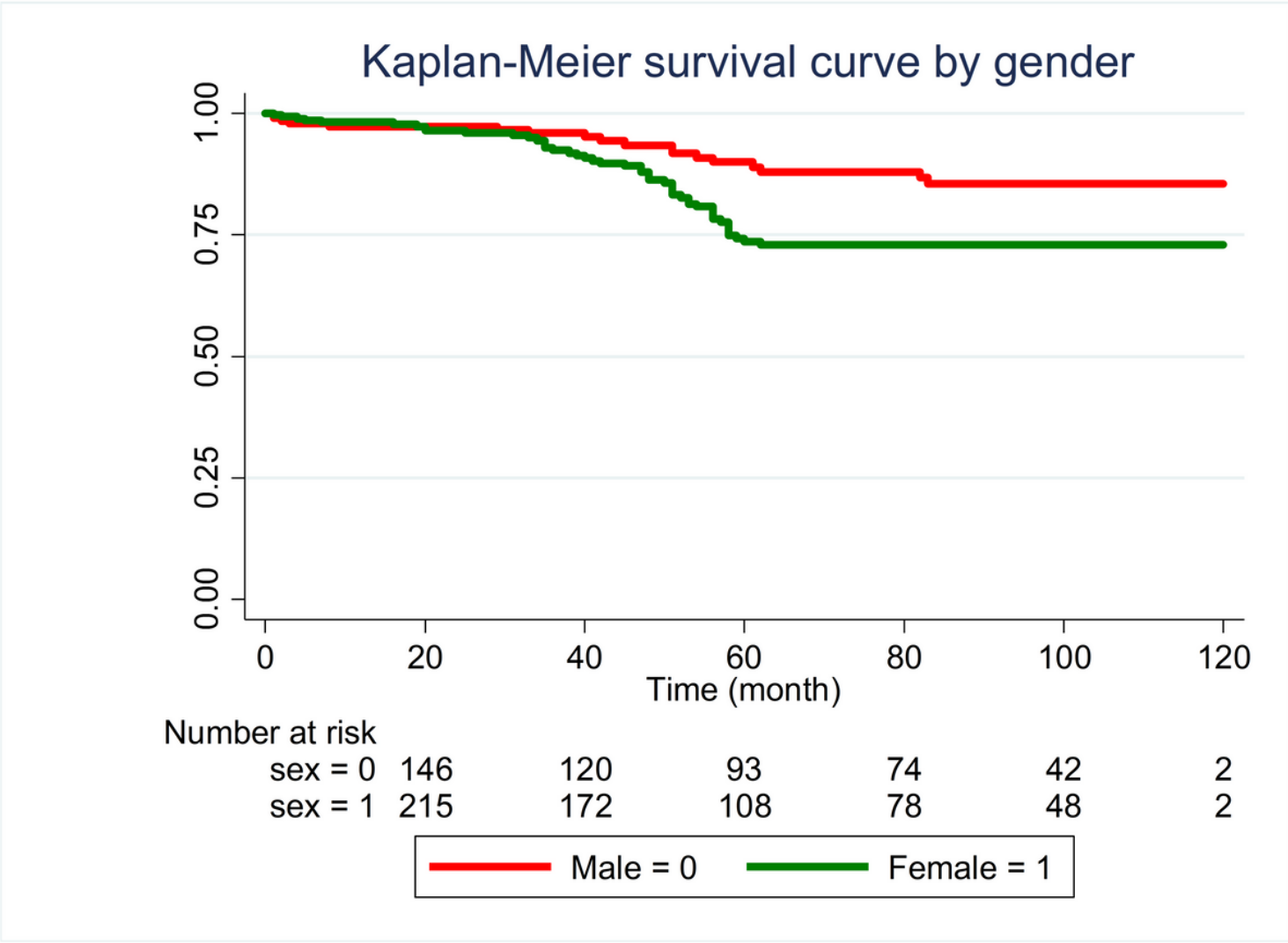

Figure 2

Kaplan Meier curves for time to the development of ADRs among HIV patients on ART by gender, Debre Markos Referral Hospital 2008 to 2018.

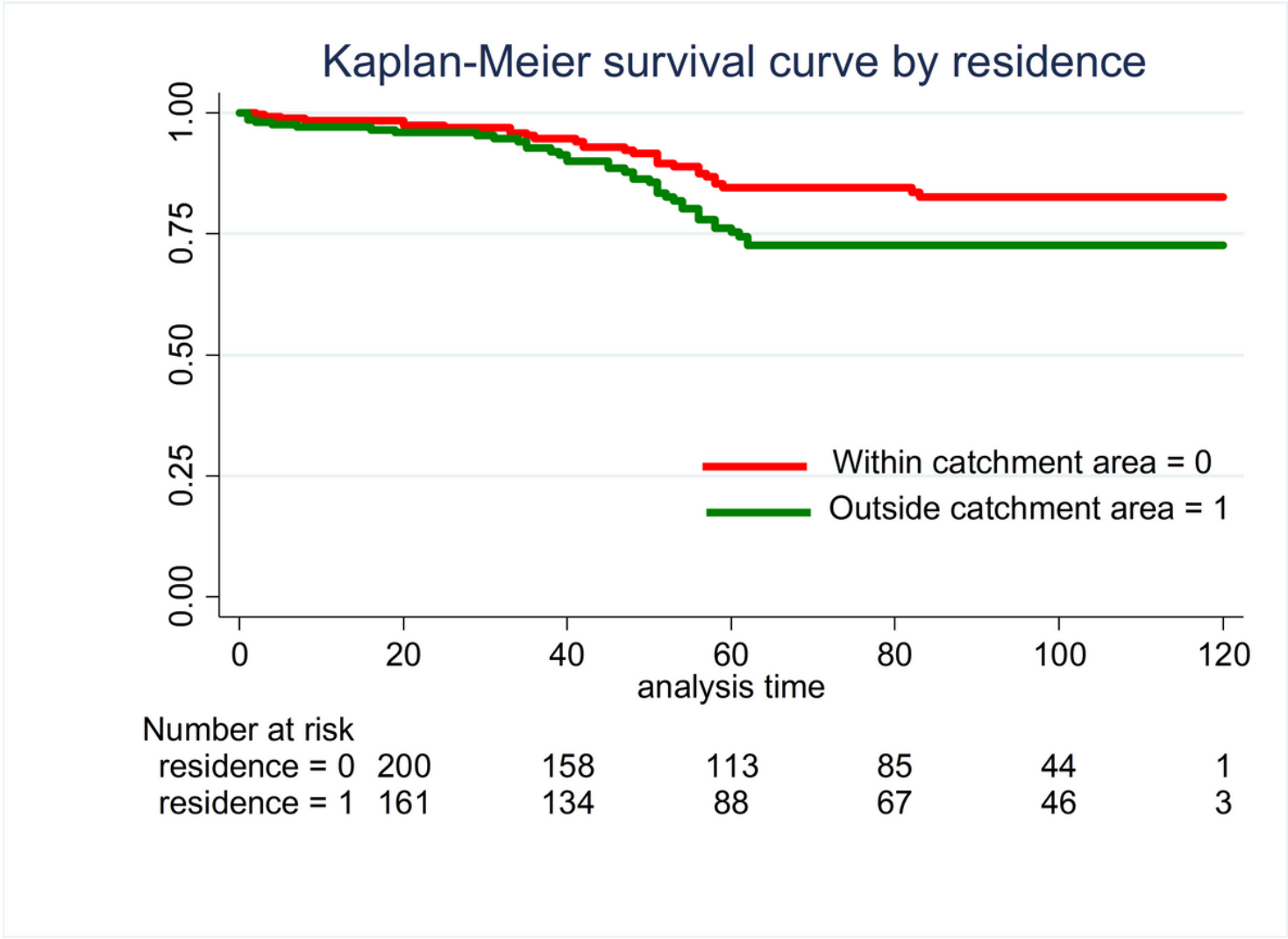

Figure 3

Kaplan Meier curves for time to the development of ADRs among HIV patients on ART by the source of residence, Debre Markos Referral Hospital 2008 to 2018.

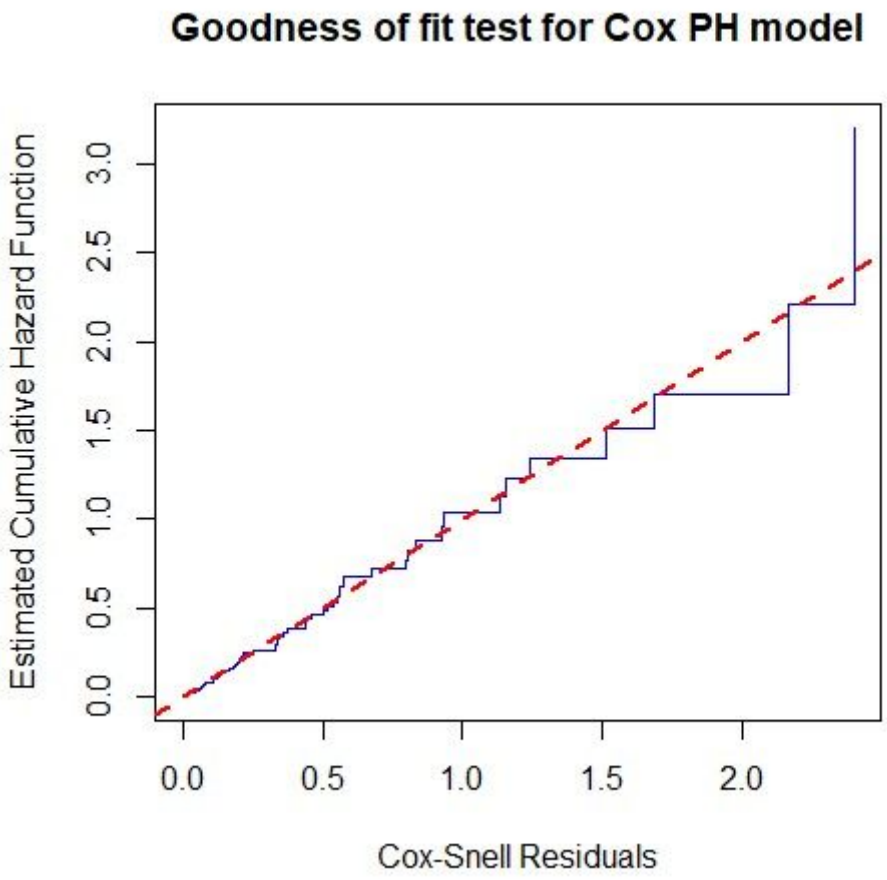

Figure 4

Goodness of fit of the final Cox proportional hazards regression model using Cox Snell Residuals.