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Time to Developments of Major Adverse Drug Reaction and Its Determinants Among Adult Hiv Positive Patients on Art in Felege Hiwot Refferal Hospital, North West Ethiopia

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TIME TO DEVELOPMENTS OF MAJOR ADVERSE DRUG REACTION AND ITS DETERMINANTS AMONG ADULT HIV POSITIVE PATIENTS ON ART IN FELEGE HIWOT REFFERAL HOSPITAL, NORTH WEST ETHIOPIA

BY:

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A THESIS SUBMITTED TO GRADUATE STUDIES OF BAHIR DAR UNIVERSITY, SCHOOL OF PUBLIC HEALTH, DEPARTMENTS OF EPIDEMIOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTERS OF PUBLIC HEALTH IN EPIDEMIOLOGY

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DECLARATION

I undersigned, declare that this is my original work and has never been presented for the degree in this or any other university and all the source materials used for this thesis have duly acknowledged.

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Acronyms

ADR - Adverse Drug Reactions

AIDS - Acquired Immune Deficiency Syndrome

ART - Antiretroviral Therapy

ARV - Antiretroviral

AZT/3TC/EFV - Zidovudine / Lamivudine / Efavirenz

AZT/3TC/NVP - Zidovudine / Lamivudine / Nevirapine

CD4 - Cluster Differentiation 4

HAART - Highly Active Antiretroviral Therapy

HIV - Human Immunodeficiency Virus

IRIS -Immune Reconstitution inflammatory Syndrome

OI -Opportunistic Infection

PLWHA - People Living With HIV/AIDS

SJS -Stevens Johnson Syndrome

SPSS - Statistical Package for Social Sciences

TDF/FTC/EFV - Tenofovir/Emtricitabine/Efavirenz

TDF/FTC NVP - Tenofovir/Emtricitabine/Niverapine

TDF/3TC/EFV - Tenofovir/Lamivudine/Efavirenz

TDF/3TC NVP - Tenofovir/Lamivudine/Niverapine

UNAIDS - United Nations AIDS

WHO - World Health Organization

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Abstract

***Background**: Antiretroviral therapy (ART) adverse events can range from acute and potentially life threatening to chronic and insidious. Serious life-threatening events require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen.*

***Objective**: To assess the time to developments of major adverse drug reaction and its determinants among adult HIV patients on ART in Felege Hiwot referral hospital, North West Ethiopia, 2017.*

***Methods**: Retrospective cohort study was conducted among patients on ART from July1/2011 - June 30/2016 at Felege Hiwot referral hospital. Data were collected using checklist and entered EPI info version 7, and analyzed using SPSS version 21 Descriptive statistics and survival analysis were computed. The p-value, hazard ratio and its confidence interval was used to show presence and strength of association between different predictor variables and time of ADRs.*

***Results**: A total of 602 subjects were followed for different period and gave 1435 person years of observation. The study showed that the overall rate of occurrence of major ADR was 4.3/100PY. The probability of surviving without major ADRS at the end of first half, one, two and end of follow up years were 0.94, 0.91, 0.89 and 0.88 respectively.*

Individuals with no formal education and primary education were more likely to report ADRs [AHR =8, 95 % CI: 2.53- 25.20, AHR = 4.9, 95 % CI: 1.65- 14.44]. Individuals working in NGOs were at risk of ADRs [AHR =4.3, 95 % CI: 1.42 – 13.31]. The study also showed that individuals with WHO stage II, III, IV were at risk of ADRs [AHR=4, 95 % CI: 1.33 -11.93, AHR=5.3, 95 % CI: 2.02-13.79 and AHR=7, 95 % CI: 2.51-20.10]. Eventually, patient who didn't take (OI) prophylaxis [AHR=3.2, 95 % CI: 1.47-7.08] were significantly associated with time to develop ADRs among HIV positive patients.

Conclusions and Recommendations:

In this study, the rate of major adverse drug reaction was found to be high and most of the change occurred within a year after initiation of HAART. *Educational status, occupation, advanced clinical stage and OI prophylaxis therapy were predictors of time to the development of major ADRs. The health workers need to give special attention and continuous counseling for non-educated patient, patient with clinical stage II and above and patients who didn't take OI prophylaxis to prevent associated ADRs.*

1) Introduction

1.1) Background

ART is changing the global HIV epidemic in significant ways. The scaling up of ART averted an estimated 4.2 million deaths in low- and middle-income countries in 2002–2012(1).

In Ethiopia, antiretroviral treatment began in 2003 and free ART was launched in January 2005. The number of patients on ART reached 308,860 by the year 2014. As a result of this, there have been dramatic declines in morbidity and mortality due to HIV. In addition, the annual total AIDS related deaths declined from 13,749 in 2011 to 6,827 in 2015 (2, 3).

Adherence to antiretroviral treatment depends on a number of factors like pill burden, existence of psychosocial support structure, the patient's readiness to start treatment, age. And possibly the most important factor of all the type and severity of adverse drug reactions experienced by the patient (4, 5).

The safety of medicines is an essential part of patient safety. Global drug safety depends on strong national systems that monitor the development and quality of medicines, report their harmful effects, and provide accurate information for their safe use. WHO defines adverse drug reactions as «any harmful or undesired response to a medication, occurring at doses used for prophylaxis, diagnosis, and treatment in humans»(6).

United States Food and Drug Administration defined serious adverse event as one when the patient outcome has one of the following eventualities: death, life-threatening, hospitalization, resulted in switching/discontinued and disability (i.e. significant impairment, damage or disruption) in the patient's body function/structure (7).

Adverse drug reactions are the single most common reason for poor adherence to treatment, identifying risk factors for the occurrence of adverse drug reactions is of crucial importance to optimize the initial choice of antiretroviral before initiating therapy and to adapt the pace of surveillance to each unique situation (8).

ART-associated adverse events can range from acute and potentially life threatening to chronic and insidious. Serious life-threatening events (eg, hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity (9). Up to 25% of patients discontinue their initial HAART regimen because of toxic effects. ART can have a wide range of adverse effects on the human body(10).

1.2) Statement of the problem

ADRs have the potential to cause significant harm in patients. There is increasing awareness of the significant global and local impact of ADRs on patient care and public health. Local factors such as the high prevalence of HIV/AIDS, tuberculosis, health systems failures and illiteracy among patients contribute to the burden of drug related morbidity and mortality in Ethiopia (11).

In Thailand the incidence ART modification was 13.8/100 person-year-observation over 2,728 person years (PY) follow up. The main reasons for regimen modification were adverse effects(12).

High frequency of regimen discontinuation and switch are observed in patients who experienced anemia, rash, hepatotoxicity, and peripheral neuropathy (13). The incidence rate of treatment modification was 18.64 per 100 person years over 946 person years of follow-up. The rate of modification was higher in the first year of ART compared to second and the third year(14). The overall ADR incidence rate was 9.5% in Malawi(15).
The prevalence of ADRs is variably reported from different studies which are 65.5% in Ethiopia, 83% in Zimbabwe and 75.4% in central India (16, 17).

In India, almost 37.70% of PLWHAV develop ADRs within 0-6 month's duration of treatment followed by 30% PLWHAV develop within the duration of 6-12 months. However there is statistically significant difference between the treatment duration and occurrence of ADR at 0.05 % level of significance (8).

Adverse reactions are among the most important factors that interfere with adherence to anti-retroviral therapy. Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients (18)

ART Adverse Effect among PLWHA half of (51.47%) the participants have faced at least one of the ART induced adverse effects. Of the adverse effects, lipoathrophy is the most (37.5%) prevalent, followed by peripheral neuropathy, anemia and dermatitis/skin rash with their respective prevalence's of 23.96%, 14.06% and 13.02%. The least frequently

occurred, ART induced adverse effect, is Hepatotoxicity with a prevalence rate of 0.52% next to renal toxicity (3.65%) and mental disorder (6.25), respectively (19)

“Serious” reactions include those that result in death, are life-threatening, result in hospitalization or prolongation of hospitalization or result in permanent harm or disability. Adverse reactions that result in treatment discontinuation and a change in ART regimen are also monitored as serious (20).

1.3) Justifications of the study

In resource limited setting including Ethiopia where treatment options were limited; knowing information about the time to development of major adverse reaction of antiretroviral therapy provides vital information for monitoring the risks ARVs new default (AZT/3TC/EFV) first line and its modified combinations. However, there was limited information about the time to development of ADRs among patients on ART in Ethiopia

Therefore, this study help to determine the incidence rate and time to development of major adverse reaction of first line HAART regimen and its predictor among adult HIV patients.

This also provides pertinent information for treatment guidelines review, regulatory authority for control, pharmaceutical planning &decision making.

1.4) Literature review

An adverse drug reaction is an expression that describes harm associated with the use of given medications at a normal dosage(21).

1.4.1) Incidence of adverse drug reaction

According to a study conducted in Swiss, among 1318 treatment -naive patients, switches or discontinuations because of drug toxicity occurred at a rate of 22 per 100 person-years. The most frequent adverse effects were gastrointestinal intolerance (29 %), hypersensitivity (18 %), central nervous system side effects (17 %), and hepatic events (12 %) (22).

A study analyzed 5026 adult HIV infected patients, who were being on ART between 1996 and 2007 in 7 Sites throughout the Caribbean and Latin America. The primary reason for change among HAART initiators were: adverse events (14%), death (5.7%) and failure (1.3%) with specific toxicities varying among sites. After change, most patients remained in first line regimens (19).

A Study done in China shows NVP is the most commonly used NNRTI because of its cost effectiveness compared to EFV. However, NVP is notorious to produce adverse cutaneous reactions, ranging from mild maculo popular rashes to fatal SJS/TEN, appears within 4-6 weeks of therapy and is also hepatotoxic (23).

A study done in Cameroon, 19.5% of patient on HAART, reported at least one ADR within a minimum period of less than a month. Hematological ADRs represented 3.8% of all ADRs of which anemia (hemoglobin <7g/dl) was the most common and the most severe, all of which were associated to AZT-containing regimens (24).

A study done in South Africa, renal impairment and anemia are the most frequently occurring ADRs. The ADRs most commonly resulting in drug substitution were anemia in those receiving AZT and renal impairment in those receiving TDF. Within the sub group of individuals requiring drug substitution due to ADRs, just over half of subjects switching (51.7%) patients substituting AZT due to anemia and 11 (68.8%) of patients substituting TDF due to renal impairment(25).

According to the study conducted in North Central Nigeria, 20.5% of all reported ADRs were attributable to nevirapine. This could include issues such as jaundice and liver toxicities, skin rashes and Stevens Johnson Syndrome(26)

A study done in Nigeria shows, most of the ADRs were observed within 6 months of initiation of ART. Eighty-eight (44.4%) of the ADRs were observed within 3 months of initiation of ART, 57 (28.8%) within 4-6 months, and 53 (26.8%) within 7-12 months (27).

In North West Ethiopia 410 study subjects who were followed for different time period. Within a follow up period, a total of (21.5 %) patients had changed their initial regimen. This makes the overall rate of initial regimen change 10.11/100 PY. The cumulative probability of surviving on initial regimen at the end of 6 months was 0.83; at the end of 1years 0.81; at the end of 3 years 0.73 and the end of follow up was 0.7. The commonest reason for regimen change was side effect which accounts for (70.45 %) of cases and contribute for the 7.13/100PY(28).

1.4.2) Factor associated with the time to developments of ADR

A study conducted in southern India, The incidence rate was 52 and 15 per 100 person-years for all reactions and severe reactions respectively. The cumulative incidence of zidovudine-induced anemia was 37.1% over 2 years. The median onset of ADR events was 18 weeks (IQR 4, 48). Fifty percent of all ADRs took place within the first 3 months of initiating ART, and 59% took place within the first 6 months. Baseline CD4 counts and type of regimen had a higher risk of experiencing a severe ADR but age, gender, baseline clinical features, co-infections and concomitant medications were not significantly associated with developing a severe ADR(29).

In Jodhpur, Rajasthan (India), incidence rate of ADRs were 20.16%. The investigate Low level of education, drug abuse, associated co-morbidities and concomitant medication were risk factors for ADRs(30).

In Bhopal Out of 129 cases on ART, 98 cases (75.6%) developed ADR. Most common ADRs were hematological (38%) followed by gastrointestinal (30%) then hepatic 29%, cutaneous (24%), neurological (24%) and metabolic in 10%. The number of ADR events were higher in patients with lower CD4 Count i.e <200(31).

According to a study conducted in Zimbabwe, the mean number of days before a clinically significant adverse drug reaction due to an N(t)RTI was lowest for stavudine (254 days), followed by zidovudine (388 days) and tenofovir (618 days). The study showed that the type of NRTI agent used had an impact on the time to occurrence of an adverse effect (32).

In South Africa, Overall 217 (37%) patients out of 590 experienced at least one ADR, most of them being females (72%). According to this study age, sex, type of ART drug regimen and durations of treatment were significantly associated with adverse drug reaction(33).

A study conducted in South Africa reported that over the first two years of ART, 10 patients had a single drug substitution from TDF 1.3 per 100 person-years. During the first 6 months of ART, the rate of single drug substitution was lowest for TDF 2.6 per 100 PYR and was similar for d4T 7.4 per 100 PYRs and AZT 8.7 PYRs(34).

In Northern Nigeria, the onset of ADR in majority (74%) of the patients was between 31 and 90 days after ARV initiation. The onset of ADR in female was significantly earlier (median 32 days) than males (median 36 days). However, the time of onset of ADRs varied from 10 to 1090 days. Baseline CD4+ cell counts >250/µL, on –therapy CD4+ cell counts >250/µL, age between 16-59 years, female gender, educational status, marital status, occupational status and type of regimen were the significant risk factors for ADRs identified in this study (35).

In eastern Ethiopia , the overall prevalence of ADRs among these study participants was 17.0%. Types of ART drug regimen had significant association with adverse drug reaction. The prevalence of ADRs was higher in those study participants who were more than 50 years of age, in females, ambulatories, in WHO stage III, with initial CD4 count 201-300 cells/µl and grade III severity level. But the difference was not statistically significant when comparisons were made within each category member (36).

According to the study done in southern Ethiopia, The probability of survival by 6^{th} month after initial ART was higher for adults compared to children and adolescents. In the study, advanced clinical stage, bedridden patients, low CD4 cell count, INH prophylactic therapy and TB co-infection were independent predisposing factors for mortality(37).

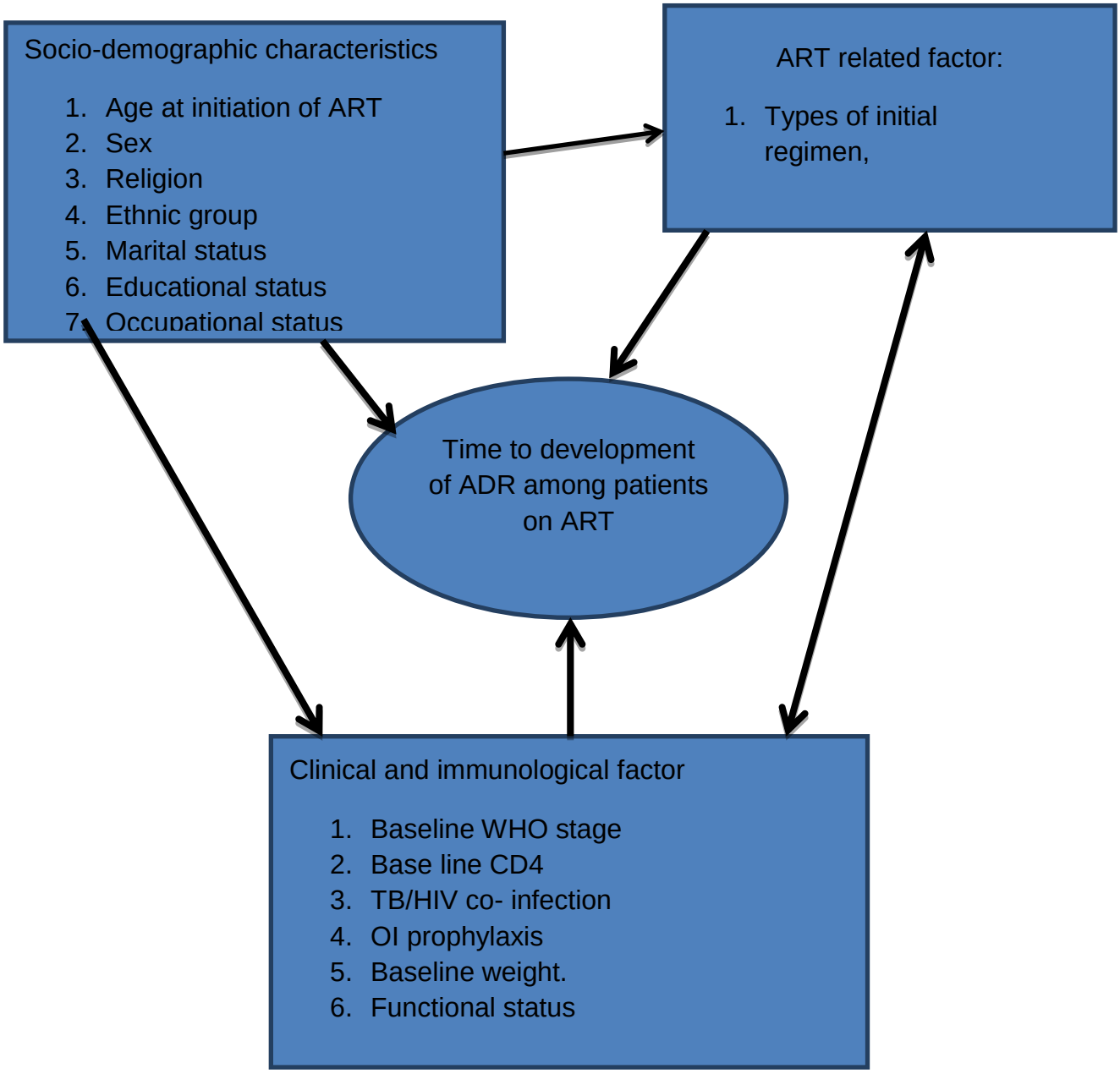

Figure 1: Conceptual framework of time to developments of major adverse drug reactions among adult patients on ART.

2) Objectives of the study

2.1) General objective

To assess time to developments of major adverse drug reaction and its determinants among adult HIV patients on ART in Felege Hiwot Referral Hospital, North west Ethiopia, 2017.

2.2) Specific objectives

- To determine time to the developments of major adverse reaction among patients on ART patients.
- To identify incidence of major adverse drug reaction among patients on ART.
- To identify factors associated with time to the development of adverse drug reaction among patients on ART.

3) Methods

3.1) Study area and period

The study was conducted at Felege Hiwot referral hospital from July 1/2011 up to June 30/2016 in Bahir Dar City, North West Ethiopia. Bahir Dar city is the capital city of Amhara region. The city is located in north western Ethiopia at a distance of 565 kilometers from Addis Ababa, the capital city of Ethiopia.

The ART clinic in Felege Hiwot referral hospital is outpatient department which is organized in to adult ART, pediatric ART and prevention of mother to child transmission (PMTCT) units. In all ART unit 17612 patients have been enrolled, and 12031 patients have been ever started ART until October 2016. Among them 6036 patients were currently on follow up. The personnel in this unit consisted of one monthly rotating resident, 1 medical doctor, 2 msc, 7 nurses, 5 data clerics, 16 case manager and adherence supporters. It has also a separate ART pharmacy with 2 pharmacists working full time. The data collection period was from December 30/2016 up to march 2017.

3.2) Study design

Facility based longitudinal retrospective cohort study was conducted.

3.3) Source Population

The source population were all patient (age >=15 year) HIV infected patients on ART who have follow-up at Felege Hiwot referral Hospital ART clinic.

3.4) Study population

All adults HIV positive patient on ART who start first line ART between July 1/2011 up to June 30/2016 in Felege Hiwot referral Hospital, ART clinic, were the study population.

3.5) Sample size determination

Sample size was determined using a single population proportion formula and Epi Info statCalc table

Considering 4% marginal error, 95% level of confidence and 37% incidence rate of ADR among Adult HIV/AIDS patients on ART in South Africa.

$N=z^2ap(1-p)/d^2$

Where:

N= required sample size

z = the value of the confidence level of 95% = 1.96

p = 0.37 incidence rate of ADR among Adult HIV/AIDS patients on ART in South Africa

d = margin of error (d = 0.04)

$N = \frac{1.96^2*0.37(1-0.37)}{(0.04)^2}$

N = 560

2) Sample size calculation using Epi Info statCalc table (variables taken from a study done in South Africa and northern Nigeria and it was included in the literature).

Assumption	Variables					
	Age	Sex	Marital status	occupation	CD4 count	Regimen type
CI	95%	95%	95%	95%	95%	95%
Power	80	80	80	80	80	80
Ratio	1	1	1	1	1	1
HR	3.5	3.16	47	6.3	4.25	4.7
% exposed	14	7.9	9.4	12.6	15.3	32.9
% unexposed	4	2.5	0.2	0.5	3.6	6.9
Sample size	294	602	210	370	228	88

Table 1: sample size determination

From the above calculated sample size the largest sample was taken as the study sample. Therefore 602 randomly selected cases of HIV/AIDS patients on ART were included in the study.

3.6) Sampling technique or procedures

The recorded list of all adult patients who start first line HAART between July1/2011 up to June 30/2016 were used as a sampling frame. From a total of 2374 adult patients who start their initial regimen 602 patients were included by systematic random sampling method. When the total number of sampling frame was divided to sample size (i.e. 2374／602) it give 3.9. Therefore every 4^{th} patient from the list was taken as a sample patient. The first card number from the first 1-4 card the third was selected with lottery method.

3.7) Inclusion and Exclusion Criteria

Inclusion criteria

- All adult patients on ART whose age was 15 years of age were included in the study.

Exclusion criteria

- Incomplete patient cards

3.8) Study variables

3.8.1) Dependent variables

The time to development of major adverse drug reaction

3.8.2) Independent variables

Socio-demographic characteristics: Age at initiation of ART, Sex, Marital status, Educational status, religion, ethnic group and occupational status.

Clinical and immunological variables: Baseline WHO stage, Base line CD4, functional status, presence of OI, presence of TB/ HIV co-infection and Baseline weight.

ART related variables: Types of initial regimen,

3.9) Operational definition

Adverse drug reaction Harmful or seriously unpleasant effects occurring at doses intended for therapeutic (prophylactic or diagnostic) effect & which call for reduction of dose or withdrawal of the drug or indicate caution in future use of the same drug.

Major adverse drug reaction event as one when the patient outcome has one of the following eventualities: death, hospitalization, resulted in switching/discontinued and disability (i.e., significant impairment, damage or disruption) in the patient's body function/structure due to ART drug adverse reaction.

Length of time- duration/ number of days from the initiation ART to the developments of death, hospitalization, discontinue, drug change and disability.

Antiretroviral drug switch/change: it is the change of one or two ARV drugs from the initial drug regimens.

Toxicity: is defined as the occurrence of adverse events such as diarrhea, nausea, vomiting, anemia, rash, fatigue, peripheral neuropathy, lipodystrophy, metabolic disturbances, CNS abnormalities or any other unwanted effect related to HAART.

3.10) Data Collection tools and procedure

The available information on the patient individual card was observed and data extracted using data extraction checklist. The check list was prepared in English language from reviewed literature sources.

Five data collectors was participated in the data collection and all data collectors were health professionals who have ART training and currently working in ART clinic. The principal investigator gave training for those data collectors. The principal investigator performed the daily supervision and checked the completed checklist.

3.11) Data Quality Management

Data collection checklist was pretested in 5% of the total sample (31 patient cards) randomly in Bahir Dar health center to check for its consistency and completeness. The data collectors and supervisors were trained in data collection, sampling methods, purpose of the study and research ethics. On receiving of filled questionnaires data was checked for completeness and accuracy. Omissions and errors was communicated with the health professionals for correction immediately on receiving. Epi-info version 7 software was used to flag out of range values or errors while data processing.

3.12) Data processing and analysis

The collected data was checked for its completeness, coded and entered in to Epi Info version 7 software package, cleaned and exported to SPSS software package version 21. Descriptive statistics were carried out to describe the socio demographics, baseline and follow up data. Incidence rate were calculated for the entire study period. The follow up duration for peoples on ART who did not develop major adverse drug reaction were calculated from the time of initiation of ART until the last visit. For those who develop major adverse drug reaction; the follow up duration was calculated from initiation of HAART to the developments of at least one major adverse drug reaction. The survival analysis technique was carried out, as this study considered time-to-event data, Cox proportional hazard model was used. Log rank test was used to compare survival curves before significance drug adverse reaction between the different categories of the explanatory variables. Both bivariate and multivariable Cox proportional hazard model were used to identify the predictors. Variables with p value <0.2 in the bivariate analysis were entered into the multivariable proportional hazard model. 95 % CI of hazard ratio were computed and variable having p value <0.05 in the multivariable Cox proportional hazards model were considered as significantly and independently associated with the dependent variable.

3.13) Ethical clearance

Ethical clearance was obtained from Bahir Dar University, school of public health ethical clearance committee and permission letter was obtained from Amhara Regional Health Bureau and Felege Hiwot Referral Hospital. The patients' clinical records were reviewed anonymously and Confidentiality of data was kept at each step of data collection and processing.

4) Results

Socio demographic characteristics

According to this study a total of 602 records were analyzed. The mean and standard deviation of the age of the clients at the initiation of ART was 35.05 ± 9.6 years.

Two hundred fifthly four (42.2 %) of the participants were in the age group between 25 and 34 years. More than half of the respondents 353 (59.1%) were females. The majority 544 (90.4%) of them were Orthodox Christian by religion.

Regarding the level of education, 175 (29.1%) had no formal education and 152(25.2%) were in primary school education.(Table2)

Table 2: Socio demographic characteristics of HIV positive adults at initiation of HAART at Felege Hiwot Referral Hospital, July 2011 to June 2016 (n = 602)

variables	Category	Frequency	Percentages
Sex	Male	246	40.9
	Female	356	59.1
Age	15-24	52	8.6
(mean±SD)=35.05±9.	25-34	254	42.2
6	35-44	193	32.1
	>=45	103	17.1
Religion	Orthodox	544	90.4
	Muslim	46	7.6
	Protestant	10	1.7
	Others	2	0.3
Ethnic group	Amhara	597	99.2
	Tigrie	5	0.8
Educational status	no formal education	175	29.1

	primary school education	152	25.2
	secondary school education	119	19.8
	higher institute education	156	25.9
Marital status	never married	99	16.4
	currently married	320	53.2
	Divorced	148	24.6
	Widowed	35	5.8
Occupational status	Governmental employee	145	24.1
	Non- governmental employee	53	8.8
	Self employed	169	28.1
	Daily labourer	74	12.3
	House wife	130	21.6
	Others	31	5.1

Clinical and immunological characteristics of the study subjects

About half (41.9 %) of patients were on WHO stage III at the time of HAART initiation. The interquartile ranges of CD4 count was 188cells/µl. About 55.1% had CD4 count less than 200 cells/µl.

Nearly three fourth (75.9%) of the patients had a body weight of less than 60 kg. Majority of (85.5%) patients had received Cotrimoxazole prophylaxis and (7.5%) of the patients had TB co-infection.

Based on the finding of this study, the predominant HAART regimen initially prescribed for them were a combination of Tenofovir, Lamivudine and Efavirenz (TDF-3TC-EFV) 353(58.6%) followed by zidovudine, Lamivudine and Nevirapine (AZT-3TC-NVP) 137 (22.8 %) (Table3).

Table 3: Clinical and immunological characteristics of HIV positive adults at initiation of HAART at Felege Hiwot Referral Hospital, July 2011 to June 2016 (n = 602)

variables	Category	Frequency	Percentages
WHO clinical stage	WHO stage I	162	26.9
	WHO stage II	138	22.9
	WHO stage III	252	41.9
	WHO stage IV	52	8.3
Weight (kg)	<60	457	75.9
(mean ±SD)=53.6±	>=60	145	24.1
9.96			
OI prophylaxis	Yes	517	85.8
	No	85	14.2
CD4 count(Cell/ml)	<200	332	55.1
IQR= 188 cell/µl	>=200	270	44.9
Functional status	Working	518	86
	Ambulatory	69	11.5
	Bedridden	15	2.5
TB co-infection	No	557	92.5
	Yes	45	7.5
Initial ART regimen	AZT + 3TC + NVP (1c)	137	22.8
	AZT + 3TC + EFV (1d)	66	11
	TDF + 3TC + NVP (1f)	42	7
	TDF + 3TC + EFV (1e)	353	58.6
	ABC+ 3TC + EFV (g)	4	0.7

AZT+3TC+NVP- zidovudine, lamivudine, nevirapine

AZT+3TC+EFV- zidovudine, lamivudine, Efavirenz

TDF+3TC+NVP- Tenofovir, lamivudine, nevirapine

ABC+3TC+EFV- abacavier, lamivudine, Efavirenz

Occurrence of major adverse reactions

In the current study, followed 602 study participants retrospectively for the last five years; was found a total of 61 (10 %) of the study participants had major adverse drug reaction in 1435 person years of observation.

Of the 61 cases of adverse drug reactions, 38 (62%) were drug change/switch, 8(13%) drug change and hospitalization, 15(26%) hospital admission were done due to drug adverse reaction. The overall rate of occurrence of major adverse drug reaction was 4.3/100 PY.

The time to the developments of major adverse reactions among 37(60.6%), 49(80.3%) and 9(14.75%) cases was within 6 months, 1 year and 2 years respectively. The cumulative probability of surviving without developing major adverse drug reaction at the end of 6 months 0.94, at the end of 1 year 0.91, at the end of 2 year 0.89 and the end of follow up was 0.88.

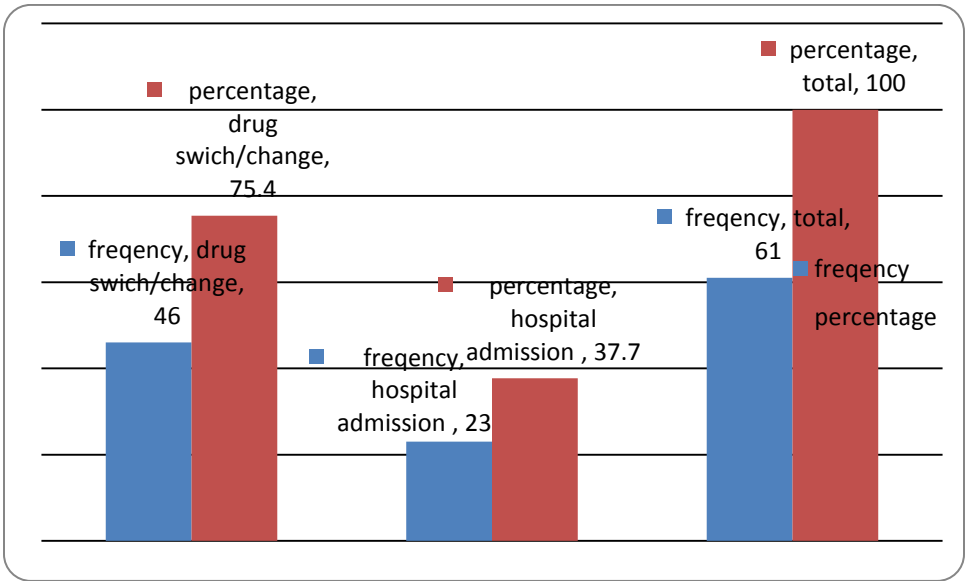

Figure 2: types of major adverse drug reaction among adult HIV positive patients in Felege Hiwot referral hospital in 2017

Table 4: life table calculation for major adverse drug reaction survival among adult HIV positive patients in Felege hiwot referral hospital in 2017

Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Probability Density	Std. Error of Probability Density	Hazard Rate	Std. Error of Hazard Rate
0	602	0	602.000	0	.00	1.00	1.00	.00	.000	.000	.00	.00
1	602	102	551.000	49	.09	.91	.91	.01	.089	.012	.09	.01
2	451	100	401.000	9	.02	.98	.89	.01	.020	.007	.02	.01
3	342	101	291.500	1	.00	1.00	.89	.01	.003	.003	.00	.00
4	240	137	171.500	2	.01	.99	.88	.02	.010	.007	.01	.01
5	101	101	50.500	0	.00	1.00	.88	.02	.000	.000	.00	.00

a. The median survival time is 5.0000

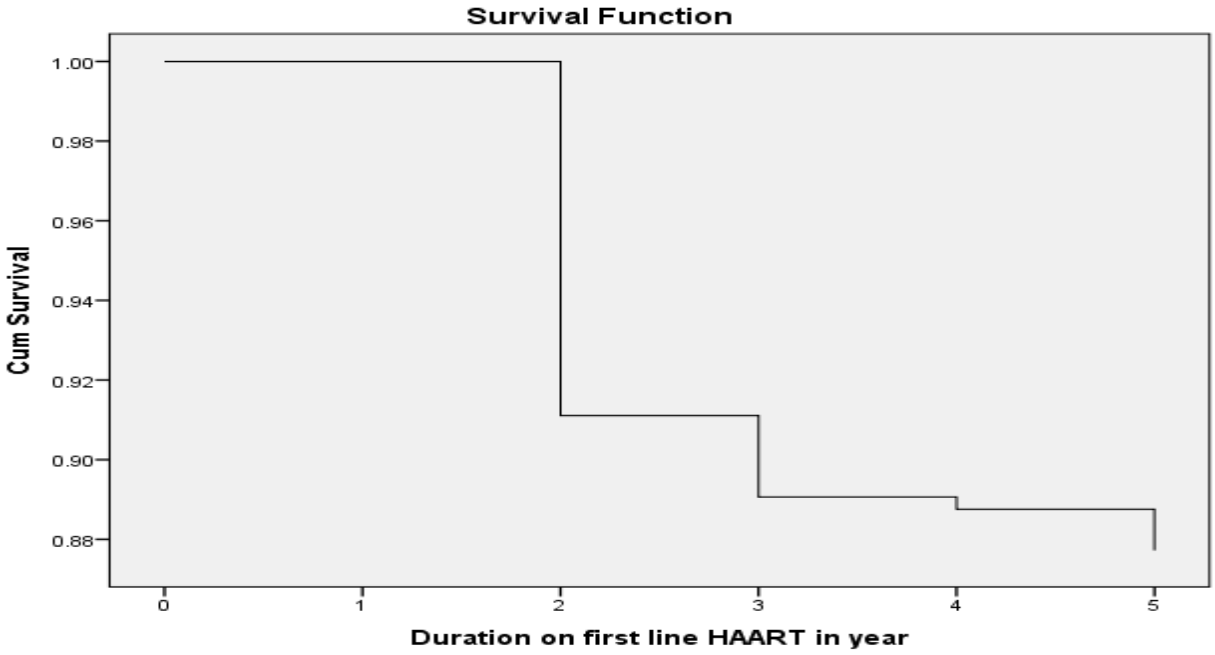

Figure 3: survival curves for time to the development of major ADRs among HIV patients on ART, Felege hiwot referral hospital, 2011–2016

In order to investigate associations between the different covariates and timing of ADRs, Kaplan-Meier survival curves were used to describe differences in the survival rate. The log-rank test was used for testing equality of the curves between categories of the respective covariates on timing to the developments ADR.

Educational status had a significant effect on timing of experiencing adverse drug reaction (log rank test = 0.001), non-educated patients had short survival time compared to those in higher education. OI prophylaxis drug intake had a significant effect on timing of experiencing adverse drug reaction (p= 0.017). Patient who had not taken OI prophylaxis had lower survival time compared to those who had taken OI prophylaxis. The survival curves with the log-rank test are shown in Figures 3-5.

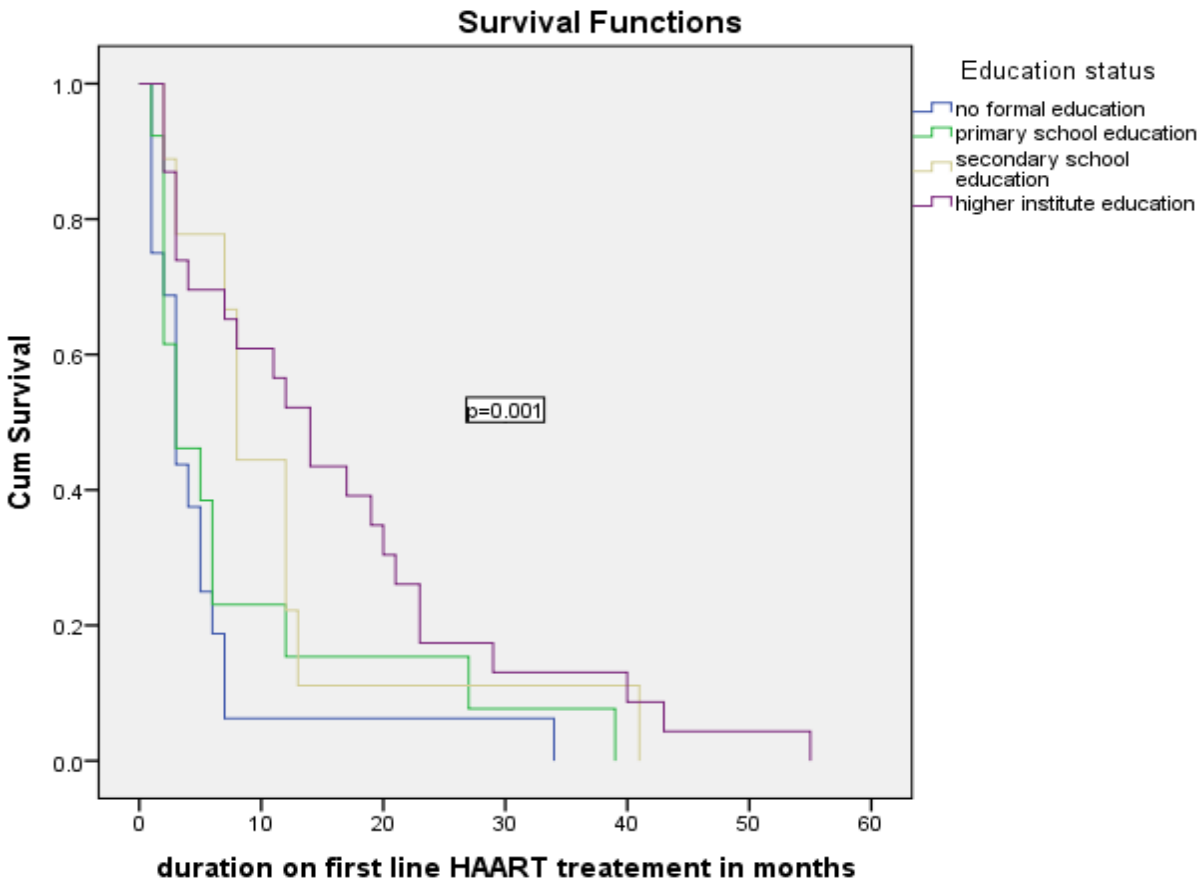

Figure 4: Kaplan Meier curves for time to the development of major ADRs among HIV patients on ART, felge hiwot referral hospital, 2011–2016 classified by educational status

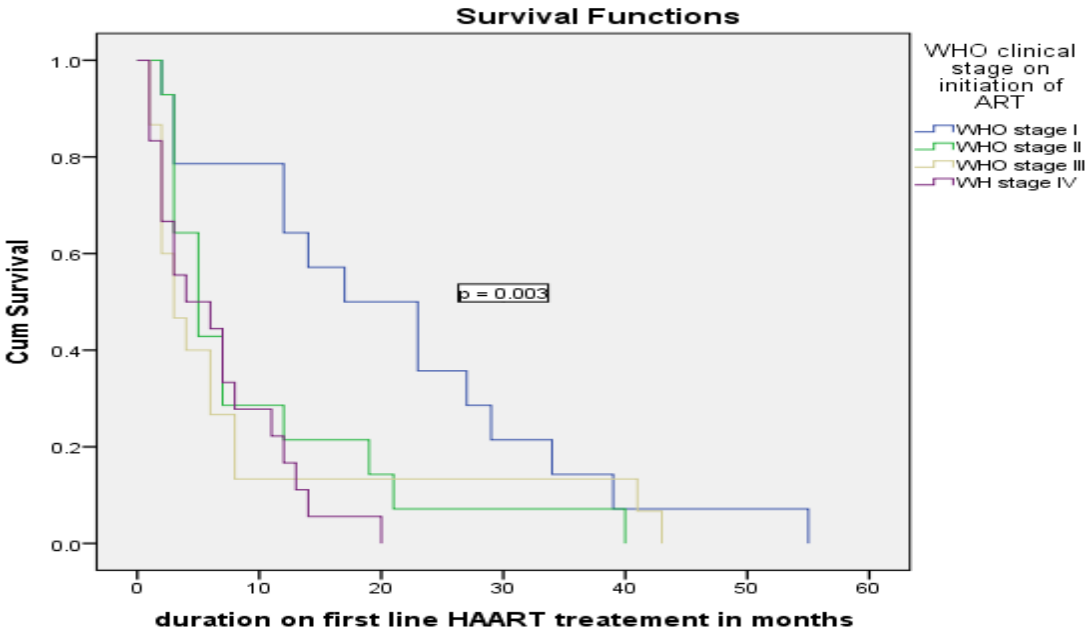

Figure 5: Kaplan Meier curves for time to the development of major ADRs among HIV patients on ART, Felege Hiwot referral hospital, 2011–2016 classified by WHO clinical stage**.**

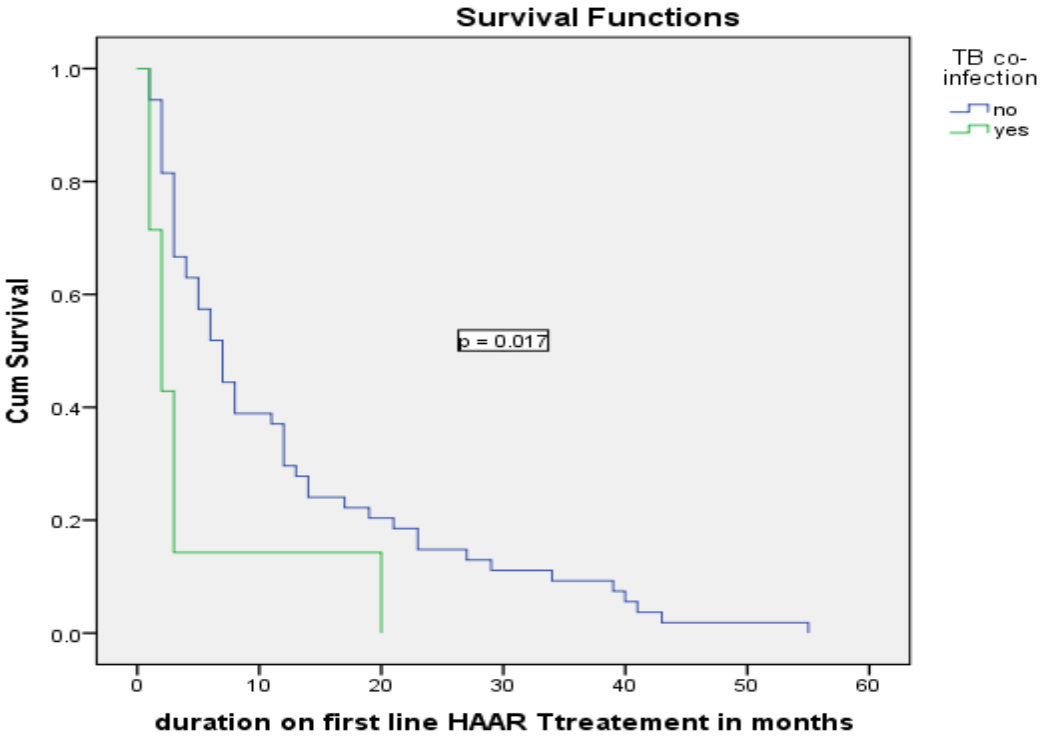

Figure 6: Kaplan Meier curves for time to the development of major ADRs among HIV patients on ART, Felege Hiwot referral hospital, 2011–2016 based on TB co-infection**.**

Association between different predictor variables and time to the development of adverse drug reaction among HIV positive patients

In the Cox-regression analysis, educational status, occupation, baseline WHO clinical stage and OI prophylaxis intake had a significant association with time to development of major ART drug adverse reaction.

In this study, those HIV positive patients who had no formal education and completed primary education at initiation of HAART increased the risk to the developments of major adverse drug reaction by 8 and 4.9 times as compared to those higher educational level patients.[p = 0.001,AHR =8, 95 % CI: 2.53- 25.20, AHR = 4.9, 95 % CI: 1.65- 14.44] respectively.

Similarly, those patients who had worked in non-governmental organization were 4.3 times at higher risk to develop major adverse drug reaction within a short period of time as compared to those worked at governmental organizations [p = 0.01,AHR =4.3, 95 % CI: 1.42 – 13.31].

Accordingly, WHO stage II, III and IV HIV patients at initiation of HAART increased the risk of adverse reaction by 4, 5.3 and 7 times as compared to those who were stage I respectively. [p = 0.001, AHR=4, 95 % CI: 1.33 -11.93, AHR=5.3, 95 % CI: 2.02-13.79 and AHR=7, 95 % CI: 2.51-20.10].

Those HIV positive patients who had not taken OI prophylaxis 3.2 times at higher risk of developing major adverse drug reaction compared to those who had taken OI prophylaxis.[p = 0.004, AHR=3.2, 95 % CI: 1.47-7.08].

Table 5: Bivariate and multivariable Cox regression analysis between different predictor variables and time to the development of adverse reaction among adult HIV positive patients on HAART regimen at Felege Hiwot Referral Hospital, July 2011 to June 2016 (n = 61)

Variables	survival status		CHR (95 %CI)	AHR (95 % CI)	P-value
	event	censored			
Educational status;					
No formal education	16	159	2.9(1.47,5.82)	8(2.53,25.20) **	
Primary school education	13	139	2.1(1.02, 4.19)	4.9(1.65,14.44) **	0.001
Secondary school education	9	110	2.1(0.60, 2.88)	1.1(0.42, 2.69)	
Higher education	23	133	1.00		
Occupation ;					
Government employee	14	131	1.00		
Nongovernment employee	6	47	1.9(0.69, 5.12)	4.3(1.42, 13.31) **	
Self employed	18	151	1.7(0.81, 3.65)	1.3(0.48, 3.52)	
Daily labourer	11	63	4(1.67, 10.23)	2(0.62, 6.72)	0.009
House wife	7	123	1(0.40, 2.70)	0.3(0.10, 1.23)	
Others	5	26	3.7(1.22, 11.16)	0.7(0.14, 3.01)	
WHO clinical Stage					
stage I	14	148	1.00	1.00	
stage II	14	124	2.1(0.96, 4.49)	4(1.33, 11.93) **	0.001
stage III	15	237	2.2(1.02,4.70)	5.3(2.02, 13.79) **	
stage IV	18	32	2.4(1.36,6.17)	7(2.51, 20.10) **	
TB co-infection					
No	54	503	1.00		
Yes	7	38	2.5(1.09, 5.51)	1.9(0.71, 4.99)	0.203
OI prophylaxis					
Yes	47	470	1.00	1.00	
No	14	71	1.8(0.94, 3.28)	3.2(1.47, 7.08) **	0.004
Baseline CD4 count (cells/µL)					
<200	42	290	1.00	1.00	
>=200	19	251	0.7(0.37, 1.19)	0.6(0.27, 1.28)	0.182

** shows significant association with the outcome variable

5) Discussion

The purpose of this study was to assess the time to developments of major adverse drug reaction and its determinants among HIV positive patients. Accordingly, of the total 602 study participants followed for five years retrospectively, 61(10%) developed ADRs. Of these events, 37(60.6%) events of adverse drug reaction occurred in the first six months, 49(80.3%) case were occurred in one year of follow up, 9(14.75%) case were occurred in two years and 3(4.9) were happened in the remaining follow up years. This finding is supported by study done in Cameroon, Nigeria and Southern India (24, 27, 29).

The cumulative probability of surviving without developing major adverse drug reaction at the end of 6 months 0.94, at the end of 1 year 0.91, at the end of 2 year 0.89 and the end of follow up was 0.88. This finding was higher than studies conducted in Gondar (28). This difference might be difference drug regimen. The majority (71%) of study participant in the current study had been taking EFV based regimen but a done in Gondar about half (54%) had been taken NVP based regimen.

In this study, the rate of major adverse drug reaction occurrence among HIV positive adult patients on HAART was 4.3/100PY. This finding was similar with the study done in south Africa 4.2/100PY (34) and lower than studies conducted in Northwest Ethiopia where the rate was 10.11/100PY and(28) . This might be due to type of HAART drug. Southern India 15/100PY (two year follow up) (29) because in India there might be better care and management of HIV treatment, better data handling mechanism if the case happened, regular supervision and follow up as a result of that all cases might be known to take action. Furthermore this might be due to the difference in follow up time because the study in India the follow up time was two years in this case as we know majority of adverse reaction occurs in the first two years.

Those HIV positive patients who had not formal education are 8 times more risk to develop major adverse drug reaction at any time as compared to patient with higher education level of education; similarly. Patients who had completed primary education are 4.9 times more likely to develop major adverse drug reaction at any time as compared

to patient with higher education. This finding is comparable to a study done in Northern Nigeria, Jodhpur-India where educational level of the study patients significantly associated with the time to develop adverse drug reactions among HIV positive patients (35, 30). It might be inferred that higher educational level offered some protection of ADR due to proper understanding of ARV drug adherence, good nutritional status and gave care for themself.

Occupation of the patients showed association with ADRs, where nongovernmental workers are 4.3 times more likely to develop major adverse reaction at any time as compared to those who works in governmental organization This finding is similar to a study done in Northern Nigeria where occupational status of the study patients significantly associated with the time to develop adverse drug reactions among HIV positive patients (35). This might be due to poor drug adherence, forgetting to take medication, drug stock out and patient losing/running out of pills because of frequent field work.

WHO stage III patients at initiation of HAART are 5.3 times at high risk to have major adverse drug reaction at any time compared to WHO stage I patients. The find is in line with the study done in North west Ethiopia, Eastern Ethiopia and Southern Ethiopia (29, 36, 37). This might be due to the fact that those patients who had advanced disease unable to resist drug side which result in drug change or hospital admission. Similarly, those WHO stage IV patients are 7 times at high risk to have major adverse drug reaction at any time compared to WHO stage I patients. This might be due to the fact that those patients who had advanced disease are likely to be on other medications which might result in drug interaction, side effect and overlapping toxicity between ART drugs and other medication which result in drug change/ hospital admission. The other possible explanation might be poor adherence due to pill burden which resulted in poor efficacy of treatment result in drug change/ hospital admission.

Those who had not taken OI prophylaxis drug are 3.2 times increase the hazard to have major adverse drug reaction at any time as compared to those who had taken OI prophylaxis drug. The possible reason might be due to prophylactic therapy successfully extend and improve the quality of life for people living with HIV.

In this study Sex, age, marital status, CD4 count and regimen type were not statistically significantly associated with time to the development of major ADR. This finding contradict other studies done Zimbabwe, South Africa and Northern Nigeria (32,33,35).This discrepancy might be explained for possible variations of the study settings, regimen type and time gap in which the studies were conducted.

6) Limitation

Since the study was retrospective the onset of time to development of adverse reaction might not correct.

Because of the retrospective nature of the study some important predictors which had a significant association with initial regimen change in other studies, like BMI

There was misclassification, Poor recording and reporting of major adverse drug reaction.

7) Conclusion

According to this study, the rate of major adverse drug reaction was found to be high and most of the adverse reaction occurred within a year after initiation of HAART. Most 37(60.6%) of major adverse reactions were occurred in the first 6 months of treatment.

In the present study, it was found that educational status, occupation, advanced clinical stage and OI prophylaxis therapy affects time to the development of major adverse drug reactions among HIV positive patients.

8) Recommendation

Federal minister of health should promote pre education program for HIV positive patients on ART in order to minimize problems associated with health risks including ADRs.

The health workers need to give attention to the educational level and provide continuous counseling for their patients in order to prevent ADRS occurrences.

Health workers should counsel about OI prophylaxis intake and strictly follow their client wither the patient take the drug or not in order to minimize the associated ADRs in patients on HAART.

Health workers in ART clinics and the hospitals in general need to give special care and attention to HIV positive patients whose WHO clinical stage is above II in order to prevent or decrease the associated ADRS.

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Table 6: **Annex1; Questionnaire**

Data Abstraction sheet

Code No _____

Code	***Questions***	***Responses***	***Skip***

Socio demographic characteristics			
101	Sex	Male Female	
102	Age at the time of ART initiation (years)		
103	Religion	Orthodox Muslim Protestant Catholic Others	
104	Education status	No formal education Primary school education Secondary school education Higher institute education	
105	Ethnic group	Amhara Tigrie Oromo Others	
106	Marital status	Never married Currently married Divorced Widowed	
107	Occupation	Governmental employee Nongovernmental employee Self employed Homemaker House wife Others	
108	ART initiation date at the first time (DD/MM/YY)		
Clinical and immunological characteristics			
201	Weight during initiation of ART		
202	WHO clinical stage on initiation of ART	stage I stage II stage III stage IV	
203	Base line CD4 count on initiation of ART		
204	Functional status	working ambulatory bedridden	
205	TB co-infection	Yes No	

206	OI prophylaxis	Co-trimoxazole Isoniazide Cotrimoxazole & Isoniazid No	
207	Initial ART regimen	AZT + 3TC + NVP (1c) AZT + 3TC + EFV (1d) TDF + 3TC + NVP (1f) TDF + 3TC + EFV (1e) ABC+ 3TC + EFV (g)	
Adverse drug reaction assessment questionnaire			
301	Drug switched/change	yes no	
302	Reasons for drug switch/change	ART drug adverse reaction Treatment failure Opportunistic infection (OI) IRIS Other unspecific cause	
If the Reasons for drug switch/change is ART drug adverse reaction answer question no 303- 306			
303	If the reason for drug switch/change is ART drug adverse reaction specify the drug		
304	If the reason for drug switch is drug toxicity, identify which one is from the list below	Anaemia Renal failure Hepatotoxicity CNS toxicity Skin rash Others	
305	CD4 count at the time of switch		
306	Date of initial ART switch (DD/MM/YY)		
307	Length of time from the initiation of ART up to drug switch in months		
308	**Hospitalization**	**yes** **no**	
309	Reason for hospitalization	ART drug adverse reaction Treatment failure Opportunistic infection (OI) IRIS Other unspecific cause	
If the Reason for hospitalization is ART drug adverse reaction answer question no "310 – 313"			
310	If the reason for drug switch/change is ART drug adverse reaction specify the drug		
311	CD4 count at the time of admission		
312	Date of admission (DD/MM/YY)		

313	Length of time from the initiation of ART up to hospital admission in month		
314	**Disability after ART drug initiation**	**Yes** **no**	
315	Reason for disability	ART drug adverse reaction Treatment failure Opportunistic infection (OI) IRIS Other unspecific cause	
If the Reason for disability is ART drug adverse reaction answer question no “316- 319”			
316	If the reason for drug disability is ART drug adverse reaction specify the drug		
317	CD4 count at the time of disability	----------	
318	Date of disability (DD/MM/YY)	----------	
319	Length of time from the initiation of ART up to disability in months	----------	
320	**Death**	**Yes** **No**	
321	Cause of death	ART drug adverse reaction Treatment failure Opportunistic infection (OI) IRIS Other unspecific cause	
If the reason for cause of death is ART drug adverse reaction answer question no “322-324”			
322	If the reason for drug switch/change is ART drug adverse reaction specify the drug		
323	Date of death (DD/MM/YY)		
324	Length of time from the initiation of ART up to death in months		
401	Major adverse drug reaction	Yes no	
402	Duration on first line HAART		