Anti-retro viral therapy Adverse Drug Reaction among Human Immuno deficiency Virus-Infected Adult Patients and Associated Factors at Nigist Eleni Mohammed Memorial Hospital, Hosanna

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Anti-retro viral therapy Adverse Drug Reaction among Human Immuno deficiency Virus-Infected Adult Patients and Factors Associated with It at Nigist Eleni Mohammed Memorial Hospital, Hosanna

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Abstract

Background: The human immunodeficiency virus (HIV) has created an enormous challenge worldwide.

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults (4.9%) living with HIV and accounting for 69% of the people living with HIV worldwide. The overall HIV prevalence in Ethiopia among adults age 15-49 is 1.5% in the 2011 EDHS.

Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of human immunodeficiency virus (HIV) care in developing countries. Like most medicines, antiretroviral drugs can cause side effects.

Objectives: To determine prevalence of ART adverse drug reaction among HIV-infected adult patients and identifying factors associated with it at Nigist Eleni Mohammed memorial hospital, Hosanna, SNNPR, Ethiopia, 2015

Methods: Institution based cross sectional study design was employed.

From a total 721 adult patient records that fulfil inclusion criteria and found to be complete based on pre-tested check list, 231 patients record were selected by SRS technique (computer generated method) from the sampling frame of 1-721.

Result: A total of 231 records were reviewed in the study. A total 82 males and 149 female's records were included and their age was 15-49years.

The finding from this study revealed that females were found more risky to develop adverse drug reaction than males (AOR=2.721, CI=1.176-6.296).

Patients with baseline WHO stage III and IV were found more risky to develop ADR than stage I and II (AOR= 13.064, CI=4.173- 40.900).

The most frequent ADRs were fatigue (18.1%), diarrhoea (7.7%), nausea (6.5%), headache (3.6%) and anaemia (2%) and others.

Conclusion: The prevalence of adverse drug reaction of ART in adults at NEMMH was low. WHO stage III and IV were found more risky to develop ADRs than WHO stage I and II and functional status ambulatory and bedridden were more risky than working status.

Commonly identified ADRs were fatigue, diarrhoea, nausea and headache.

Key words: HIV/AIDS, ADR, ART

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List of abbreviation

ADR	Adverse Drug Reactions
AIDS	Acquired Immune deficiency syndrome
ALT	Alanine aminotransferase
3TC	Amivudine
ART	Anti Retroviral Therapy
ARV	Antiretroviral drugs used for the treatment of HIV infection
BMI	Body mass index
EDHS	Ethiopian demographic health survey
HAAR	highly active antiretroviral therapy
HIV	Human immune virus
MOH	ministry of health
NEMMH	Nigist Eleni Mohamed Memorial Hospital
NFV	Nelfinavir
PLWHA	People living with HIV and manifestations of AIDS
PMTCT	prevention of mother to child transmission
SNNPR	South nation nationality and people region
D4T	Stavudine
WHO	World health organization
VCT	Voluntary Counselling and Testing
ZDV	Zidovudine

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Chapter-One: Introduction

1.1 Background

The human immunodeficiency virus has created an enormous challenge worldwide [1]. Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012 [2]. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV [3]. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults (4.9%) living with HIV and accounting for 69% of the people living with HIV worldwide [3].

The overall HIV prevalence in Ethiopia among adults age 15-49 is 1.5% in the 2011 EDHS [4]. Ethiopia is among the selected countries that had shown Changes in the incidence rate of HIV infection among adults (15–49) years old, in 2001–2011 by decreasing greater than 50% [3].

Antiretroviral therapy can help prevent people living with HIV from dying from AIDS and from developing tuberculosis, becoming ill and transmitting tuberculosis and HIV. Emerging science indicates that people should start HIV treatment earlier to realize these benefits [2].

Since 1995, antiretroviral therapy has saved 14 million life-years in low- and middle income countries, including 9 million in sub-Saharan Africa [3].

As of December 2012, an estimated 9.7 million people in low- and middle-income countries were receiving antiretroviral therapy, an increase of 1.6 million over 2011[2].

The massive scale up of antiretroviral therapy is saving more lives [5].In 2013, an additional 2.3 million people gained access to the life-saving medicines. This brings the global number of people accessing ART to nearly 13 million by the end of 2013[6]

Africa is leading the world in expanding access to antiretroviral therapy, with 7.6 million people across the continent receiving antiretroviral therapy as of December 2012, including 7.5 million people in sub-Saharan Africa [7].

The number of people receiving antiretroviral therapy (ART) in eastern and southern Africa increased from 625 000 in 2005 to approximately 6.3 million in 2012. The region accounts for about 84% of the estimated 7.5 million people who received ART in Africa and 65% of the estimated 9.7 million people who received ART globally in 2012[8].

The number of people receiving ART in Ethiopia increased from less than 9,000 in 2005 to more than 439,000 in 2013[9]

1.2. Problem Statement

Like most medicines, antiretroviral drugs can cause side effects. These unwanted effects are often mild, but sometimes they are more serious and can have a major impact on health or quality of life. [10]

Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of human immunodeficiency virus (HIV) care in developing countries [11]. The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anaemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease. [11]

ART adverse reaction prevalence varies from region to region (in different set ups), country to country [1, 12, 13] and severity and profile of ART drug reaction also varies from patient to patients ,from drug regimen to regimen[13-16].

Continuous evaluation and reporting of unusual effects/ADR/ of ART drug is important for those people receiving ART to get all the help they need to minimize the impact of side effects/adverse reactions.

As many countries have ADRs monitoring center, Ethiopia has also ADRs monitoring center which is responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluations are made and safety measures are taken to protect the public from unnecessary harm.

Nevertheless information on the type and severity of ADRs to ART is inadequate. Therefore, the aim of this study is to gain knowledge on the profile of ADR associated with ARV drugs, the burden of adverse drug reactions of ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

Chapter-Two: Literature Review

2.1 Magnitude of ADRS of ARV Drugs

Like most medicines, antiretroviral drugs can cause side effects. These unwanted effects are often mild, but sometimes they are more serious and can have a major impact on health or quality of life [10]. Prospective observational study on ADR in South Africa indicated that among HIV-infected patients, those receiving antiretroviral therapy (ART) were more likely to be admitted with an ADR than those not receiving ART [14].

Side effects vary from person to person and it is impossible to predict exactly how each individual will be affected [10]. In a study conducted in Mbeya region, Tanzania, females were found to be more prone to ADRs than males [17]. However, a study in Tamilnadu, India indicated that 60 ADRs were identified, out of which 34 (56.67%) were in male and 26 (43.33%) in female patients [18].A prospective multicentre cohort study conducted in paediatric general medical wards in five hospitals in five countries including Australia, Germany, China [Hong Kong (HK)], Malaysia and the United Kingdom (UK) indicated that almost equal proportions of ADRs were identified for female and male patients (17.0 and 16.4%respectively)[19].

Old people seem to be more prone to both minor and serious ADRs than young patients.[15]. A Study in Tamilnadu, India indicated that Patients in the age group 41-60 years experienced 32 (53.33%) ADRs, followed by 14 (23.33%) in 21-40, 10 (16.66%) in 61-80 years [18].

Another study conducted in Zimbabwe showed that older age (>40yrs) is a risk factor for peripheral neuropathy, particularly for those on stavudine containing regimens [20]. Adverse drug reaction monitoring in Ethiopia: analysis of case reports, 2002-2007 showed that from the total reported ADR cases, 221 (95%) were in the age group 11 to 60 while 84 (36%) were between 31 to 40 years [21].

The study which was conducted in Gandhi hospital, India, among 58 patients who were on second line ARV drugs, ADRs were reported in 44 (75.86%) patients [22]. Studies from Jimma University Specialized Hospital and Debre Markos Referral Hospital reported the prevalence of ADR to be 65.5%(5) and 51.44%(23) respectively. Evaluation of the Prevalence, Progression and Severity of Common Adverse Reactions in Zimbabwe had shown that the main reasons for modification of treatment regimen were toxicity/side effects (80.3%)[18].

The most frequently observed ADRs were nausea (12.25%), followed by insomnia (10.29%), loss of appetite (9.31%) malaise (7.35%) and vomiting (7.35%).[22].

Mild but commonly reported adverse effects were gastrointestinal and CNS adverse effects while anaemia, peripheral neuropathy, rash and hepatotoxicity were severe effects resulted in

high rate of regimen switch. [8]. But a study in Zewditu Memorial Hospital, Ethiopia showed that the most frequent ADR was anaemia which accounted for 33.9% followed by Peripheral Neuropathy (28.2%) and Elevated ALT (25%)[24]. However, a study on ADR in Tamilnadu, India indicated that the most commonly identified adverse drug reaction was skin rash in 18(30.0%) cases followed by nausea and vomiting in 7(11.66%) cases, headache in 4(4.66%) cases and hyperglycaemia in 3(5.0%) cases.[14].

But a study in Nekemt Hospital, Oromia regional state, Ethiopia, from all toxicity reported, lipoatrophy accounted 58.8% being the most common followed by rash (12.3%) and CNS toxicities (11.4%)[16].

It was observed that, 60 (37.50%) ADRs were reported from the regimen ZDV+3TC+NVP followed by 56 (35.0%) ADRs from STV+3TC+NVP, 20 (12.5%) ADRs from STV+3TC+EFV, 19 (11.87%) ADRs from ZDV+3TC+EFV, 3 (1.87%) ADRs from TDF+3TC+EFV and 1(0.62%) ADR each from TDF+3TC+LPV/r and TDF+ZDV+LPV/r [25]. However, a study in Zimbabwe Common Adverse Reactions indicated that the frequencies of ADRs for d4T/3TC/NVP were in the following decreasing order PN>LD>CNS>SH and for those on d4/3TC/EFV+TB (RHEZ/RH) the frequencies were PN>CNS>SH>LD.[18]

Fourteen percent of the patients on a nevirapine regimen have Nevirapine-induced hypersensitivity rash and 48% of the patients on a non-nevirapine regimen [18].

A study on adverse drug reactions in HIV infected patients at ART centre of tertiary care hospital in Guwahati, India, showed that efavirenz use was observed as a risk factor for insomnia, parasthesia and central nervous system problems in patients. [19]. The ADRs that were found to be associated with the use of AZT/3TC/NVP regimen included anaemia (.71%), skin rashes (3.935) and peripheral neuropathy (6.43%)[18].

Distribution of ADRs by various organ systems affected, indicated 50 (31.25%) ADRs were related to gastrointestinal system, 38 (23.75%) to skin, 26 (16.25%) to central nervous system, 19 (11.87%) to blood and cardiovascular system, 15 (9.37%) to musculoskeletal system, 2 (1.25%) to hepatic abnormalities and 10 (6.25%) belongs to other organ systems.[19]. A study which was conducted in Ambo zonal hospital Ethiopia, showed that the frequency of GI tract adverse reactions were found to be 75 (48.7%) followed by CNS, 55 (35.7%) and skin reactions accounted for 29 (18.8%) [12].

Different factors affect the development of ADRs in different degrees [26]. A study on ART adverse reactions in Ambo hospital, Ethiopia indicated that BMI, the presence of other diseases, types of regimen used, duration of therapy and CD4+ lymphocyte less than 400cell/mm3 were strongly associated with the occurrence of adverse drug effects[12]. Similarly a study on

Baseline CD4+ cell counts >250/μL, on –therapy CD4+ cell counts>250/μL, age between 16-59 years, female gender, and type of regimen were the significant risk factors for ADRs [27]. Also a study conducted in Zimbabwe in 2013 indicated that a higher body mass index was associated with development of lipodystrophy during treatment for those on HAART [18].

A study in Ghana showed-a relatively higher CD4 cell counts (250 cells/mm3 or more) were associated with a greater chance of an ADR, compared to lower CD4 counts (less than 250 cells/mm3)[23].

The type of ADRs that the patient developed was very much associated with the duration of treatment and the regimen that the patient was on. Similarly, the severity of ADRs was also associated with type of ADRs and the duration of treatment [12].

Factors like BMI, the presence of other diseases, types of regimen used, duration of therapy and CD4+ lymphocyte were strongly associated with the occurrence of adverse drug effects [12]. Thus, it is expected that these and other several unknown factors can also affect the prevalence of ADRs among patients taking ART in our setup.

Many studies on ART drug adverse reaction in our countries were carried out by reviewing records of limited years. The limitation of such studies is either compromising or exaggerating drug adverse reactions within this limited period.

But this study will try to use patients' information from the start of ART service to the last visit for the service to review records. This study will try to fill the gaps of the previous studies.

Generally in SNNPR, there is no any study done on ART drug adverse reaction on adult patients or any zones of the region because as it was seen in the studies done in other regions in our countries the prevalence, severity and profile of ADR of ART were different for different set ups(different from country to country and even different among regions with in a country), so this study will try to address prevalence, severity and profile of the ADR of ART in our set up although it does not represent the region.

Therefore, this study assessed the prevalence of ADRs and identified factors associated in adult patients taking ARV drugs at Nigist Elleni Mohammed Memorial Hospital.

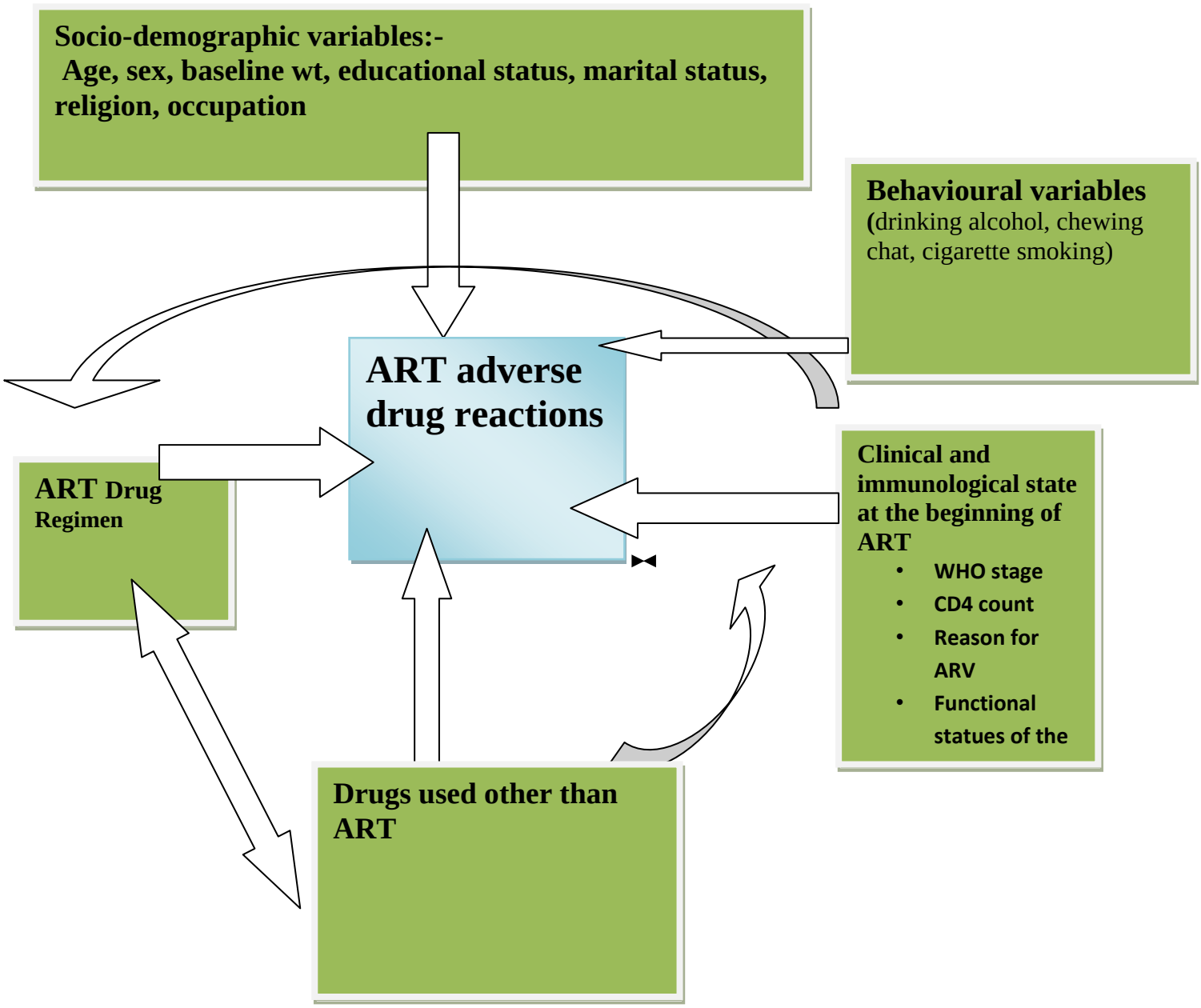

Fig.1:-Conceptual framework-which was prepared after reviewing literatures.

2.2. Significance of the Study

All medicines including ART drugs have their own side effects/adverse reaction that affect patients' quality of life and sometimes may be dangerous and life threatening.

Due to the adverse reactions patients are also forced to stop the drug by themselves, although they know there are no other options to replace ART drug or forced to change the regimen by consulting the health professionals. So studying ADR of ART is very crucial since:-

Knowledge of antiretroviral ADRs prevalence and its severity provides vital information for monitoring the risks and benefits of the medication to HIV/AIDS patients. And it provides the information on the rate of known side effects and occurrence of rare ADR. This pertinent information will be used for treatment guidelines review, regulatory authority for control, pharmaceutical planning &decision making.

Chapter-Three: Objectives

General Objective

To assess the prevalence of ART adverse drug reaction among HIV- infected adults and associated factors with it at Nigist Elenni Mohammed Memorial hospital Hosanna.

Specific Objectives

1. To assess prevalence of adverse drug reactions (ADRs) in patients on ART
2. To describe the types of ADR associated with ARV drugs among patients on ART
3. To identify factors associated with ADRs among patients on ART

Chapter-Four: Methods and Materials

4.1. Study area and study period

The study was conducted in Nigist Eleni Mohamed Memorial Hospital which is one of the Hospitals in SNNPR. It is one of the early established Governmental Hospitals during Derge era. It is located 230 and 194kilometres away from the capital city of Ethiopia (Addis Ababa) and SNNPR (Hawassa), respectively. The Hospital is found in Hosanna Town. This hospital renders comprehensives HIV/ AIDS related services including VCT, PITC (provider initiated testing and counselling), PMTCT and ART program. Currently, there were about **721** HIV/AIDS adult patients attending ART in the hospital. Study period was cover from start of ART service to last visit before data collection period for randomly selected records (from 2005 to 2014 records).

4.2. Study Design

Institution based cross sectional design was used.

4.3 Population

4.3.1 Source Population:

Consists of all adult patients ((age >15 years old) on Anti retroviral treatment at NEMM Hospital.

4.3.2. Study population:

All Selected adult patients on ART who fulfilled the inclusion criteria of the study.

4.4 Sample Size and Sampling Technique /Sampling Procedures

Sample size was determined by using a single population proportion formula; considering 5% margin of error, 95% level of confidence and 65.5% prevalence (which is the prevalence of ADR among Adult HIV/AIDS patients on ART which was done at the ART clinic of Jimma University Specialized Hospital in 2012[13]. Correcting for finite population, 231 sample size was used from HIV/AIDS adult patients who were on ART. Total HIV/AIDS adult patients on ART in NEMMH are 721& the required Sample size is 231.

From the adult patient's records that had fulfilled the inclusion criteria and found to be complete, 231 samples were taken by applying simple random sampling (by computer generated method from sampling frame of 1-721).

4.5. Inclusion and Exclusion Criteria

4.5.1. Inclusion Criteria

All adult patients 15 years and above who had follow up for at least 6months on ART were included to the study.

Those patients who had complete records.

4.6. Study Variables

4.6.1. Dependent Variables

ART adverse drug reactions

4.6.2. Independent Variables

1. Socio-demographic and behavioural variables

- age
- sex
- wt
- educational status
- marital status
- Occupation
- drinking alcohol
- chewing chat
- cigarette smoking

Clinical and immunological state at the beginning of ART

- Reason for ARV
- WHO stage
- Functional status
- CD4 count

Anti Retroviral Treatment (ART)

- Initial regimen
- Current treatment status
- If initial regimen changed, reason for changing regimen
- Current regimen patient on
- If stopped, reason for stopping ART

Drug used other than ARV drugs

Any drug used when patient develop ADR

4.7. Data Collection Procedures

From a total of 721 records, 231 samples were taken by using simple random sampling technique.

Pre-checked check list was used to collect data from the patients' records whose records were selected by simple random sampling technique (computer generated method) from 1- 721 sampling frame.

Records review covered patients' information from beginning of ART service (2005-2014) to the last visit before the data collection on randomly selected records.

Data was collected by 3 trained data collectors by using check list from April 15-25, 2015. The trained supervisor regularly supervised the data collection process. Checking of questionnaires before, during and at the end of each day of data collection for consistency, and completeness was done.

4.8 Data Quality Assurance

Both the data collectors and supervisors were trained on the objective and methodology of the research, data collection approach. Data collection format/check list was checked and necessary modification was done before data collection.

Supervisor daily conducted follow up during data collection period for completeness and consistency.

4.9. Data Analysis Procedures

Data was cleaned, checked and entered in to Epi data 3.1version software, then imported to SPSS version 16 software for analysis. The prevalence of ART Adverse effects among the study subjects was estimated using simple descriptive summary statistics such as frequency and proportion. Similarly, the magnitude of independent study variables was summarized using numerical summary measures. Tables and graphs were used to present the result of the analyzed data.

Bivariate analysis was employed to identify candidate variables for further analysis in multivariate analysis based p-value criteria<0.25.

The magnitude of the association between the different independent variables in relation to dependent was measured using OR and 95% CI and P <0.05 was considered as statistically significant.

Finally, fit model was checked

4.10. Ethical Consideration

Ethical clearance was requested and approval obtained from Jimma University, College of public health and medical sciences ethical review committee. Permission was obtained first from Hadiya zone health bureau and from NEMM Hospital medical director office before beginning the study. Data were handled confidentially during all phases of research activities.

4.11. Dissemination Plan

The findings of this study will be disseminated to Jimma University College of public health and medical sciences, NEMM Hospital, Hosanna town administrative health office, Hadiya zone Health bureau and Hosanna College of health science. The findings also will be presented in various Seminars/workshops and may be also published in a peer review scientific journal.

4.12. Operational Definitions

a- An adverse drug reaction (ADR) (WHO def.) - unintended and noxious (harmful) response that occurs at normal doses of the drug used for prophylaxis, diagnosis and treatment of diseases.

Symptoms reported by the participants, as well as laboratory abnormalities were defined as ADRs while patients on ART after 6^{th} follow up.

b- A side effect is– the weak form of the adverse effect which is unpleasant but generally acceptable. The marked changes in dosage schedule or drug withdrawal are usually not necessarily.

c- Severity of ADR-those individuals with one drug changed and regimen changed are considered due to the severity of ADR

5: Result

Socio-demographic characteristics

A total of 231 records were reviewed in the study. A total 82(35.5%) males and 149(64.5%) female's records were included and their age was from 15-49years with 31.31 mean age, 7.63 standard deviation, 15 minimum and 49 maximum age.

Concerning marital status, 173(74.9%) were married and 16(6.9%) were divorced.

Majority 104(45%) of the females were housewives and concerning education most of the respondents attended primary school.

Table 1: Socio-demographic characteristics of the respondents, in NEMMH Hosanna, April, 2015 (N=231)

Variables	**Total (N and %), N =231**	
Age	No	%
15-19	6	2.6
20-24	30	12.99
25-29	60	25.98
30-34	64	27.7
35-39	32	13.86
40-44	23	9.95
45-49	16	6.92
Marital status		
Single	23	10
Married	173	74.9
Divorced	16	6.9
Widowed	19	8.2
Sex		
Female	149	64.5
Male	82	35.5
Religion		
Orthodox	88	38.1
Islam	36	15.6
Protestant	104	45
Catholic	2	0.9
Others	1	0.4

Occupation		
Housewife	104	45
Merchant	31	13.4
Government employed	39	16.9
Self employed	20	8.7
Unemployed	1	9.1
Farmer	21	9.1
Student	15	6.5
Educational status		
No formal education	69	29.9
Primary education	96	41.6
Secondary education	57	24.7
Tertiary education	9	3.9

Initial weight in KG		
<40kg	27	11.7
40-45kg	45	19.5
46-50kg	46	19.9
>50kg	113	48.9

Clinical and behavioural state at the beginning of ART

Among the selected individuals more than 50 % of them had started ARV at WHO stage III but (5.6%) started at stage I. Regarding initial CD4 count, more than 94% of them started ARV with less than or equal to 350 CD4 count.

From the participants included in the study, 17 (7.4%) had drinking and 17(7.4%) had chat chewing history. And 1 person (0.4%) had history of smoking cigarettes.

Table: 2 *Clinical and behavioural state at the beginning at NEMMH , Hosanna in April 2015.*

Variables	Total in No_231	%
Behavioural factors		
Drinking history		
Yes	17	7.4%
No	214	92.6%
Chat chewing history		
Yes	17	7.4%
No	214	92.6%
Cigarettes smoking history		
Yes	1	0.4%
No	230	99.6%
WHO stage		
I	13	5.6
II	76	32.9
III	120	51.9
IV	22	9.5
Initial CD4 count		
=<350	219	94.8
>350	12	5.2
Functional status		
Working	104	45
Ambulatory	76	32.9
Bed ridden	51	22.1

ART drug regimen

Out of 231 patients on ART, only 81(35.1%) patients were on initial regimen during study period and 150(64.9%) were not.

From those who had changed the regimen, replaced by other regimen 38(16.5%) and only one drug changed 3 (1.3%)

The main reasons of modification of regimen in 37 patients were due to toxicity 31(13.4%) and due to pregnancy 6(2.6%).

A total of 15 patients stopped ART follow up, from these 3 patients due to toxicity and 12 due to unspecified reasons.

Table: 3 ART drug regimens at NEMMH, Hosanna, in April 2015.

Variables	**Total No_231**	**%**
Initial regimen		
D4T/3TC/NVP	123	53.2
AZT/3TC/NVP	49	21.2
AZT/3TC/EFV	10	4.4
Other	49	21.2
For those regimen changed, current regimen	Number=49	
AZT/3TC/NVP	20	40.8
ZDV/3TC/NVP	3	6.1
AZT/3TC/EFV	12	24.5
Other	14	28.6

Drugs used other than ART

During the study period31(23.4%)out of 231 patients did not have history of taking drugs other than ART and from those who took drug other drugs than ART around (196)84.8% patients were on cotrimoxazole and 9(3.9)% patients were on INH prophylaxis.

From 231 patients 59(25.5%) had TB cases in addition to HIV/AIDS.

Table:4 Drugs used other than ART at NEMMH, in April 2015.

Variables	Total No_200	%
Number of drugs used other than ARV drugs		
1-2	144	72
3-4	45	22.5
>5	11	5.5

Types and frequencies of ADRs

From a total of 231 patients, 53(22.9%) patients developed ADR. So prevalence of adverse drug reaction in adults among HIV/AIDS patients in NEMMGH during the study period was 22.9%. For the total ADR, starting with D4T/3TC/NVP contributed 57.4% and in among who had changed the regimen, 20% due to AZT/3TC/EFV. The most frequent ADRs among in initial drug regimen and regimen changed patients were fatigue.

Table: 5 Types of adverse drug reactions at NEMMGH, in April 2015.

	Initial regimens					Current regimens				
Variable	D4T/3TC/NVP	AZT/3TC/NVP	AZT/3TC/EFV	Other	Total (%)=108	AZT/3TC/NVP	ZDV/3TC/NVP	AZT/3TC/EFV	Other	Total (%) =40
ADRs										
Fatigue	35	6	1	3	45(41.69%)	0	13	6	4	23(57.5%)
Diarrhoea	8	4	3	4	19(17.6%)	1	3	0	3	7(17.5%)
Nausea	9	3	1	3	16(14.81%)	2	1	0	2	5(12.5%)
Headache	4	4	0	1	9(8.33%)	0	0	1	1	2(5%)
Rash	2	2	4	0	8(7.4%)	0	0	0	1	1(2.5%)
Vomiting	2	0	1	1	4(3.7%)	0	0	0	0	0
Anaemia	1	1	1	2	5(4.62%)	0	0	1	1	2(5%)
Peripheral neuropathy	1	1	0	0	2(1.85%)	0	0	0	0	0
Total no ADRs	62(57.4%)	21(19.4%)	11(10.2%)	14(13%)	108(100%)	3(7.5%)	17(42.5%)	8(20%)	11(27.5%)	40(100%)

Mentioned more than one time*

Factors associated with adverse drug reaction

Variables that were significantly associated at the bivariate analysis with p-value< 0.25 were further examined in the logistic regression to see their relative effect on adverse drug reaction. Results of bivariate analysis showed that sex (p<.25), WHO stage (p<0.001) and functional status of the patient (p<0.001) were identified as candidate for multivariate analysis at p-value <0.25.

Table: 6 A table that shows bivariate analysis in NEMMH, in April 2015.

	Adverse drug reaction			
Socio-demographic variables				
Sex	Yes	No	COR at 95% CI	p-value
Female	42(79.2%)	107(60.1%)	2.534(1.223-5.249)	0.012
Male	11(20.8%)	71(39.9%)	1	
Religion				
Orthodox	22(41.5%)	66(37.1%)	0.000(000-.)	1
Muslim	10(18.9%)	26(14.6%)	.000(000-.)	1
Protestant	19(35.8%)	85(47.8%)	0.000(0.000-.)	1
Catholic	2(3.8%)	0	0.000(.000-.)	0 .999
Other	0	1(0.6%)	1	
Educational status				
No primary education	24(45.3%)	45(25.3%)	0.937(0.215-4.085)	0.932
Primary education	17(32.1%)	79(44.4%)	2.324(0.528-10.224)	0.265
Secondary education	9(17%)	48(27%)	2.667(0.561-12.666)	0.217
Tertiary education	3(5.7%)	6(3.4%)	1	
Marital status				
Single	7(13.2%)	16(9%)	0.429(0.094-1.959)	0.274
Married	41(77.4%)	132(74.2%)	0.604(0.168-2.175)	0.440
Divorced	2(3.8%)	14(7.9%)	1.312(0.191-9.021)	0.782
Widowed	3(5.7%)	16(9%)	1	
Initial weight in Kg				
<40kg	4(7.5%)	23(12.9%)	1.390(0.436-4.432)	0.578
40-45kg	17(32.1%)	28(15.7%)	0.398(0.186-0.853)	0.180
46-50kg	10(18.9%)	36(20.2%)	0.870(0.375-2.018)	0.746
>50kg	22(41.5%)	91(51.1%)	1	
Occupation				
Housewife	31(58.5%)	73(41%)	0.362(0.77-1.702)	0.198

Merchant	6(11.3%)	25(14%)	0.641(0.113-3.634)	0.615
Government employee	7(13.2%)	32(18%)	0.703(0.129-3.844)	0.685
Self-employee	5(9.4%)	15(8.4%)	0.462(0.076-2.793)	0.462
Unemployed	0	1(0.6%)	2.485B8(0.000-)	1
Farmer	2(3.8%)	21(10.7%)	1.462(0.182-11.735)	0.721
Student	2(3.8%)	13(7.3%)	1	
Behavioural factors				
History of drinking				
Yes	3(5.7%)	14(7.9%)	1.423(0.393-5.151)	0.591
No	50(94.3%)	164(92.1%)	1	
History of chat chewing				
Yes	4(7.5%)	13(7.3%)	0.965(0.301-3.095)	0.952
No	49(92.5%)	165(92.7%)	1	
Clinical and Immunological factors				
WHO stage				
III&IV	49(92.5%)	93(52.2%)	11.196(3.876, 32.342)	0.000
I&II	4(7.5%)	85(47.8%)	1	
Functional status				
Bedridden	26(47.2%)	26(14.6%)	15.705(5.833-42.282)	0.000
Ambulatory	22(41.5%)	54(30.3%)	2.360(1.126-4.945)	0.023
Working	6(11.3%)	98(55.1%)	1	
Initial CD4 count				
<=350	51(96.2%)	168(94.4%)	0.659(0.140-3.105)	0.598
>350	2(3.8%)	10(5.6%)	1	
ART drug regimen				
Initial drug regimen				
D4T/3TC/NVP	27(50.9%)	96(53.9%)	1.524(0.369-6.293)	0.561
AZT/3TC/NVP	11(20.8%)	38(21.3%)	1.481(0.327-6.701)	0.610
AZT/3TC/EFV	3(5.7%)	7(3.9%)	1.321(0.295-5.929)	0.716
Other	12(22.6%)	37(20.8%)	1	
Drugs other than ARVS				
Cotrimoxazole				
Yes	46(86.8%)	150(84.3%)	0.815(0.33-1.988)	0.653

No	7(13.2%)	28(15.7%)	1	
INH prophylaxis				
Yes	1(1.9%)	8(4.5%)	2.447(0.299-20.022)	0.404
No	52(98.1%)	170(95.5%)	1	
Patients on TB drugs				
Yes	16(30.2%)	43(24.2%)	0.737(0.373-1.453)	0.378
No	37(69.8%)	135(75.8%)	1	

Based on the p-value <0.25 criteria, sex, WHO and functional status of patients were selected as candidates for further analysis in multivariate analysis. In multivariate logistic regression analysis sex, functional analysis and WHO stage were significantly associated with ADR.

The finding from this study revealed that females were around 3 times more risky to develop ADR than males (AOR=2.721, CI=1.176-6.296) and regarding clinical and immunological factors WHO stage and functional status of patients were significantly associated with ADR. Patients with baseline WHO stage III&IV were found to more risky to develop ADR around 13 times than WHO stage I &II(AOR=13.064,CI=4.173-40.900) and also patients with baseline functional status ambulatory and bedridden were more risky to develop ADR than working patients.

Table: 7 Multivariate analysis table in NEMMH, in April 2015.

	Adverse drug reaction			
Sex	Yes	No	COR at 95% CI	AOR at 95%CI p-value
Female	42(79.2%)	107(60.1%)	2.534(1.223-5.249)	2.721(1.176-6.296), 0.019
Male	11(20.8%)	71(39.9%)	1	1
WHO stage				
III&IV	49(92.5%)	93(52.2%)	11.196(3.876, 32.342)	13.064(4.173-40.900), 0.000
I&II	4(7.5%)	85(47.8%)	1	1
Functional status				
Bedridden	26(47.2%)	26(14.6%)	15.705(5.833-42.282)	18.004(6.066-53.433), 0.000
Ambulatory	22(41.5%)	54(30.3%)	2.360(1.126-4.945)	3.062(1.286-7.289), 0.011
Working	6(11.3%)	98(55.1%)	1	1

6: Discussion

The prevalence of adverse drug reaction in adults among HIV/AIDS patients in NEMMGH during the study period was 22.9%. This prevalence is similar with prevalence in Zewditu Memorial Hospital which was 24% in 2007 [23] and lower than the finding in Guwahati Hospital, India, 31% ADRs cases 2011[22], 51.44% in Debre Markos [21], 65.5% Jimma specialized teaching Hospital [11], and 81.5% Ambo Hospital [10].

Lower prevalence in this study might be due to reviewing data of smaller sample size in long period (2005-2014) and using patient data after 6 month follow up when compared with other studies. Using data of a patient from the 6^{th} month of enrolment until data collection period created a chance to incorporate the whole history of adverse drug reaction of patients and this might have compromised prevalence of adverse drug reaction. Even though current study and other studies were done by cross section design, the above studies with high prevalence might be due to using large sample size in short periods of time.

Regarding sociodemographic variables, only sex did show significant association with the development of ART drug reactions. Out of 53 individuals who had reported ADR 42(79.2%) were females and 11(20.8%) males.

The finding from this study revealed that females were found more risky to develop adverse drug reaction than in males (AOR=2.721, CI=1.176- 6.296). Which is consistent with the studies in Mbeya Region, Tanzania 2012 [15], tertiary hospital in Ghana (COR: 1.52, p=0.01; AOR: 1.66, p=0.01, CI=1.16-2,36) [29]. However, in contrast with the study done at Gandhi Hospital, India ADRs in males (81.58%) was stronger than in females (65%) in 2011 [20].

This difference might be due to differences in weight and body mass index between men and women that may play an important role. Sex differences in fat composition and the impact on drug distribution may also play a role, as may the genomic constitutional difference that exists between men and women and the way in which this difference affects the levels of various enzymes involved in drug metabolism [29].

Regarding clinical and immunological factors WHO stage and functional status of the patients were significantly associated with the ART adverse drug reactions.

Patients with baseline WHO stage III and IV were found more risky to develop ADR than stage I and II (AOR= 13.064, CI=4.173- 40.900) which is similar with the finding with the study in India in 2011 that means clinical stage III and IV more likely to develop ADR than clinical stage I and II (AOR=0.63, CI=0.33 1.23) [28]. And baseline WHO stage III/IV is indicators of poor clinical status of the patients in Ahmadabad, Gujarat, India in 2011[30]. But a study in Ghana

reported that;-WHO stages were not significantly associated with the development of adverse drug reactions in these patients [29].

Poor clinical status of the patients might be leading factor to adverse drug reactions due to patient's drug intolerance, physiological disturbance, using drugs other than ARVs to treat other opportunistic infections or psychological burden plays crucial role in developing ARDs.

Functional stage at initiation of treatment did show significant association with the development of ADRs. Patients whose functional stage was either ambulatory or bedridden during initiation of treatment were found to be more risky to develop ADR than bedridden patients. Which is inconsistent with the study in Zewditu Memorial Hospital, Working and ambulatory patients tend to follow their treatment as bed ridden ones tend to get lost from follow up [23]

Types and frequency of adverse drug reaction that were identified based on the initial regimen in NEMMGH were fatigue, diarrhoea, nausea and headache with 41.2%, 17.6%, 8.3% and 7.4% respectively. And frequency of adverse drug reaction based on the initial regimen with their respective overall drug reactions were D4T/3TC/NVP/ (57.4%), AZT/3TC/NVP (19.4%) and AZT/3TC/EFV (10.2%). The adverse drug reaction and frequencies to which regimen had changed were fatigue (57.5%), diarrhoea (17.5%), nausea (12.5%) and headache (5%) and overall frequencies of adverse drug reactions based on the substituted regimen were ZDV/3TC/NVP (42.5), AZT/3TC/EFV (20%) and AZT/3TC/NVP (7.5%).

7. Limitation of the study

As being cross-sectional in the design, it does not predict cause-effect relationship.

Age <15 years and >49 were excluded

Small sample size might have affected the prevalence of adverse drug reaction in NEMMGH.

Patient data from initiation of ART to the first 6 month were excluded.

Since the study was done by reviewing records, poor recording of adverse drug reaction and reporting by the health professional is the main limitation

8. Conclusion

The prevalence of adverse drug reaction of ART in adults at NEMMH was low (22.9%).

Sex, functional status of patients and WHO stages HIV/ AIDs have showed significant association with adverse drug reaction in adults in NEMMGH in Hosanna.

Females were found to be more likely to develop ADRs than males.

WHO stage III and IV were found more risky to develop ADRs than WHO stage I and II and functional status ambulatory and bedridden were more risky than working status.
Commonly identified ADRs were fatigue, diarrhoea, nausea and headache.

9. Recommendation

Early initiation of ART drugs prevents ADRs; therefore every effort should be made to initiate ART early (before reaching WHO Stages III and IV).

Bedridden and ambulatory patients need close follow up from health care providers to minimize prevalence of ADRs during initiation of ARVs.

Females need special attention during initiation of ART to decrease drug reactions.

Improve the clinical recording of patients on ART by keeping complete clinical record including initial and follow up laboratory investigation results. The patient follow up chart have to be improved in such a way that it is easy to monitor adherence and ADRs.

Prospective study is recommended to overcome the limitations of retrospective cross sectional study

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Annex I: Checklist to Review Record.

Demographic and behavioural variables

S.N	Variables	Categories	Code
PART-I SOCIO- DEMOGRAPHIC VARIABLES			
1	Unique ART No		
2	Age in years	_____	
3	Sex	i- Male ii- female	
4	Initial wt in KG _____	_____	
5	Marital status	1- Single 2- Married 3- Divorced 4- widowed	
6	Educational status	1-No formal education 2- Primary education 3-Secondary education 4-Tertiary education	
7	Religion	1- Orthodox 2- Islam 3- Protestant 4- Catholic 5- Other	
8	Is there history of smoking during ART enrolment?	1- Yes 2-- No	
9	Is there any history of drinking alcohol during ART	1- Yes 2- No	

	enrolment?		
10	Is there history of chat chewing during ART enrolment?	1-Yes 2- No	

PART–II clinical and laboratory state at the beginning of ART

1-	Date of HIV+ confirmation.		
2-	Reason for ARV	1- Treatment 2- PEP 3- Other specify	
3-	WHO stage	1- I 2- II 3- III 4- IV	
4-	Functional	1- Working 2- Ambulatory 3- Bed ridden	
5-	Initial CD4 count		

PART-III ART treatment

6-	Treatment Naïve	1- Yes 2- No	
7-	Initial regimen	1- D4T/3TC/NVP 2- ZDV/3TC/NVP 3- D4T/3TC/EFV 4- ZDV/3TC/EFV 5- other	
8-	Date treatment started	_____/_____/___ E.C _____/_____/____ G.C	
9-	Current treatment status	1- On initial regimen 2- Only one drug changed 3- Changed other regimen 4- All drug regimen stopped 5- Loss to follow up 6- Unknown	

		7- Other, specify	
10-	If initial regimen changed, reason for changing regimen	1- Toxicity/side effect 2- Pregnancy 3- Failure of treatment 4- Poor adherence 5- Illness/hospitalization 6- Drug out of stock 7- Patient lack of finance 8- Other, specify	
11-	Current regimen started	____/_____/_____E.C ____/____/_____G.C	
12-	Current regimen patient on	1- D4T/3TC/NVP 2- ZDV/3TC/NVP 3- D4T/3TC/EFV 4- ZDV/3TC/EFV 5- Other, specify	
13-	If stopped, reason for stopping ART	1- Toxicity/side effects 2- Pregnancy 3- Failure of treatment 4- Poor adherence 5- Illness/hospitalization 6- Drug out of stock 7- Patient lack of finance 8- Planned treatment interruption 9- Other specify	

PART- IV drugs used other than ARV drugs

14-	Are there any drugs used when the patient develop ADR.	1- Yes 2- No	
15-	Number of drugs used other than ARV drugs	1- 1-2 2- 3-4 3- >5	
16-	Cotrimoxazole prophylaxis	1- Yes 2- No	
17-	INH prophylaxis	1- Yes 2- No	
18-	Is the patient on TB treatment	1- Yes 2- No	

Part v -ADRs

19-	Does patient develop ADR	1- Yes 2- No	

Clinical description of ADRs measures taken- 1 reassurance only -2 supportive treatment only-3 one drug changed-4 regimen changed 5- all drug stopped

		Measures taken			
20-	Nausea				
21-	Vomiting				
22-	Diarrheal				
23-	Headache				
24-	Fatigue				
25-	Peripheral neuropathy				
26-	Rash				
27-	Other specify				

N.B measures taken

1- Reassurance only =mild (grade I) 2- supportive treatment only=moderate (grade II) 3- one drug changed and regimen changed =severe (grade III) 4- all drug stopped =life threatening (grade IV)