Adverse Drug Reactions, Its Consequences and Contributing Factors among Peoples Taking Highly Active Antiretroviral Therapy at Jimma University Specialized Hospital, Southwest Ethiopia

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Abstract

***Background**: Human Immunodeficiency virus remains a major global health problem and is the leading cause of death from an infectious disease worldwide. The expansion of antiretroviral therapy has yielded remarkable achievements in the era of the disease. There are now many antiretroviral drugs available and so there are a number of possible drug combinations. Knowledge of antiretroviral toxicities is very crucial in choosing among these combinations.*

***Objective**: The study aims to assess adverse drug reactions, its consequences and predisposing factors among people on Highly Active Antiretroviral Therapy at Jimma University Specialized Hospital, Southwest Ethiopia.*

***Methods**: A two year retrospective cohort study was employed at Jimma University Specialized Hospital, South west Ethiopia. Data was collected through medical record reviews of peoples using a medical card. Data was analyzed using Statistical Package for Social Sciences, version 16.0. Binary and multivariable logistic regressions were used to determine the association between different variables and the occurrence of adverse drug reactions. Comparison of factors contributing for adverse drug reactions was shown using odds ratio. Statistical significance was considered at p-value <0.05. Adverse drug reactions management and consequences of the reactions were described.*

***Results**: Among 390 peoples, 22.56% developed at least one adverse drug reactions, Peripheral neuropathy and skin rash being frequent in the cohort. Females were 2.3 times more likely to develop adverse drug reactions than males. The likelihood of reporting adverse drug reactions was more than three in educated peoples than uneducated ones. Pregnant women were 2.5 times more likely to develop adverse drug reactions than non pregnant women in the study. The adverse drug reactions were also high in divorced individuals. The use of cotrimoxazole and fluconazole prophylaxis had preventive effect against adverse drug reactions in the study. 40%of all reactions were treated and 52.27% of peoples with adverse drug reactions faced at least one type of negative consequences. Overall, the probability of being risk free decreased over time.*

***Conclusion:** The prevalence of adverse drug reactions in peoples on highly active antiretroviral therapy at Jimma University Specialized Hospital was high. Female sex, high educational level and being pregnant significantly increased the risk, which alarms the need of pharmaceutical care. Only less than half of the reactions were treated and more than half of peoples who developed adverse drug reactions had experienced at least one type of negative consequences.*

***Key words**: Adverse Drug Reaction, Highly Active Antiretroviral Therapy, Adult, Jimma Ethiopia*

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List of Acronyms and Abbreviation

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti-Retroviral Treatment
AZT/ZDV	Zidovudine
CD4	T–lymphocyte cell bearing CD4 receptor
CI	Confidence Interval
CNS	Central Nervous System
COR	Crude Odds Ratio
D4T	Stavudine
EFV	Efeveranz
FMoH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral Therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
INH	Isoniazid
JUSH	Jimma University Specialized Hospital
NNRTI	Non Nucloside/tide Reverse Transcriptase Inhibitor
NVP	Neverapine
PMTCT	Prevention of Mother-to-child Transmission
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TDF	TenofovirDisoproxilFumarate
WHO	World Health Organization

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1. Introduction

1.1. Background

The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled-up antiretroviral therapy and the steady decline in HIV incidence since the peak in 1997. In 2011, this decline continued, with evidence that the drop in the number of people dying from AIDS-related causes is accelerating in several countries [1].

AIDS has claimed at least 1 million lives annually in sub-Saharan Africa since 1998. Since then, however, the number of people dying from AIDS-related causes has steadily decreased, as antiretroviral therapy free of charge became more widely available in the region [2].

The estimated 1.2 million people dying from AIDS related illnesses in 2010 were 29% fewer than in 2005. Almost half the deaths occurred in southern Africa. In 2011, 1.7 million people died from AIDS-related causes worldwide. This represents a 24% decline in AIDS-related mortality compared with 2005 (when 2.3 million deaths occurred). The number of people dying from AIDS-related causes in sub-Saharan Africa declined by 32% from 2005 to 2011, although the region still accounted for 70% of all the people dying from AIDS in 2011[1-2].

The expansion of antiretroviral therapy has yielded remarkable health dividends in countries in which an HIV diagnosis was regarded as a death sentence only decades ago. The scaling up of antiretroviral therapy in low- and middle-income countries has transformed national AIDS responses and generated broad-based health gains. Since 1995, antiretroviral therapy has saved 14 million life-years in low- and middle-income countries, including 9 million in sub-Saharan Africa [1, 3].

Expanding coverage is saving lives, since about half of the people with a CD4 count less than 350 per ml, the current threshold for initiating treatment, would be expected to die within two years if they did not get antiretroviral therapy. Initiation of antiretroviral therapy at advanced stages of AIDS has implications beyond the obvious risk of morbidity and mortality due to opportunistic infections. Low CD4 cell count at treatment initiation is a risk factor for multiple adverse effects. The high burden of opportunistic infection in patients with low CD4 cell counts increases overlapping toxicities between HAART and opportunistic infection treatments, which

is a problem of particular concern for patients receiving ART. Therefore, earlier HAART initiation, before the development of a low CD4 cell count and opportunistic infection, may reduce the incidence of adverse effects [1, 4].

In Ethiopia, 176 632 peoples were receiving HAART in 2009 with 52-65% ART coverage as per 2010 guideline which resulted in 160,000 life years gain among adults due to ART between 1996 and 2009[3].

There are now many antiretroviral drugs available and so the number of possible HAART combinations is huge. Choosing between many of these combinations is, therefore, increasingly dependent upon knowledge of antiretroviral toxicities [5].

Although current ARV regimens are potent from an ARV perspective, they often fail because of non-adherence. Treating physicians must focus on early detection and prevention of ADRs, when possible and distinguishing those that are self-limited from those that are potentially serious. And to achieve this, even WHO guideline of 2010 was revised to use less toxic and more patient-friendly options: reduce the risk of adverse events and improve adherence by using less toxic drugs and fixed-dose antiretroviral therapy combinations [1, 4, 6].

The unpleasant, often painful, and potentially disfiguring side effects sometimes associated with the drugs may have a significant negative impact on quality of life and on an individual's ability or willingness to adhere to the prescribed regimen. Ensuring that HIV treatment is efficacious, safe, accessible, and affordable is important for successful and sustainable ART programs in resource-limited settings. This is because management of side effects can be more difficult in resource-limited settings, where drug substitution may not always be feasible due to limited access to the full array of antiretroviral drugs licensed for use in high-income countries. Implementation of protocols for regular clinical screening of patients, especially during the initial months of therapy, may help detect toxicities earlier [6-8].

1.2. Statement of the Problem

Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly class-specific adverse effects may occur. After starting antiretroviral therapy, the probability of remaining free from adverse events seems to decrease over time [9-10].

Despite of promising achievements in the era of HAART, approximately 25% of patients change their regimens within the first year owing to drug-related adverse events. WHO recommendations as of 2010 put all patients with CD4 counts of ≤350 cells/mm3 on HAART irrespective of the WHO clinical stage. There is a concern about the increased risk of adverse events, in addition to fear of resistance to first-line ARVs, drug stock outs, and unavailability of second-line regimens. Such earlier initiation of HAART will expose the patients to longer exposure to HAART and the possibility of more HAART-related side effects [11-12].

Up to one quarter of patients on HAART report at least one ADR within a minimum period of less than a month and ADR remains the major cause of drug therapy discontinuation. Some ADRs are severe in intensity and even require further symptomatic treatment and necessitate withdrawal of suspected drug. Some patients continue to suffer from the ADRs even after the change of treatment regimens though majority of patients recover. Following ADRs, most patients become non-adherent and miss their dose that causes significant economic implications by complicating the disease management and its subsequent health care and social costs. Studies support the fact that ADRs to be the most important factor resulting in non-adherence. And generally, ADRs are adding to the problem of non-adherence which was by itself a big problem in the era of HAART [13-15].

Studies found that up to 8% women changed or discontinued HAART as a result of drug toxicity. Some ADRs like lactic acidosis, rash, liver enzyme elevation, dyslipidemia, and insulin resistance are gender associated [16-19].

A study conducted in Madrid over seven years showed that nearly half of the patients on ARV therapy were admitted to hospital and, ARV-related toxicities were the main or secondary reason for hospital admission in 7%. Liver toxicity was the most frequent complication, of which one-third were associated with NVP use and 80% occurred in subjects with underlying chronic

hepatitis C virus (HCV) infection. In other studies, life threatening adverse drug reactions like hepatotoxicity may occur in up to 15.6% of all patients. Pregnant women with high CD4 cell counts may experience higher rates of symptomatic hepatotoxicity and thus require careful clinical and laboratory monitoring [20-22].

Different studies showed different independent predictors for ADRs. Baseline CD4 counts ≤ 100 and age >40 are independent predictors for ADR. Elevated baseline liver test values and older age are considered as strong predictors for NVP related hepatotoxicity. Development, type and prevalence of adverse drug reactions are dependent on duration on HAART. The prevalence of at least one ADR increased from 29% in the first 12 months to 58% by the 48^{th} month. There seemed to be a plateau phase after 48 months on HAART. The median time to development of first ADR ranged from two months for rashes to 29 months for lipid abnormalities [7, 23-24].

In Ethiopia, grade III/IV toxicity that required withholding or change of treatment occurred in nearly 10% of the patients. Toxicity is the main reason for initial HAART modifications and it is as high as 66%-80.3% of all reasons resulted in regimen change. Lipoatrophy, anemia and peripheral neuropathy were the common ADRs and D4T and ZDV based regimens were the most common regimen carrying high risk of ADRs [25-29].

By reducing antiretroviral drug options, toxicities may have a significant socioeconomic impact on low-income patients in developing countries. The overall direct cost associated in treating ADRs to HAART was found to be higher. ADRs to HAART increases the overall health care cost in the management of HIV/AIDS as well as reflects high economic burden to HIV/AIDS patients [4, 30].

The prevalence of ADRs and contributing factors are not well known among patients taking HAART in JUSH and nearby facilities. Therefore, it would be better to look for the prevalence and identifying factors that can help to predict ADR occurrence which will help to identify those patients that are at a higher risk of ADR while being treated on HAART. With this information, clinicians could give such patients special attention during their follow-up in order to prevent occurrence of ADRs.

2. Literature Review

2.1. Literature Review

Knowing the prevalence and understanding the predisposing factors for adverse drug reactions are important in knowing individual peoples and drug regimens with high risk and treating accordingly. The prevalence and predisposing factors were studied in different parts of the world with different recommendations as described as follow:

Most literatures discussed that different socio-demographic factors affect ADRs to HAART [6, 10, 21, 31].

One study done in India showed that there is a need of active pharmaceutical care with intensive monitoring for ADRs in patients who are illiterate, both gender, with CD4 count $\leq$250 cells/mm^3 with comorbid conditions. A continuous, longitudinal, prospective follow up study of 400 patients conducted in a single ART center in India found that the incidence of adverse drug reactions was more, independently, in female gender and an age of <40 years. Proportion of adverse drug reactions among patients with WHO Clinical stage I & II was 26.5%, while in the stage III & IV was 21.9% [6, 31].

A prospective observational study in Thai men and women receiving neverapine based regimen in 244 pregnant women, 87 non pregnant women and 78 men showed prevalence of hepatotoxicity and rash to be 15.6% and 16.1%, respectively. In this study, it was seen that men had a significantly higher rate of asymptomatic hepatotoxicity. Pregnant women receiving HAART for PMTCT (92% had CD4 cell counts >250 cells/microL) had a significantly higher rate of symptomatic hepatotoxicity (P=0.0003) than pregnant women receiving HAART for therapy. Other study confirmed that female and older patients of either gender showed a higher risk of treatment discontinuation for drug-related adverse effects [10,21].

A retrospective study conducted at the anti-retroviral department, Rajiv Gandhi Institute of Medical Sciences, Kadapa, India observed the significant ADRs associated with the use of HAART. In this study, the prevalence of ADRs was higher in female population (41.82% compared with males (33.05%). The incidence rates of ADRs were higher in age group 31 to 40 years with (40.84%). The majority of ADRs observed in males (60%) under the age group 31 to 40 years (40.84%) of (18 [25.35%]) patients were observed and regression analysis identified,

CD4 count <250 cells/mm^3 as a risk factor. Hematological abnormalities (16.19%) were more with zidovudine-containing HAART regimen and an improvement in hemoglobin level was observed on discontinuation of zidovudine. A highly significant association between zidovudine and anemia was documented. Peripheral neuropathy was observed in patients who were on stavudine-containing regimen for more than 4 months. In 10.47% (11/105) of these cases, stavudine was discontinued and the patient recovered [6].

A prospective observational study was conducted to identify the adverse drug reactions (ADRs) to antiretroviral therapy (ART) and to assess their impact on treatment compliance in patients with HIV/AIDS in India. In this study, 235 patients who received ART were monitored for ADRs for 6 months. 90.6% of 235 patients experienced ADR with a total of 618 ADRs involving various systems were observed. Majorities of ADRs were related to gastrointestinal (42.39%) and central nervous (25.57%) system. 23.1% ADRs were severe in nature and resulted in drug withdrawal in17.4% patients. 87.8% of patients who complained severe ADRs were on combination of stavudine, lamivudine and nevirapine. Causality assessment was done by dechallenging test revealing 6.63% ADRs were probable and 93.3% ADRs were possible. These ADRs are associated with ART non-compliance in about 28.9% patients. In other observational study in the same country, the overall incidence of ADRs to HAART was found to be 50.9%. Causality assessment was done and majorities were 'probable' and 'possible' by WHO probability scale. Based on level of severity, 10.7% were mild, 75% ware moderate and 14.3% were severe [14, 30].

One prospective study was done on the outcome of NNRTI-containing HAART in the Johns Hopkins Hospital HIV Clinic regarding the incidence of severe hepatotoxicity. It was done among 568 patients receiving NNRTI-containing antiretroviral therapy including 312 and 256 patients prescribed EFV and NVP, respectively. Hepatitis C virus (HCV) and hepatitis B virus (HBV) were detected in 43% and 7.7% of patients, respectively. Severe hepatotoxicity was observed in 15.6% of patients prescribed NVP and 8.0% of those prescribed EFV. Only 32% of NVP and 50% of EFV associated episodes were detected during the first 12-weeks of therapy. The risk was significantly greater among persons with chronic viral hepatitis (69% of cases) and those prescribed concurrent protease inhibitors (82% of cases). Severe hepatotoxicity occurs throughout the course of NNRTI therapy. It is more common among patients prescribed

nevirapine; those coinfected with HCV or HBV, and those co administered protease inhibitors [22].

A cross sectional clinical chart review of adult Cameroonian patients at Douala General Hospital was done. The finding showed that 19.5% of the 339 patients on HAART reported ADRs. Among those who reported ADRs, 29.6% were on D4T-3TC-EFV regimen, 29.3% on D4T-3TC-NVP, 16% on AZT-3TC-EFV and 10.8% on AZT-3TC-NVP. Of all, the most common ADR was peripheral neuropathy accounting 21.2%. Patients on D4T containing regimens were more likely to develop ADR and 56.1% of all ADRs were associated to D4T. Hematological ADRs represented 3.8% of all ADRs of which anemia (Hgb<7g/dl) was the most common and the most severe, all of which being associated to AZT-containing regimens. Severe anemia had resulted in hospitalization. Similarly, retrospective cohort analysis in three health facilities in Nigeria showed the ADR incidence rate of 4.6/100 person-years with 54% of ADRs reported by patients on AZT with 54(47%) of these occurring in patients taking AZT/NVP together. Other study in India showed that among the patients with 1 year of follow-up, D4T therapy was significantly associated with developing peripheral neuropathy and anemia and hepatitis often occurs within 12 weeks of initiating generic HAART [13, 32-33].

A retrospective cohort study conducted in Kenyatta national hospital among patients initiated HAART between 2003 and 2006 revealed prevalence of at least one ADR in 48.6% of the patients while 12.3% had two or more ADRs. The median time to development of first ADR ranged from two months for rashes to 29 months for lipid abnormalities. First cases of most ADRs were seen early except for renal and lipid abnormalities whose first cases occurred in the second year of HAART. Prevalence of all the ADRs generally increased with time on HAART. The prevalence of at least one ADR increased from 29% in the first 12 months to 58% by the 48^{th} month. There seemed to be a plateau phase after 48 months on HAART [24].

In other study in adults living in urban areas of Kenya, three hundred ninety-nine episodes of clinical ART toxicity were reported among 341 (26.5%) patients on therapy. The cumulative incidences of clinical toxicity were 24.5% at 6 months and 44.1% at 12 months. Neuropathy was the highest reported toxicity, accounting for 66.7% of observed toxicities (20.7% overall). The median time to development of clinical toxicity was 158 days (range: 0–682 days).

The only significant predictors of development of clinical toxicity were baseline CD4 count ≤100 cells/mm3 (HR = 1.3, 95% CI: 1.001 to 1.70; P = 0.049) and age >40 years (HR = 1.37, 95% CI: 1.05 to 1.78; P = 0.02) [7].

A home based AIDS care program conducted in rural Uganda with 1029 adults on d4T/3TC/NVP [96%] and d4T/3TC/EFV [4%] for 11,268 person-months of observation. Toxicities developed in 543 instances in 411 (40%) patients (incidence rate = 4.47/100 person-months): 36% peripheral neuropathy (9% severe); 6% rash (2% severe); 2% hypersensitivity reaction; 0.5% acute hepatitis, anemia, acute pancreatitis, or lactic acidosis; and 13% other. In this study, probabilities of remaining free from any toxicity at 6, 12, and 18 months were 0.76, 0.59, and 0.47 and from any severe toxicity at 6, 12, and 18 months were 0.92, 0.86, and 0.85, respectively. 222 single-drug substitutions were made for 217 patients (21%) mostly because of peripheral neuropathy or rash. Among 76 deaths with different causes in the cohort, one was attributed to antiretroviral toxicity and was on stavudine, lamivudine, and nevirapine. Retrospective laboratory evaluation of a specimen drawn just before death revealed an ALT of 1328 U/L and an AST of 1133 U/L and finally diagnosed as hypersensitivity reaction to nevirapine. The probabilities of continuing to take the original regimen without a toxicity related single-drug substitution at 6, 12, and 18 months were 0.87, 0.78, and 0.73, respectively [34].

2.2. Significance of the study

This study assessed the prevalence, risk factors, consequences and management of adverse drug reactions among peoples taking HAART. The study will, therefore, help health care professionals and health care system to identify the common ADRs and their contributing factors for better management and risk minimization.

In the past years, limited studies in Ethiopia hinder both clinicians and policy makers to identify individuals/groups of peoples at higher risk of HAART related adverse events and drugs carrying high risks. This study will minimize these gaps to its maximum effort by identifying the prevalence and types of common ADRs, predisposing factors and time of development of ADRs. This study also helps in identifying risky peoples and risky drugs for prevention and rational management. Again it will help as a baseline to perform further studies in the area of adverse drug reactions in Ethiopia.

2.3. Conceptual framework

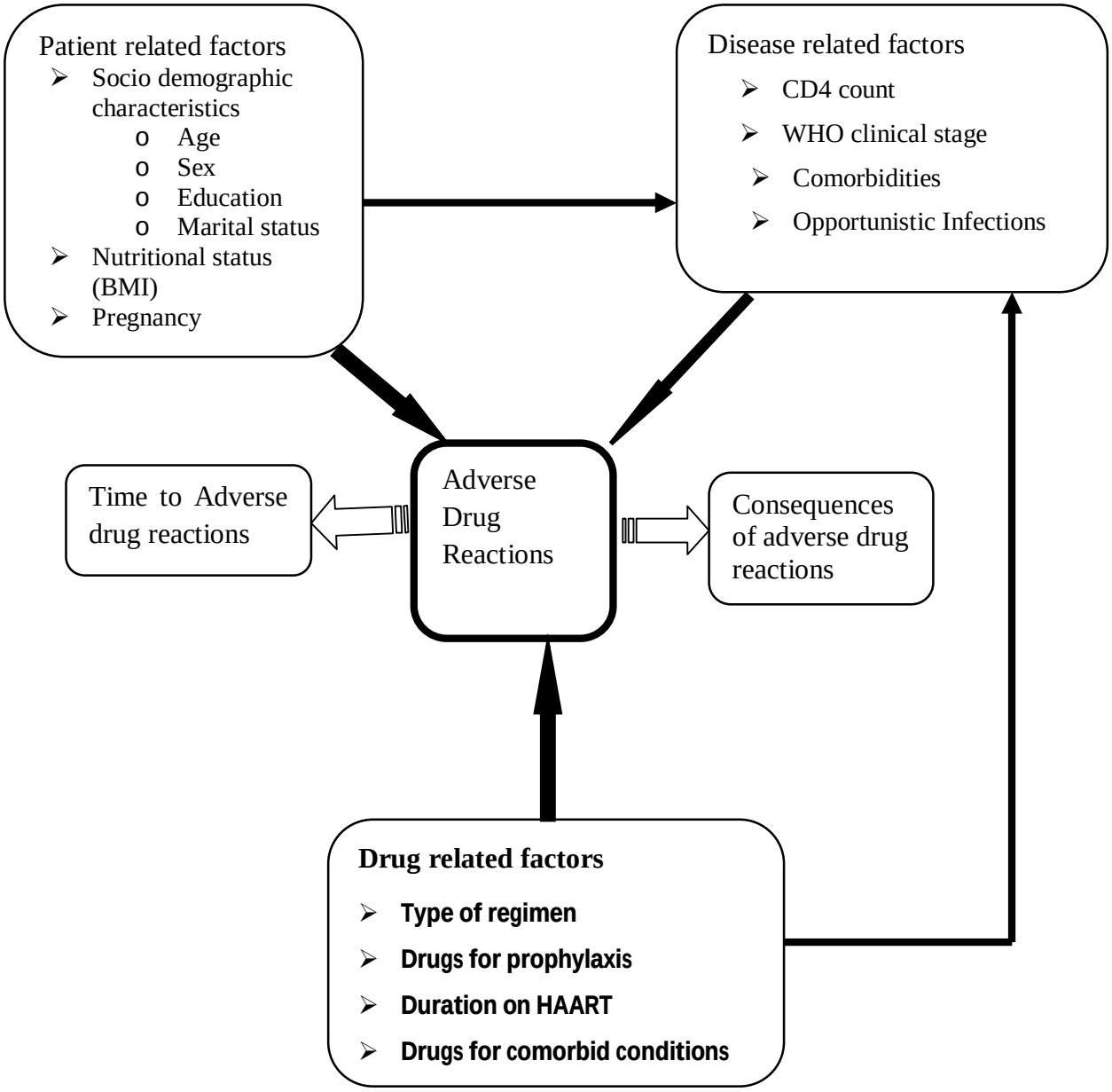

Figure 1: Conceptual Framework showing adverse drug reactions and factors associated with it.

3. Objective

3.1. General Objective

To assess Adverse Drug Reactions, its consequences and contributing factors among peoples taking HAART at Jimma University Specialized Hospital, South West Ethiopia

3.2. Specific objectives:

- To determine the prevalence of adverse drug reactions among peoples on highly active antiretroviral therapy (HAART).
- To identify types of adverse drug reactions among peoples on highly active antiretroviral therapy (HAART).
- To describe the management of adverse drug reactions among peoples on highly active antiretroviral therapy (HAART).
- To identify the consequences of adverse drug reactions among peoples on highly active antiretroviral therapy (HAART).
- To identify predictors of adverse drug reactions among peoples on highly active antiretroviral therapy (HAART).

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4. Methods and Participants

4.1. Study Area and period

The study was conducted in Jimma University specialized Hospital. Jimma is the town located in Jimma Zone of the Oromia Region, Southwest Ethiopia and about 350km far away from Addis Ababa.

Jimma University Specialized Hospital is one of the oldest public hospitals found in the country running under Jimma University which is currently the only teaching and referral hospital in the South Western region of the country. The total population served by the hospital is about 15 million. It serves for about 80,000 outpatients and 9,000 in patients annually. The hospital has ART clinic with about 3700 patients. The study period was from February 24 to March 24, 2014.

4.2. Study design

Hospital- based retrospective general cohort study was employed.

4.3. Source population

All HIV infected adult peoples who were on HAART at JUSH ART clinic from January 01, 2011 to December 31, 2012.

4.4. Study participants

All selected adult peoples who started HAART from January 01, 2011 to December 31, 2012 fulfilling the inclusion criteria and those not excluded.

Inclusion criteria

- peoples on HAART
- Peoples older than 14 years old.

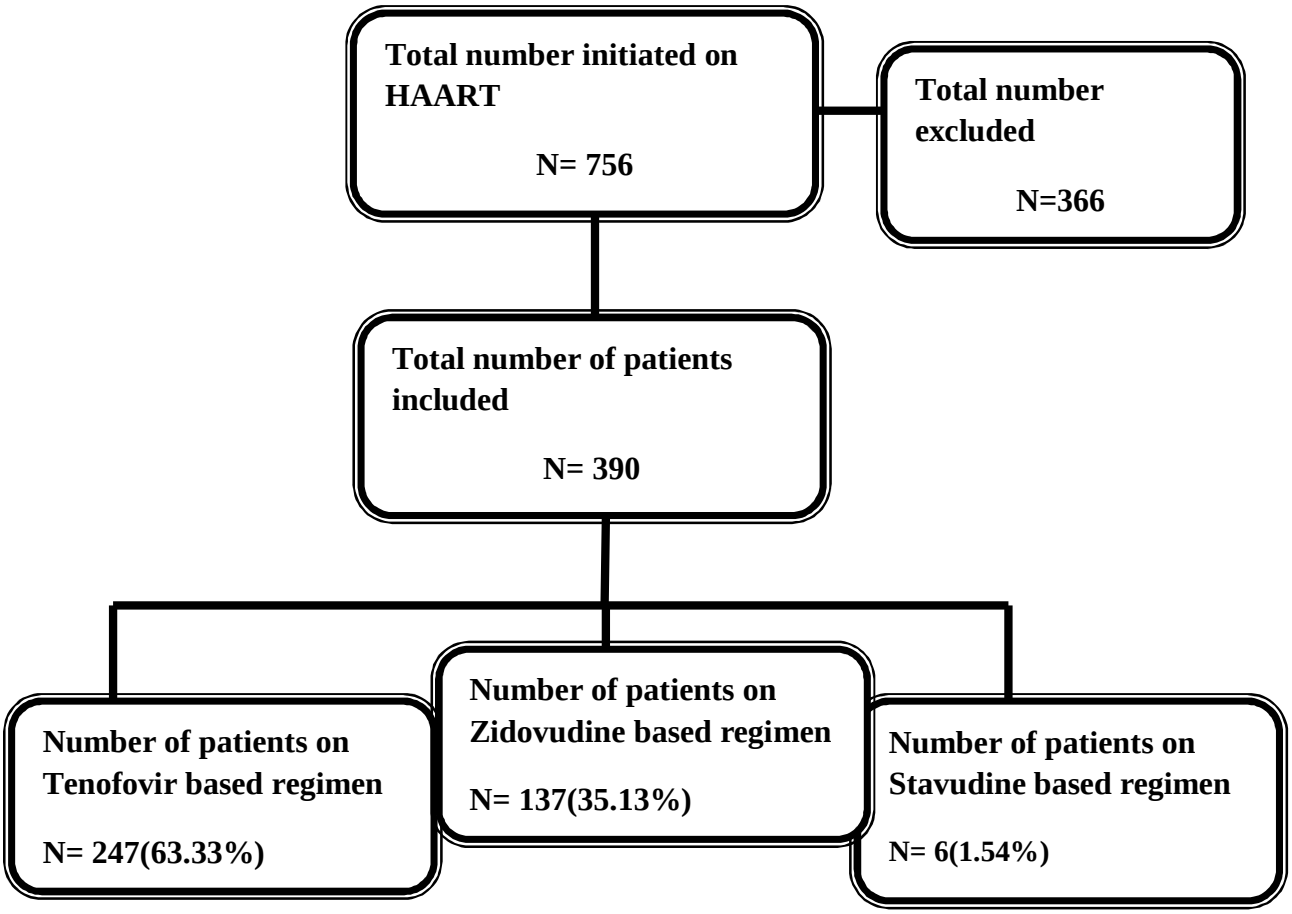
Exclusion criteria

- Transferred in peoples
- Transferred out peoples
- Incomplete patient data
- Deaths not related to ADRs
- Lost to follow up peoples

4.5. Sample size determination and sampling technique

All successive HIV infected adult peoples who started HAART from January 01, 2011 to December 31, 2012 fulfilling the inclusion criteria were studied and no sampling method was employed. The study participants were screened as shown in figure 1.

Figure2: Chart flow of study participants screening and their regimen at JUSH from January 01, 2011 to December 31, 2012.



4.6. Instrument & Data collection Procedure

The data collection tool was adapted from different literatures, WHO guidelines, Ethiopian national ART clinic intake form, HIV care/ART follow up form of FMoH and ARV drugs and patient information sheet (ARV/PIS-12).

Two pharmacists (B.pharm) and two registered nurses were assigned as data collectors with principal investigator acting as supervisor. One day training was conducted for data collectors on data collecting tool and general procedures of data collection. Pharmacists collected those data that present in antiretroviral drugs and patient information sheet and the nurses collected data from ART clinic intake form, HIV care/ART follow up form and patient sheet.

4.7. Variables in the study

4.7.1. Dependent variables

- Primary outcome
  - Adverse drug reactions
- Secondary outcome
  - Time to adverse drug reactions
  - Consequences of adverse drug reactions

4.7.2. Independent variables

- Patient Related Factors:
  - Socio-demographic and economic factors
    - Age
    - Sex
    - Educational Status
    - Pregnancy
    - Marital status
  - Nutritional Status
    - Body mass index(BMI)

- Drug Related Factors
  - Types of regimen
  - OI prophylaxis
    - ✓ INH prophylaxis
    - ✓ Cotrimoxazole prophylaxis
    - ✓ Fluconazole prophylaxis
- Diseases Related Factors
  - Baseline CD4 count
  - WHO clinical Staging
  - Comorbidity
    - ✓ Opportunistic Infections
      - HIV/TB co-infection
      - HIV/Hepatitis B&C co-infection
    - ✓ Non infectious diseases
      - Anemia
      - Cardiovascular disorders
      - Psychiatric disorders
      - Dermatologic problems

4.8. Operational Definition and Definition of Terms

- **Adult:** age above 14 years
- **Adverse Drug Reaction**: is a response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis, therapy or for the modifications of physiological function or diagnosed as adverse drug reaction by physician. This definition excludes therapeutic failures, intentional and accidental poisoning.
- **Anemia**: is a reduction in one or more of the major red blood cell (RBC) measurements: hemoglobin concentration, hematocrit, or red blood cell count; or diagnosed as anemia by physicians.
- **Co-morbidity**: is any kind of illness which had occurred to the patient other than HIV/AIDS.
- **Highly active antiretroviral therapy(HAART):** The regimen that combines three or more different drugs to aggressively suppress viral replication and progression of disease
- **Negative consequences:** any unwanted/bad events that occur as a result of adverse drug reactions which involves events like dose missing, regimen modification, regimen change, hospitalization/prolonging hospitalization and death.
- **OI prophylaxis**: is any preventive medication the patient is taking in order to prevent opportunistic infections.(e.g. INH and Cotrimoxazole)
- **Peripheral neuropathy**: any of the symptoms ranging from mild tingling sensation, numbness, muscle weakness and pain to severe incapacitating pain and inability to walk. Or diagnosed as peripheral neuropathy by physicians.
- **Pregnancy**: is a conception which had occurred immediately before or while the patient is on HAART.
- **Skin rash**: any skin conditions ranging from mild cases of erythema and pruritus to severe mucous membrane involvement (e.g., Stevens-Johnson syndrome).

4.9. Data analysis

The Statistical Package for Social Science (SPSS) programs version 16.0 for windows was used to enter, encode and analyze the collected data. Binary logistic regression model was fit to determine the association between each variables and the occurrence of adverse drug reactions which was later tested with multivariate analysis for which binary logistic regression yielded p< 0.25. Comparisons of factors contributing for adverse drug reactions were discussed with odds ratio. P-value of less than 0.05 was considered as statistically significant.

4.10. Data Quality Assurance

The study questionnaire was carefully adapted that enabled collect all necessary information needed. Pilot study was conducted on 5% of study participants by systematically selecting from peoples' medication record. Data was collected by trained pharmacists (B.pharm) and BSc nurses with previous data collection experience under supervision. In addition, the checklists were rechecked by the principal investigator for any missed, incorrect and unreadable information whilst collecting data

4.11. Ethical consideration

Ethical clearance was obtained from the Ethical Review Committee of Jimma University College of Public Health and Medical Sciences. Letter of permission was obtained from office of clinical Director of Jimma University Specialized hospital. Confidentiality was assured during data collection and analysis by collecting in isolated room, not mentioning peoples name and medical record number.

4.12. Dissemination plan

This finding will be presented to responsible bodies such as Pharmacy department of Jimma University, JUSH administrators, Ethiopian Federal Ministry of Health, Ethiopian Food, medicines and health care Administration and Control Authority. Finally, this finding will be submitted to reputable professional journal for publication so as to serve as baseline for further studies.

5. Results

5.1. Patient related characteristics

From about 756 peoples enrolled in HAART between 2011 and 2012, 390 peoples fulfilled inclusion criteria and retrospectively followed for 15 months for the development of any HAART related adverse reactions as summarized in Fig.2**.** The rest were excluded due to transfer, censoring and incompleteness of data.

Total of 390 adult peoples living with HIV and on HAART were followed for 15 months retrospectively. Of total, 212 (54.4%) peoples were females. The mean and median ages of peoples were 33.16 and 32 years. Eighty two (21.03%) of the peoples had no education and 11.28% had followed to the tertiary level. The rest attended to the level of primary or secondary education. About half of the peoples (48.72%) were orthodox religion followers while Muslims and Protestants were 35.38% and 12.31% respectively. The rest were other religion followers. More than half of the peoples (56.92%) were married. 15.64% of all peoples were never married and 7.96% were widowed (Table 1).

Table 1: The patient related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Variable	**Categories**	**Number of** peoples **receiving HAART Regimens (%) N=390**	**Number of** peoples **who reported ADRs (%) N=88**	**Proportion of** peoples **who reported ADRs (%)**
Sex	Male	178(45.64)	26(29.55)	14.61
	Female	212(54.36)	62(70.45)	29.25
Age category	15-24	49(12.56)	13(14.77)	26.53
	25-34	180(46.15)	42(47.73)	23.33
	35-44	115(29.49)	25(28.41)	27.74
	45-54	37(9.49)	6(7.95)	18.92
	55 and above	9(2.31)	2(1.14)	11.11
Religion	Muslim	138(35.38)	33(37.50)	23.91
	Orthodox	190(48.72)	44(50.00)	23.16
	Protestant	48(12.31)	9(10.23)	18.75
	others	10(2.56)	2(2.27)	20.00
	Unknown	4(1.03)	0(0.00)	0.00
Marital status	Never married	61(15.64)	14(15.90)	22.95
	Married	222(56.92)	48(54.55)	21.62
	Separated	43(11.02)	15(17.05)	34.88
	Divorced	24(6.15)	1(1.14)	4.17
	Widowed	31(7.96)	7(7.95)	22.58
	Unknown	9(2.31)	3(3.41)	33.33
Educational Level	No education	82(21.03)	29(32.95)	35.37
	Primary education	138(35.38)	34(38.64)	24.64
	Secondary education	117(30.00)	20(22.73)	17.09
	Tertiary education	44(11.28)	5(5.68)	11.36
	Unknown	9(2.31)	0(0.00)	0.00
Body mass Index[BMI]	Below 18.5	148(37.9)	37(42.05)	25.00
	18.5 and above	242(62.1)	51(57.95)	21.07
Pregnancy[n=212]	No	188(88.68)	50(80.65)	26.88
	Yes	24(11.32)	12(19.35)	50.00

5.2. Disease related characteristics

On initiation of HAART, the baseline CD4 count of 388 (99.49%) peoples were determined, where CD4 count of as low as 7 and as high as 807 were found with the mean value of 168.63. Among the 388 peoples with known baseline CD4 count, 244(62.56%) peoples had CD4 count 200 and below, and 144(36.92%) of them had CD4 count of more than 200.

On baseline, 53.58% of peoples were found in WHO clinical stage I and II. The rest were in stage III and IV, 124(31.79%) peoples being in stage III following stage II with 135(34.62%) peoples.

129(33.08%) of peoples on follow up had at least one type of comorbid illness. 15(3.85%) peoples had more than one comorbid illness. TB/HIV comorbidity was the highest comorbid condition found in 62(48.06%) peoples followed by anemia, which were 36(27.91%) (table 2).

Table 2: The disease related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Variable	**Categories**	**Number of** peoples **receiving HAART Regimens N=390(%)**	**Number of** peoples **reported ADRs N=88(%)**	**Proportion of** peoples **reported ADRs (%)**
CD4 Baseline	CD4 count </= 200	244(62.57)	56(63.64)	22.95
	CD4 count >200	144(36.92)	32(36.36)	22.22
	Unknown	2(0.51)	0(0.00)	0.00
WHO clinical Stage	WHO clinical stage I	74(18.97)	11(12.50)	14.86
	WHO clinical stage II	135(34.62)	21(23.86)	15.56
	WHO clinical stage III	124(31.79)	41(46.59)	30.06
	WHO clinical stage IV	57(16.62)	15(17.05)	26.32
Comorbidity	Anemia	36(27.91)	5(5.68)	13.89
	Cardiac	9(6.98)	3(3.41)	33.33
	Hepatic	7(5.42)	1(1.14)	14.29
	Renal	2(1.55)	0(0.00)	0.00
	Tuberculosis	62(48.06)	15(17.05)	24.19
	Other Diseases*	13(10.08)	0(0.00)	0.00

**= malaria(2), deep venous thrombosis(1), pneumonia(2), Asthma(2), urinary tract infection(2),psychiatry(2),psoriasis(1),ophthalmologic(1)*

5.3. Drug related characteristics

Among the country's approved first line regimens Tenofovir/Lamivudine/Efavirenz was the most common drug initiated followed by Zidovudine/Lamivudine/Nevirapine, both being 44.61% and 30.26% respectively. In 63.33% of all peoples, Tenofovir was used as a backbone regimen while only 1.54% of peoples started on Stavudine as a first line. The rest were on Zidovudine based regimen.

During the follow up, 362(92.8%) of peoples received atleast one type of prophylactic agent. 351(90%) peoples received cotrimoxazole prophylaxis during the whole follow up time and 26(6.67%) peoples did not started on cotrimoxazole for the purpose of opportunistic infection prophylaxis. 94(24.10%) and 11(2.82%) peoples have received INH and Fluconazole prophylaxis respectively (table 3).

Table 3: The drug related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Variable	**Categories**	**Number of** peoples **On HAART N=390(%)**	**Number of** peoples **reported ADRs N=88(%)**	**Proportion of** peoples **reported ADRs (%)**
Regimen	Stavudine/Lamivudine/Nevirapine	3(0.77)	1(1.14)	33.33
	Stavudine/Lamivudine/Efavirenz	3(0.77)	2(2.27)	66.67
	Zidovudine/Lamivudine/Nevirapine	118(30.26)	31(35.23)	26.27
	Zidovudine/Lamivudine/Efavirenz	19(4.87)	5(5.68)	26.32
	Tenofovir/Lamivudine/Efavirenz	174(44.61)	31(35.23)	17.82
	Tenofovir/Lamivudine/Nevirapine	73(18.72)	18(20.45)	24.66
Cotrimoxazole	Not Received Cotrimoxazole	26(6.67)	5(5.68)	19.23
	Received for 1-12 months	13(3.33)	8(9.09)	61.54
	Received for more than12 months	351(90.00)	75(85.23)	21.37
INH	Received	94(24.10)	21(23.86)	22.34
	Not Received	296(75.90)	67(76.14)	22.64
Fluconazole	Received	11(2.82)	7(7.95)	63.63
	Not Received	379(97.18)	81(92.05)	21.37
Totaldrugs[§§]	Up to two drugs	347(88.97)	80(90.91)	23.05
	Three and above	43(11.03)	8(9.09)	18.60

§§= total number of drugs in addition to the HAART

Among the peoples on follow up for 15 months, 105 adverse drug reactions were documented in 88(22.56%) individuals. Thirteen (14.78%) peoples had experienced more than one type of adverse drug reactions and one individual had suffered from four types of reactions.

Skin rash and peripheral neuropathy were more common than other forms of adverse drug reactions each representing 16.19 %(Table4). Nephrotoxicity and diarrhea were among the least common forms and each represent less than 1% of the reactions.

Regimens having Tenofovir and Zidovudine as a backbone were the regimens from which most ADRs were documented representing 58(55.24%) and 44(41.90%) reactions respectively. Among all regimens TDF/3TC/EFV shares 39(37.14%) of all adverse drug reactions.

Table 4: Frequency distribution of ADRs segregated by HAART regimens in peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

ADR Descriptions	**HAART Regimen (%)**						
	D4T/3TC /NVP	D4T/3TC /EFV	AZT/3TC /NVP	AZT/3TC/ EFV	TDF/3TC /EFV	TDF/3TC /NVP	**Total**
Peripheral Neuropathy	0(0.00)	0(0.00)	2(11.76)	1(5.88)	10(58.82)	4(23.53)	**17(16.19)**
Skin rash	0(0.00)	0(0.00)	9(52.94)	1(5.88)	6(35.29)	1(5.88)	**17(16.19)**
Anemia	0(0.00)	1(7.14)	8(50.14)	2(14.29)	2(14.29)	1(7.14)	**14(13.33)**
Gastritis	0(0.00)	0(0.00)	3(30.00)	0(0.00)	4(40.00)	3(30.00)	**10(9.52)**
Hepatotoxicity	0(0.00)	0(0.00)	3(33.33)	1(11.11)	3(33.33)	2(22.22)	**9(8.57)**
Abdominal Pain	0(0.00)	0(0.00)	4(50.00)	0(0.00)	4(50.00)	0(0.00)	**8(7.62)**
CNS toxicity	0(0.00)	0(0.00)	1(14.29)	0(0.00)	5(7.43)	1(14.29)	**7(6.67)**
Unspecified	0(0.00)	0(0.00)	2(33.33)	1(16.67)	1(16.67)	2(33.33)	**6(5.71)**
Fat changes	1(20.00)	1(20.0)	0(0.00)	0(0.00)	1(20.00)	2(40.00)	**5(4.76)**
Myalgia	0(0.00)	0(0.00)	2(50.00)	0(0.00)	1(25.00)	1(25.00)	**4(3.81)**
Dizziness	0(0.00)	0(0.00)	2(66.67)	0(0.00)	1(33.33)	0(0.00)	**3(2.86)**
Fatigue	0(0.00)	0(0.00)	1(33.33)	0(0.00)	1(33.33)	1(33.33)	**3(2.86)**
Diarrhea	0(0.00)	0(0.00)	1(100.00)	0(0.00)	0(0.00)	0(0.00)	**1(0.95)**
Nephrotoxicity	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(100.00)	**1(0.95)**
Total	**1(0.95)**	**2(1.9)**	**38(36.19)**	**6(5.71)**	**39(37.14)**	**19(18.10)**	**105(100.00)**

Factors associated with Development of ADR

Association between patient related factors and ADR

The association between patient related factors and ADR was analyzed as summarized in table 5 and those having significant association were displayed in ***table 8***. Sex has strong association with the development of ADR. Female patients were about 2.3 times at risk of developing adverse drug reactions from HAART when compared to males (AOR [CI] ==2.360, 95%CI: 1.310, 4.250).

When compared with peoples with no education, educated peoples seem to be at increased risk for ADR. Peoples with Secondary and tertiary level of education were more than 3 times at risk of reporting ADR than uneducated peoples (AOR=3.696, 95%CI: 1.720, 7.940] and 3.384[1.126, 10.171]) respectively. Peoples who had primary education were also at about two fold increased risk of developing ADR relative to peoples with no education (AOR= 3.384, 95%CI: 1.126, 10.171], but not statistically significant (p= 0.073). Female peoples who were pregnant during or after HAART initiation were 2.5 times (AOR = 2. 501, 95%CI: 1.103, 5.092) at risk of adverse drug reaction compared to females who did not have pregnancy during study period.

Regarding the marital status, peoples who made divorce ahead of HAART initiation has an increased risk of developing adverse drug reactions from HAART. They are about 10 times (AOR= 9.733, 95%CI= 1.044, 90.727]) at risk than peoples who never married. Patients who were married and with their partners (p=0.933), patients who were married but separated (p=0.444) and widowed patients (p=0.944) have no difference in risk of developing ADR when compared with patients who were not married at all.

Among patient related factors, age at which the HAART was started (p= 0.834), religion (p=0.896) and body mass index (p= 0.369) had no association with the development of ADRs (table 5). Being the followers of any religion did not affect the probability of developing ADR. Being under weight or of normal weight did not affect the probability of developing ADR (COR = 1.248, 95%CI= 0.770, 2.025).

Table 5: Bivariate analysis of patient related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Characteristics	Adverse Drug Reactions			
	Yes N=88	No N=302	COR [95%CI]	P-Value
Sex	**88**	**302**		
Female	62(70.45)	150(49.67)	2.416[1.450,4.026]	0.001
Male	26(29.55)	152(50.33)	1.00	
Age category	**88**	**302**		
15 to 24	13(14.77)	36(11.92)	1.00	
25 to 34	42(47.73)	138(45.70)	1.187[0.576,2.443]	0.643
35 to 44	25(28.41)	90(29.80)	1.300[0.600,2.818]	0.506
45 to 54	6(6.82)	29(9.60)	1.548[0.548,4.373]	0.410
55 and above	2(2.27)	9(2.98)	2.889[0.329,25.389]	0.339
Religion	**88**	**298**		
Orthodox	44(50.00)	146(48.99)	1.00	
Muslim	33(37.50)	105(35.23)	0.959[0.572,1.607]	0.873
Protestant	9(10.23)	39(13.09)	1.306 [0.587,2.904]	0.513
Others	2(2.27)	8(2.69)	1.205[0.247,5.886]	0.817
Marital status	**85**	**296**		
Never married	14(16.47)	47(15.88)	1.00	
Married	48(56.47)	174(58.78)	1.080[0.549, 2.125]	0.824
Separated	15(17.65)	28(9.46)	0.556[0.234, 1.321]	0.184
Divorced	1(1.18)	23(7.77)	6.851[0.848, 55.344]	0.071
Widowed	7(8.23)	24(8.11)	1.021[0.364, 2.866]	0.968
Educational Level	**88**	**293**		
No education	29(32.95)	53(18.09)	1.00	
Primary education	34(38.64)	104(35.49)	1.674[0.922, 3.037]	0.090
Secondary education	20(22.73)	97(33.11)	2.654[1.371, 5.138]	0.004
Tertiary education	5(5.68)	39(13.31)	4.268[1.516, 12.018]	0.006
BMI(Kg/m2)	**88**	**302**		
Below 18.5	37(42.05)	111(36.75)	1.248[0.770,2.025]	0.369
18.5 and above	51(57.95)	191(63.25)	1.00	
Pregnancy[n=212]	62	150		
No	50(80.65)	138(92.00)	1.00	
Yes	12(19.35)	12(8.00)	2.720[1.147, 6.449]	0.019

BMI= body mass index
COR: crude odds ratio
CI: confidence interval

Association between disease related factors and ADR

WHO clinical stages of the peoples have an association with the development of adverse drug reactions. When compared to peoples in WHO clinical stage I, the risk of developing ADR in peoples under WHO III is decreased by 63.20 %(AOR= 0.368, 95%CI= 0.156, 0.869). Also for peoples in WHO clinical stage IV, the risk was decreased by 56.20% (AOR =0.438,95%CI= 0.156, 1.231]) but not statistically significant (p=0.117).The risk of developing ADR for peoples in WHO clinical stage II was not statistically different from peoples in clinical stage I (p=0.911) (table 6).

The Number of CD4 counts at base line did not affect the likelihood of developing ADR. The probability of being affected with HAART related ADR for those peoples with CD4 count less than or equal to 200 was not different from those with that of above 200(COR= 0.959, 95%CI= 0.586, 1.571). The effect of presence or absence of comorbid condition was analyzed and there was no strong association between comorbidity and development of adverse drug reactions. Presence of atleast one type of comorbid condition increased the likelihood of developing adverse drug reactions by about 1.3 times even though it was not statistically significant (p=382). Again there was no risk difference in developing ADR among peoples with one (p= 0.491) and above one (p= 0.999) comorbid conditions.

Table 6: Bivariate analysis of disease related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012

Characteristics	Adverse Drug Reaction		COR [95%CI]	P-Value
	Yes: N=88	No: N=302		
CD4 Baseline	**88**	**300**		
CD4 count </= 200	56(63.64)	188(62.67)	0.959[0.586,1.571]	0.869
CD4 count > 200	32(36.36)	112(37.33)	1.00	
WHO Stage	**88**	**302**		
WHO stage I	11(12.50)	63(20.86)	1.00	
WHO stage II	21(23.86)	114(37.75)	0.948[0.429, 2.092]	0.895
WHO stage III	41(46.59)	83(27.48)	0.353[0.168, 0.742]	0.006
WHO stage IV	15(17.05)	42(13.91)	0.489[0.205, 1.168]	0.107
Comorbidity	**88**	**302**		
Yes	22(25.00)	90(29.80)	1.274[0.741,2.190]	0.382
No	66(75.00)	212(70.20)	1.00	

COR: crude odds ratio
CI: confidence interval

Association between drug related factors and ADR

Among drug related factors, the type of regimen the patient was taking had no association with ADR (p= 0.293). Regarding different types of prophylactic agents during HAART, the use of cotrimoxazole and fluconazole was associated with the development of ADR. The use prophylactic INH had no association with ADR. The use of cotrimoxazole prophylaxis for up to one year reduced the risk of developing adverse drug reactions by 82.80% (AOR= 0.172, 95%CI= 0.033, 0.891) compared with those who did not received cotrimoxazole prophylaxis. But receiving cotrimoxazole for more than a year did not decreased the risk (AOR= 1.269, 95%CI=0.416, 3.870). The use of prophylactic fluconazole also decreased the risk of developing ADR by about 91.20 %(AOR = 0.088, 95%CI= 0.021, 0.368) compared to those who did not received fluconazole.

The effect of number of drugs the patient took in addition to HAART was analyzed and it was not associated with the development of ADR. Receiving three and above different drugs in addition to HAART was not different from receiving less than three different drugs in the development of ADR (p= 0.558) (table 7).

Table 7: Bivariate analysis of drug related characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Characteristics	Adverse Drug Reaction		COR [95%CI]	P-Value
	Yes N=88	No N=302		
Regimen				
Tenofovir/Lamivudine/Efavirenz	31(35.23)	143(47.35)	1.00	
Stavudine/Lamivudine/Efavirenz	2(2.27)	1(0.33)	0.108[0.010,1.233]	0.073
Zidovudine/Lamivudine/Nevirapine	31(35.23)	87(28.81)	0.608[0.346,1.070]	0.085
Zidovudine/Lamivudine/Efavirenz	5(5.68)	14(4.64)	0.607[0.204,1.810]	0.370
Stavudine/Lamivudine/Nevirapine	1(1.14)	2(0.66)	0.434[0.038,4.933]	0.501
Tenofovir/Lamivudine/Nevirapine	18(20.45)	55(18.21)	0.662[0.343,1.280]	0.220
Cotrimoxazole				
Not Received	5(5.68)	21(6.95)	1.00	
Received for 1-12 months	8(9.09)	5(1.66)	0.149[0.034,0.656]	0.012
Received for more than12 months	75(85.23)	276(91.39)	0.876[0.320,2.401]	0.797
INH				
Received	21(23.86)	73(24.17)	1.017[0.583,1.774]	0.953
Not Received	67(76.14)	229(75.83)	1.00	
Fluconazole				
Received	7(7.95)	4(1.32)	0.155[0.44,0.544]	0.004
Not Received	81(92.05)	298(98.68)	1.00	
Total No of drugs[§§]				
Up to two drugs	80(90.91)	267(88.41)	1.00	
Three and above	8(9.09)	35(11.59)	1.273[0.567,2.862]	0.558

§§= total number of drugs except the HAART
COR: crude odds ratio
CI: confidence interval

Table 8: Multivariate analysis of different characteristics of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Characteristics	Adverse drug reaction		AOR [95%CI]	P-Value
	Yes	No		
Sex	**88**	**302**		
Female	62(70.45)	150(49.67)	2.360[11.310, 4.250]	0.004
Male	26(29.55)	152(50.33)	1.00	
Education Level	**88**	**293**		
No education	29(32.95)	53(18.09)	1.00	
Primary education	34(38.64)	104(35.49)	1.859[0.944, 3.664]	0.073
Secondary education	20(22.73)	97(33.11)	3.696[1.720, 7.940]	0.001
Tertiary education	5(5.68)	39(13.31)	3.384[1.126, 10.171]	0.030
Marital Status	**85**	**296**		
Never married	14(16.47)	47(15.88)	1.00	
Married	48(56.47)	174(58.78)	1.033[0.486, 2.196]	0.933
Separated	15(17.65)	28(9.46)	0.682[0.256, 1.819]	0.444
Divorced	1(1.18)	23(7.77)	9.733[1.044, 90.727]	0.046
Widowed	7(8.23)	24(8.11)	0.895[0.289, 2.768]	0.944
Pregnancy status[n=212]	**62**	**150**		
No	50(80.65)	138(92.00)	1.00	
Yes	12(19.35)	12(8.00)	2.501[1.103, 5.092]	0.021
WHO Stage	**88**	**302**		
WHO stage I	11(12.50)	63(20.86)	1.00	
WHO stage II	21(23.86)	114(37.75)	1.054[0.422, 2.629]	0.911
WHO stage III	41(46.59)	83(27.48)	0.368[0.156, 0.869]	0.023
WHO stage IV	15(17.05)	42(13.91)	0.438[0.156, 1.231]	0.117
Cotrimoxazole Prophylaxis	**88**	**302**		
Not received	5(5.68)	21(6.95)	1.00	
Received for 1-12 months	8(9.09)	5(1.66)	0.172 [0.033, 0.891]	0.036
Received for more than12 months	75(85.23)	276(91.39)	1.269[0.416, 3.870]	0.675
Fluconazole	**88**	**302**		
Received	7(7.95)	4(1.32)	0.088[0.021, 0.368]	0.001
Not Received	81(92.05)	298(98.68)	1.00	

AOR: adjusted odds ratio
CI: confidence interval

The time to development of adverse drug reaction was calculated using Kaplan Maier model. The median onset of adverse drug reactions was 132+/-26.7 days [95%CI: 79.599, 184.401]. Fifty percent of all ADRs took place within the first 5 months of initiating ART, and 58.6% took place within the first 6 months. The median of AZT-related ADRs were less than 90 days (95%CI: 34.7, 115.9). Females tend to have a shorter [130+/-17.05, 95%CI: 96.579, 163.421] median onset of adverse drug reactions as compared to male [246.0+/-71.386, 95%CI: 106.083, 385.917].

Among all regimens, ZDV based regimens tend to have a shorter median onset of adverse drug reactions [median time of less than 3 months (ZDV/3TC/NVP=86+/-26.155days, ZDV/3TC/EFV=88+/-14.241 days.] whereas TDF based regimen tends to have a longer [median time of more than 7 months (TDF/3TC/NVP=231+/-48.790days, TDF/3TC/EFV=235+/-60.657days].

The probability of developing adverse drug reactions increased with time in this cohort. The probability of being free from any HAART related adverse drug reactions at three months, six months and twelve months were 0.915, 0.874, and 0.805 respectively.

Table 9: Mean and median of time to adverse drug reactions of peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012

Mean			Median		
Estimate	SE	95% CI	Estimate	SE	95% CI
78.295	14.180	[150.503, 206.088]	132.000	26.735	[79.599, 184.401]

SE: standard error
CI: confidence interval

Adverse Drug Reactions management and Consequences of ADRs

Adverse drug reaction management was low in this study. Among the all 105 different types of ADRs in 88 peoples, only 42(40%) reactions were treated in 37(42%) peoples and the rest were left untreated. Some ADRs like dizziness, diarrhea, nephrotoxicity and all unspecified reactions were not treated at all. Peripheral neuropathy was the reaction for which the treatment was given most and was treated in 82% of the cases.

Table 10: The management of ADR for peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

ADR type	**Frequency (%)**	**ADR Treated (%)**
Abdominal Pain	8(7.62)	4(50%)
Anemia	14(13.33)	6(42.86)
CNS toxicity	7(6.67)	1(14.29)
Dizziness	3(2.86)	0(0.00)
Diarrhea	1(0.95)	0(0.00)
Fat changes	5(4.76)	1(20.00)
Fatigue	3(2.86)	1(33.33)
Gastritis	10(9.52)	5(50.00)
Hepatotoxicity	9(8.57)	2(22.22)
Myalgia	4(3.81)	3(75.00)
Nephrotoxicity	1(0.95)	0(0.00)
Peripheral neuropathy	17(16.19)	14(82.35)
Skin rash	17(16.19)	5(29.41)
Unspecified	6(5.72)	0(0.00)
Total	105(100%)	42(40.00)

Of all 88 peoples who developed ADR, 46(52.27%) peoples had experienced atleast one type of negative consequences defined as from missing a single dose to hospitalization. The rest 42(47.73%) peoples recovered without bad consequences.

ZDV/3TC/NVP and TDF/3TC/EFV were the common regimens that resulted in regimen modification and changes representing 16(38.10%) and 12(28.57%) of the 42 modifications and changes.

Among the four HAART discontinuation made, Zidovudine based regimen was responsible for three (75.00%) of them and one was from Tenofovir based regimen. Two of them developed hepatotoxicity. Peoples who developed hepatotoxicity were both female sex and were on Zidovudine/Lamivudine/Nevirapine based regimen. One was pregnant when she developed hepatotoxicity and the other was not. The other ADRs led to HAART discontinuation were ZDV induced severe anemia and unspecified reaction from Tenofovir based regimen. Both peoples with hepatotoxicity were managed in inpatient setting and one was improved. The patient with ZDV induced severe anemia was transfused two units of blood and was discharged with improvement.

During follow up, one patient was died of HAART induced hepatotoxicity. The patient was 32 years old female with baseline CD4 count of 308 and WHO clinical stage of II. The baseline AST and ALT were 31 and45 respectively. She was on cotrimoxazole prophylaxis for 8 months and she developed both mild type skin rash and hepatotoxicity after 11 days of Zidovudine/Lamivudine/Nevirapine regimen. She died after two weeks of hepatotoxicity diagnosis.

Table 11: The consequences of ADR for peoples living with HIV at JUSH, who were on HAART from January 01, 2011 to December 31, 2012.

Consequences	**Frequency of events**	**percentages from the consequences**	**Percentages from total ADR**
Regimen modification and change	42	72.41	40.00
Dose missing	7	12.07	6.67
HAART discontinuation	4	6.90	3.81
Hospitalization/prolongation	4	6.90	3.81
Death	1	1.72	0.95
Total	58*		

= *the total is > 46, because some* peoples *had more than one consequence

6. Discussion

The result of this study showed that the prevalence of ADR among peoples on HAART was 22.56%. But a prospective cohort studies done in different parts of India showed the prevalence of 48.6% to 90.6 % [14, 31]. This may be because of difference in study design as this study was retrospective cohort study. The prevalence of ADR in this study was high compared to the retrospective cohort study conducted from 2010 to 2011 in Nicaragua [35] and from 2005 to 2007 in India [36] in which prevalence of 6.4% and 12.36% respectively was documented.
Again in a cross sectional clinical chart review of adult Cameroonian patients at Douala General Hospital, the finding showed that 19.5% of the 339 peoples on HAART reported ADRs [13].
This difference may be due to difference in documentation and clinicians skill in diagnosing ADR.

In this study 105 adverse drug reactions were documented in 88 individuals. Thirteen (14.78%) of peoples had more than one type of adverse drug reactions.

In most studies peripheral neuropathy was the most common adverse drug reaction documented [24, 36]. In this study peripheral neuropathy and skin rash were the most common forms of ADRs documented and were 16.19 % each. This was in line with a prospective, observational cohort study conducted in a remote resource-restricted tribal population of Chhattisgarh [37]. Unlike a study conducted in ART clinic of Gonder University Hospital in which nausea (56.5%) and headache (54.9%) were the most common adverse drug reactions reported[38], this study didn't found nausea and headache as common adverse drug reactions. This may be because the study conducted in Gonder University Hospital was self-reported cross sectional study in which patients may report whatever they feel whereas this study was retrospective cohort study in which only clinically significant reactions were documented.

In this cohort study, neither CD4 count (p= 0.829) nor TB treatment (p= 0.616) was found to be a risk factor for the development of adverse drug reactions. A cross sectional study done at Douala General Hospital, Cameroon in 2011 showed that low CD4 count(<200/mm3) and history of anti-tuberculosis treatment were strongly associated with ADR[39]. This difference might be due to high prevalence of history of TB treatment in Cameroon and other population variance.

Unlike a prospective observational study done in tertiary care hospital in India, which reported Stavudine based regimen as a risk of ADRs[14], this study documented the regimen having Tenofovir and Zidovudine as a backbone were the regimen from which most ADRs were documented. Tenofovir and Zidovudine based regimen shared 55.24% and 41.90% of ADRs respectively. This may be because Stavudine was not preferable first line regimen in Ethiopia during this study and only few patients were started on the regimen.

Among patient related factors, different studies showed that female sex is at an increased risk of adverse drug reactions [6, 21, 35, 37]. In line with such studies, this study showed that female sex was independent predictor for the development of ADR (AOR =2.360, 95%CI: 1.310, 4.250). But a retrospective study conducted in Nigeria health facilities didn't show a risk difference in sex [32]. In other study conducted in India to assess incidence of ADRs in HIV patients using highly active antiretroviral therapy, male gender was observed to be the risk factor for ADRs [40]. Such differences may be attributed from study population characteristics.

Literacy was an independent predictor for ADR in this cohort. Compared with peoples with no education, peoples with secondary and tertiary level of education were more than 3 times at risk of developing ADR than uneducated peoples (AOR =3.696, 95%CI: 1.720, 7.940 and AOR= 3.384, 95%CI: 1.126, 10.171) respectively. But study in India reported illiteracy as a risk for the development of adverse drug reactions [41]. The reason may be due to the fact that educated peoples report ADRs more frequently than uneducated ones.

Female peoples who were pregnant during or after HAART initiation were 2.5 times (AOR = 2.501, 95%CI: 1.103, 5.092) at risk of adverse drug reactions compared to females who did not have pregnancy during study period. No well controlled study was present that showed the association between pregnancy and ADR. One prospective observational study in Thai men and women receiving Nevirapine based regimen showed Pregnant women receiving HAART for PMTCT had a significantly higher rate of symptomatic hepatotoxicity (P=0.0003) than pregnant women receiving HAART for therapy[16]. This study was not comparable to our cohort as it was done only for hepatotoxicity with Nevirapine based regimen only.

Some ADRs may be age specific. Independent studies conducted in Kigali, Rwanda and Blantyre, Malawi showed older age as a risk factor for peripheral neuropathy [23, 42]. But in this study, in which peripheral neuropathy was the most common ADR, age was not associated with adverse drug reactions. In other large cohort study done in South African HIV infected subjects, age didn't appear to increase the risk of any adverse events after HAART initiation [43]. Such difference may be due to difference in regimen. Those studies were done using stavudine based regimen and stavudine was not commonly used in this study.

In this study, the proportion of adverse drug reactions among peoples with WHO Clinical stage III & IV was more than two fold than peoples in with WHO Clinical stage I & II. The above difference was considered to be statistically significant. But in a continuous, longitudinal, prospective follow up study conducted in India, proportion of adverse drug reactions among peoples with WHO Clinical stage I & II was 26.5%, while it was 21.9% in the stage III & IV[31]. The difference may be due to difference in proportion of each group of WHO clinical stage and most patients in our case were in WHO stage III and IV.

Advanced HIV disease increases the risk of neuropathy [23]. In this study, WHO clinical stages of the peoples had an association with the development of adverse drug reactions but number of CD4 counts at base line did not affect the likelihood of developing ADR. When compared to peoples in WHO clinical stage I, the risk of developing ADR in peoples under WHO III was decreased by 63.20%. The probability of being affected with HAART related ADR for those peoples with CD4 count less than or equal to 200 was not different from those with that of above 200(COR= 0.959, 95%CI: 0.586, 1.571). But in a study conducted in South Africa, CD4 counts and WHO staging at baseline did not associated with adverse drug reactions [43]. And other study conducted in India with spontaneous reporting and intensive monitoring from ART center showed that CD4 <200 cells/microl was reported as a risk factor [41]. The reason for this difference might be due to difference in study design.

A prospective active surveillance study conducted at ART Centre, District Government Hospital, Udupi, India, from August 2009 to May 2012showed opportunistic infection comorbidity as a risk factor for ADRs [44]. Other study conducted in the same country reported tuberculosis in HIV patients as influential risk factor for occurrence of ADRs [41]. In this study, comorbidity at all was not associated with ADR. Presence of atleast one type of comorbid condition increased the likelihood of developing adverse drug reactions by about 1.3 times alarming the need of active pharmaceutical care. But it was not statistically significant (p=382). Again there was no risk difference of developing ADR among patients with one (p= 0.491) and above one (p= 0.999) comorbid conditions. This difference may be due to difference in methodology as this study was retrospective where some data were not well registered or prevalence comorbid condition might be high in that study. Like this study, another 18-month retrospective case-control study conducted in India showed a need of active pharmaceutical care with intensive monitoring for HIV patients with comorbid conditions [40].

No well controlled study showed the effect of nutritional status on the development of ADR. Prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India tried to see the effect of BMI on ADR, specifically anemia. With 101 events of drug-related anemia, low BMI did not have any effect on the development of anemia [45]. In a cross-sectional retrospective study conducted with reviewing data of 2042 patients initiated on HAART from 2003 to 2007 at a tertiary hospital in Ghana, the effect of baseline weight of the patient was studied. It showed that weight of less than 60 kg was protective compared with 60 kg or more, but it was not statistically significant (p=0.19) [46]. In line with these two different studies, nutritional status of the patient was not significantly associated with the development of ADR. But in a follow up study conducted in Thailand where patients were randomized to regimens with nevirapine, efavirenz or both, high body mass index (>21.3 kg/m2) was showed to be a risk factor for rash[16]. Such difference may be due to difference in study population, and study design where demography of Thai patients was followed throughout the study.

In this cohort, maximum adverse drug reactions (37.14%) were observed in patients who were prescribed regimens Tenofovir /Lamivudine/Efavirenz followed by Zidovudine/Lamivudine/Neverapine(36.19%). This was almost in line with an 18-month retrospective case-control study of 208 patients newly registered in ART center of Kadapa, India

where the incidence of ADRs (53.52%) was higher with Zidovudine + Lamivudine + Nevirapine combination [40]. Again this study was in agreement with other study conducted in India which showed Zidovudine+Lamivudine with Nevirapine or Efavirenz, regimen as a risk factor [41]. But a prospective observational study conducted during May 2006 to April 2007 in India, showed Stavudine/Lamivudine/Nevirapine followed by Stavudine/Lamivudine/Efavirenz as risk factor [14]. This may be because of difference in the regimen patients were receiving.

Studies show that skin rash was associated with NVP based regimen [33, 34]. This study was in line with those studies showing that 58.82% of skin rash were associated with NVP based regimen. This cohort found that the total number of drugs the patient was receiving was not related to adverse drug reactions. Taking three or more different drugs was not different from patients receiving less than three drugs in the risk of ADR. This was not in line with a study conducted in India in which polypharmacy was an independent risk factor for ADRs [44]. The difference may be due to difference in total number of drugs, study duration and study design.

After starting antiretroviral therapy, the probability of remaining free from any adverse events seems to decrease over time [9]. The probability of being free from any HAART related adverse drug reactions at three months, six months and twelve months were 0.915, 0.874, and 0.805 respectively. This probability was slightly greater than probability of being free from any HAART related adverse drug reactions at six and twelve months in a home based AIDS care program study conducted in rural Uganda with 1029 adults. This study in Uganda reported the probability of being risk free at six and twelve months as 0.79 and 0.59[34]. This difference may be attributed to difference in regimen as all peoples in a study done in Uganda were on Stavudine based regimen.

Adverse drug reaction management was low in this cohort. Among the all 105 different types of ADRs in 88 peoples, only 42(40%) reactions were treated in 37(42%) peoples and the rest were left untreated. This percentage was higher than that of a prospective observational study conducted in India, in which 23.1% of ADRs were symptomatically treated [14]. But these two studies were not comparable as only severe ADRs were treated in the case of the study done in India.

In this cohort, HAART was discontinued in four peoples. Among these, Zidovudine based regimen was responsible for three (75.00%) of them and one was from Tenofovir based regimen. This was in contrary with a study done in rural Uganda where clinically apparent toxicities were common but no peoples had discontinued HAART secondary to toxicity [34]. The difference might be due to that the Ugandan study assessed only clinically apparent toxicities and were unable to describe toxicities that required laboratory diagnosis like anemia and hepatitis.

In this cohort, four peoples were hospitalized. It was in line with a study conducted in largest public hospital in Nicaragua where five peoples were hospitalized or had a prolonged hospitalization secondary to ADRs [35]. In contrast to this Nacaragua study, one death was documented in this cohort.

7. Strengths and Limitations of the Study

7.1. Strength of the study

The study was comprehensive in nature and efforts were made to assess all forms of adverse drug reactions. In other way, our study takes strength in its study methods. Not only adverse drug reactions and their risk factors, time to adverse drug reactions and consequences of adverse drug reactions were also studied.

7.2. Limitation of the study

Although the study is comprehensive and cohort in nature, the study being a retrospective, it relied on pre-recorded information which may have been incomplete or inaccurate. As the follow up time is short, some ADRs may be missed due to their nature of occurring late in time. On the other hand, adverse drug reactions that required laboratory diagnosis may have been missed because tests were not done routinely due to availability and affordability limitations. The other limitation is that causality assessment was not done and the severity of the reactions were not graded.

8. Conclusion

This cohort study showed the prevalence of adverse drug reaction to be high during the follow up of 15 months, skin rash and peripheral neuropathy being more common than others. Among patient related factors, sex of the patient, educational level, marital status and pregnancy were associated with the development of adverse drug reaction. Being female, educated patient, divorced and pregnancy were independent predictors of adverse drug reactions and close monitoring is warranted. The use of cotrimoxazole and fluconazole prophylaxis had some kind of preventive measure which needs further study for strong conclusion. On the other hand, baseline WHO stage had some association with ADR while baseline CD4 count and comorbid conditions including opportunistic infections had no effect on ADR.

The probability of being free from any HAART related adverse drug reactions decreased over time showing ADRs are expectable in HAART. More than half of all ADRs took place within the first 5 months of initiating ART, and 58.6% took place within the first 6 months with the median of AZT-related ADRs less than three months. ADR management was very poor and less than half of the peoples were treated for their adverse drug reaction in a situation where the consequences of ADR range from a single dose missing to death.

9. Recommendation

- The prevalence of ADR in this cohort is high. Close monitoring is warranted specially during early time of initiation as ADRs were more frequent during these times.
- As most of the ADRs in this cohort were diagnosed clinically, routine lab tests are recommended to increase the detection rate and diagnose earlier.
- Jimma University Specialized Hospital and other stake holders are strongly recommended to give due attention for adverse drug reaction management.
- This cohort was retrospective and done for a short duration in which ADRs might have been under reported. Again these ADRs where not well characterized and graded. So, we recommend prospective study with long duration to solve those limitations.

10.References

1. WHO. Global report: UNAIDS report on the global AIDS epidemic;2012. Available from: *http://wwwunaidsorg/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_unaids_global_report_2012_with_annexes_enpdf* [Last accessed November 10, 2013].
2. WHO. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report; 2011 . Available from: h*ttp://whqlibdocwhoint/publications/2011/9789241502986_engpdf* [Last accessed November 10, 2013].
3. WHO. Global report: UNAIDS report on the global AIDS epidemic. Geneva, Switzerland; 2010. Available from: *http://wwwunaidsorg/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_enpdf* [Last accessed November 10, 2013].
4. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse Effects of Highly Active Antiretroviral Therapy in Developing Countries. *Clinical Infectious Diseases.* 2007;45:1093.
5. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *The Lancet*. 2000; 356(9239):1423-30.
6. Srikanth BA, Babu C, Jain SK. Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy. *J Adv Pharm Technol Res.* 2012;3(1):62-7.
7. Hawkins C, Achenbach C, Fryda W, D.Ngare, R.Murphy. Antiretroviral Durability and Tolerability in HIV-Infected Adults Living in Urban Kenya. *J Acquir Immune Defic Syndr* 2007;45:304-10.
8. WHO. Report on the global AIDS epidemic/treatment and care; 2008. Available at: *http://wwwamarcorg/documents/manuals/JC1510_2008GlobalReport_enpdf* [Last accessed November 10, 2013].
9. Montessori V, Press N, Montaner JS. Adverse effects of antiretroviral therapy for HIV infection. *CMAJ*. 2004;170(7):229-38.

10. Prosperi MC, Fabbiani M, Fanti L, Zaccarelli M, Colafigli M, Annalisa Mondi1, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug related adverse events in HIV-infected patients: a retrospective cohort study. *BMC Infectious Diseases*. 2012;12.
11. Koda-Kimble, Yee L. The Clinical Use Of Drugs. In: Dumond JB, editor. Applied Therapeutics2008.
12. WHO. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. Available at: *http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf*. [Last accessed; November 10, 2013]. Geneva, Switzerland 2010.
13. Luma HN, Doualla M-S, Choukem S-P, Temfack E, Ashuntantang G, Joko HA, et al. Adverse drug reactions of Highly Active Antiretroviral Therapy (HAART) in HIV infected patients at the General Hospital, Douala, Cameroon: a cross sectional study. *Pan African Medical Journal*. 2012;12(87).
14. Nagpal M, Tayal V, Kumar S, Gupta U. Adverse drug reactions to antiretroviral therapy in AIDS patients at a tertiary care hospital in India.*Indian Journal of Medical Sciences*. 2010;64(6):245.
15. Cicconi P, A Cozzi-Lepri, A Castagna, EM Trecarichi, Antinori A, Gatti F, et al. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. *HIV Med*. 2010;11(2):104-13.
16. Ananworanich J, Moor Z, Siangphoe U, Chana J, Cardielloa P, Chris Duncombea, et al. Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. *AIDS*. 2005;19(2):185-92.
17. Jamisse L, Balkus J, Hitti J, Gloyd S, Manuel R, Osman N, et al. Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens.*J Acquir Immune Defic Syndr*. 2007;44(4):371-6.
18. Kondo W, Astori Ade A, K Gomes. Evaluation of the adverse effects of nevirapine in HIV-infected pregnant women in a South Brazilian University Hospital. *Rev Bras Ginecol Obstet.* 2008;30(1):19-24.

19. Ofotokun I, Pomeroy C. Sex Differences in Adverse Reactions to Antiretroviral Drugs. *International AIDS Society-USA Topics in HIV*. 2003;11(2):55-67.
20. Nunez MJ, Carbonero LM, Moreno V, Valencia E, Garcia-Samaniego J, Castillo JG, et al. Impact of Antiretroviral Treatment-Related Toxicities on Hospital Admissions in HIV-Infected Patients. *AIDS Research and Human Retroviruses*. 2006;22(9):825-9.
21. Phanuphak N, Apornpong T, Teeratakulpisarn S, Chaithongwongwatthana S, Taweepolcharoen C, Mangclaviraj S, et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. *HIV Med*. 2007 8(6):357-66.
22. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity Associated With Nevirapine or Efavirenz-Containing Antiretroviral Therapy: Role of Hepatitis C and B Infections. *Hepatology*. 2002;35(1):182-9.
23. Griensven Jv, Zachariah R, Rasschaert F, Mugabob J, Attea EF, Reida T. Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 2010;104(2):148-53.
24. Mwangangi L, Juma R, Scott DK, Nyamu DG, Kuria K. Prevalence of Adverse Drug Reactions in Adult Patients on Antiretrovirals at Kenyatta National Hospital, Comprehensive care Center. *East African Medical Journal*. 2009;86(12):558-64.
25. Jima YT, Angamo MT, Wabe NT. Causes for antiretroviral regimen change among HIV/AIDS patients in Addis Ababa, Ethiopia.*Tanzania Journal of Health Research*. 2013;15(1).
26. Mulugeta A, Chanie T. Cause of Antiretroviral drug changes among Patients on Antiretroviral Therapy at the ART center in Dessei Regional Referral Hospital, Ethiopia. . *IJPSR*. 2012;3(1):120-5.
27. SG Abdissa, D Fekade, Y Feleke, T Seboxa, E Diro. Adverse drug reactions associated with antiretroviral treatment among adult Ethiopian patients in a tertiary hospital. *Ethiop Med J*. 2012;50(2):107-13.
28. Weldemedhin B, Tajure NW. The Reason for Regimen Change Among HIV/AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Southern Ethiopia. *North Am J Med Sci*. 2012;4(1):19-23.

29. Wube M, Tesfaye A, Hawaze S. Antiretroviral Therapy Regimen Change Among HIV/AIDS Patients in Nekemt Hospital: A Primary Care Hospital in Oromia Regional State, Ethiopia. *J App Pharm Sci*. 2013;3(08):36-40.
30. Rajesh R, Vidyasagar S, M.Varma D. Evaluation of direct cost of adverse drug reactions to highly active antiretroviral therapy in Indian human immunodeficiency virus positive patients. *Journal of Clinical Research in HIV AIDS and Prevention*. 2012;1(1):1-11.
31. Divakar B, Mistry SD, Kantharia ND, Mamtarani. The study of adverse drug reactions (ADR's) in HIV patients taking highly active antiretroviral therapy in art centre, NCH, surat, India. *Int J Med Pharm Sci*. 2012;03(2):9- 18.
32. Eluwa GI, Badru T, Akpoigbe KJ. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clinical Pharmacology*. 2012;12(7).
33. Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lal AR, Saghayam S, et al. Spectrum of Adverse Events After Generic HAART in Southern Indian HIV-Infected Patients. *AIDS Patient Care and STDs*. 2008;22(4):337-44.
34. Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermin J, et al. Clinical Toxicity of Highly Active Antiretroviral Therapy in a Home-Based AIDS Care Program in Rural Uganda. *J Acquir Immune Defic Syndr*. 2007;44:456-62.
35. M Lorio, J Colasanti, S. Moreira, G Gutierraz, C Quant. Adverse Drug Reactions to Antiretroviral Therapy in HIV-Infected Patients at the largest Public Hospital in Nicaragua. *J Int Assoc Provid AIDS Care*. 2014;pii: 2325957414535978.
36. SR Anwikar, MS Bandekar, B Smrati, AP Pazare, PA Tatke, NA Kshirsagar. HAART induced adverse drug reactions: a retrospective analysis at a tertiary referral health care center in India. *Int J Risk Saf Med*. 2011;23(3):163-9.
37. Singh H, Dulhani N, Tiwari P, Singh P, Sinha T. A prospective, observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. *Indian J Pharmacol*. 2009;41(5):224-6.
38. WT Tadesse, AB Mekonnen, WH Tesfaye. Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. *BMC Pharmacol Toxicol*. 2014;15(32).

39. Luma HN, Tchaleu BC, Doualla MS, Temfack E, Sopouassi VN, Mapoure YN, et al. HIV-associated sensory neuropathy in HIV-1 infected patients at the Douala General Hospital in Cameroon: a cross-sectional study. *AIDS Research and Therapy*. 2012;9(35).
40. Srikanth BA, Babu SC, Yadav HN,Jain SK. Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy. J *Adv Pharm Technol Res.* 2012;3(1):62-7.
41. Modayil RR, Harugeri A, Parthasarathi G, Ramesh M, Prasad R, Naik V et al. Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India. *Pharmacoepidemiol Drug Saf*. 2010 19(3):247-55.
42. Oosterhout Jv, Mallewa J, Kaunda S, Newton Chagoma, Yassin Njalale, Elizabeth Kampira, et al. Stavudine Toxicity in Adult Longer-Term ART Patients in Blantyre, Malawi. *PLoS ONE*. 2012;7(7).
43. Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine associated toxicities in a large cohort of South African HIV infected subjects. *BMC Infectious Diseases*. 2011;11(244).
44. Rajesh R, Vidyasagar S, Varma DM, Naik A, Hegde BM, Guddattu V, et al. A prospective study of highly active antiretroviral therapy in Indian human immunodeficiency virus positive patients. *The International Journal of Risk and Safety in Medicine*. 2013;25(1):53-65.
45. Shet A, Antony J, Arumugam K, Dodderi SK, Rodrigues R, DeCosta A. Influence of Adverse Drug Reactions on Treatment Success: Prospective Cohort Analysis of HIV-Infected Individuals Initiating First-Line Antiretroviral Therapy in India.*PLoS ONE* 2014;9(3).
46. Lartey M, Asante-Quashie A, Ama Essel2 EK, Ganu V, Neequaye A. Adverse drug reactions to antiretroviral therapy during the early art period at a tertiary hospital in Ghana. *Pan African Medical Journal*. 2014 18(25).

ANNEX I: Data collection check list

Jimma University

College of Public Health and Medical sciences

Department of Pharmacy

Dear,

This data collecting format is prepared to collectdata on ***"Adverse Drug Reactions, Its consequences and Contributing Factors among Peoples living with HIVon Highly Active Antiretroviral Therapy at Jimma University Specialized Hospital, ART clinic".*** This study is conducted as part of my MSc thesis in collaboration with Jimma University School of graduate studies**.** The aim of this study is to assess the prevalence, type, predisposing factors, consequences and management of adverse drug reactions to HAART in peoples with HIV. The finding of this study will help in identifying risky patients and risky drugs for prevention and rational management of adverse drug reactions. The information extracted from patients' medical record will be kept confidential and not exposed to other parties.

Data collector:

Name: _____

Sign._____

Supervisor: _____

Name: _____

Sign._____

Instruction

A. Select your answer for the questions by marking "√" in the box provided

B. If your answer is out of the choice provided; write your answer in the space provided

Part I: Patient Related Factors ***Code.*_____**

101	Sex	Male ☐ Female ☐	
102	Age		
103	Weight (Kg)		
104	Educational level	No education ☐ Primary education ☐ Secondary education ☐ Tertiary education ☐	
107	Marital status	Never Married ☐ Married ☐ Separated ☐ Divorced ☐ Widowed ☐	
108	Pregnancy Status*	Date of confirmed pregnancy/months	Date of delivery
		_____/_____/_____	_____/_____/_____
		_____/_____/_____	_____/_____/_____

= for female patients only

Part II: Clinical data on Initiation

<table>
<tr><td>201</td><td>ART initiation date</td><td colspan="5">____/____/_____ (dd/mm/yyyy)</td></tr>
<tr><td rowspan="2">202</td><td rowspan="2">Initial HAART initiation</td><td>Age</td><td>Baseline CD4 count</td><td>WHO clinical stage [I,II,III,IV]</td><td>Baseline LFT</td><td>Baseline CBC/other lab</td></tr>
<tr><td></td><td></td><td></td><td>AST_____
ALT _____
ALP _____
Others, specify_____</td><td>Hgb:_____
_
Hct:_____
Sr. Cr:____
Others, specify_____</td></tr>
<tr><td>203</td><td>Is the patient on Prophylaxis</td><td colspan="5">No ☐ Yes ☐
If Yes,
<table>
<tr><th>Drug used for prophylaxis</th><th>Date started</th><th>Date stopped</th></tr>
<tr><td>Cotrimoxazole</td><td>__/____/__</td><td>__/____/__</td></tr>
<tr><td>INH</td><td>__/____/__</td><td>__/____/__</td></tr>
<tr><td>Fluconazole</td><td>__/____/__</td><td>__/____/__</td></tr>
<tr><td>other</td><td>__/____/__</td><td>__/____/__</td></tr>
</table></td></tr>
<tr><td>204</td><td>Initial HAART regimen</td><td colspan="5"></td></tr>
</table>

<table>
<tr><td>205</td><td>Comorbidity</td><td>No ☐ Yes ☐
If yes,<table><tr><td>No.</td><td>Assessment</td><td>Date treatment started</td><td>Medications</td></tr><tr><td>1</td><td></td><td>____/____/_____</td><td></td></tr><tr><td>2</td><td></td><td>____/____/_____</td><td></td></tr><tr><td>3</td><td></td><td>____/____/_____</td><td></td></tr><tr><td>4</td><td></td><td>____/____/_____</td><td></td></tr></table></td></tr>
<tr><td>206</td><td>Body mass index [BMI in Kg/m^2]</td><td></td></tr>
<tr><td rowspan="2">207</td><td rowspan="2">Consecutive CD4 count</td><td>At six month</td><td>At 12 month</td></tr>
<tr><td></td><td></td></tr>
</table>

Part III: Adverse Drug Reaction related data on Initiation

<table>
<tr><td>301</td><td>Is there documented ADR</td><td colspan="4">Yes ☐ No ☐
If No, do not go through the rest of questions</td></tr>
<tr><td>302</td><td>Date on which ADR was established</td><td>Types of ADR</td><td>Date</td><td>Confirmation/lab,clin.</td><td>CD4 count</td></tr>
<tr><td></td><td></td><td></td><td>___/____/___</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>___/____/___</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>___/____/___</td><td></td><td></td></tr>
<tr><td>304</td><td>HAART regimen during ADR establishment</td><td colspan="4">_____
If the regimen is different from Q204 above;
<table>
<tr><td>Date of ART interruption</td><td>Reason for ART interruption or stopping ART</td><td>Date Restarted</td><td>new regimen started</td></tr>
<tr><td>__/____/__</td><td></td><td>__/____/__</td><td></td></tr>
<tr><td>__/____/__</td><td></td><td>__/____/__</td><td></td></tr>
<tr><td>__/____/__</td><td></td><td>__/____/__</td><td></td></tr>
</table></td></tr>
<tr><td>305</td><td>ADR management/intervention</td><td>Date</td><td>Specific ADR</td><td>Management/pharm. & non pharmacologic</td><td>Outcome</td></tr>
<tr><td></td><td></td><td>__/____/___</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td>__/____/___</td><td></td><td></td><td></td></tr>
<tr><td>306</td><td>Consequences following the ADR</td><td colspan="4">Regimen modification ☐ Hospitalization (if O/P) ☐
Dose missing ☐ Prolong hospitalization (if I/P) ☐
Regimen change ☐ Death ☐
HAART discontinuation ☐ Other, specify _____ ☐</td></tr>
</table>