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ASSESMENT OF ART ADVERSE EFFECTS AND POTENTIAL MANAGEMENT STRATEGIES AMONG PATIENTS TAKING ART IN SHAMBU HOSPITAL/ART CLINIC, HORRO GUDURU WOLLEGA, OROMIA,WESTERN ETHIOPIA

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ABSTRACT

Background: The combination of antiretroviral therapy (ART) is the cornerstone of management of patients with HIV-infection. Though ART can reduce viral load to undetectable level, improve the immunity and prolong the life of patients, antiretroviral drugs are associated with many adverse effects that may be severe and affect patient adherence and quality of life where management of these adverse effects is crucial. **Objective:** To assess antiretroviral associated adverse effects and potential management strategies undertaken among patients taking ART in Shambu Hospital/ART clinic. **Methods:** A retrospective review of patient record charts (from 2013-2016) was done to assess ART associated adverse effects and potential management strategies undertaken. A sample of 320 patients was selected by random cluster sampling technique. **Result:** Drug adverse effects were seen in 82 (25.63%) of patients on ART follow-up and the majority of adverse effects reported were dyspepsia 25 (15.06%), lipodystrophy 18 (10.84%), peripheral neuropathy (PN) 17 (10.24%), rash 13 (7.83%), and anemia 12 (7.23%). To manage these adverse effects, switching ART and giving of palliative medicine were undertaken as management strategy in majority of the patients. **Conclusion:** Common adverse effects encountered were gastrointestinal upsets, lipodystrophy, neurological problems, skin reactions, hematological (anemia) and others like hepatotoxicity, headache, fatigue that were managed by switching drug responsible, giving palliative medicine, cessation of non-ART drugs and dose reduction. **Recommendations:** Health professionals should work hard to minimize adverse effects of ART drugs and maximizing the success of ART, identify the drugs responsible in occurrence of adverse effects and take measures to improve the quality of the clients life. Also the health professionals who work in ART clinic should write the necessary information on patients card and arrange the cards properly to have reliable information.

KEYWORDS: Adverse effects, Highly Active Antiretroviral Therapy, management strategies.

INTRODUCTION

Background

HIV/AIDS has created an enormous challenge worldwide since the recognition of the disease. HIV has infected close to 33.4 million people and more than 30 million have died due to AIDS. More than 66% of the 30 million plus people living with HIV/AIDS (PLWHA) are in sub-Saharan African countries, where AIDS is the leading cause of death. Ethiopia is among those countries most affected by the epidemic (as per 2005 WHO report).[1]

Much progress has been made in treating HIV infection in the last several years. In the United States of America, mortality among people infected with HIV/AIDS has decreased from 29.4/100 patients to 8.8/100 patients (1995-1997) and people infected with HIV are now living longer, healthier life. What was once considered a progressive, ultimately lethal disease has become, in developed countries, a chronic condition that can be managed for longer term. In large part, this challenge has resulted from the introduction of Highly Active Antiretroviral Therapy (HAART).[2]

The combination antiretroviral therapy (ART) or (HAART) is the cornerstone of management of patients with HIV infection. HAART is a global standard of care; still access is limited to very few infected people where the burden of HIV is greatest especially in sub-Saharan Africa.[3]

The major classes of HAART available for treatment of HIV-1 infection include the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the protease inhibitors (PIs). Other classes of HAART include integrase inhibitors, entry (fusion) inhibitors, mutation inhibitors and broad-spectrum inhibitors.[4]

The treatment of naïve patients is initiated with a combination of three drugs (triple therapy), unless special conditions exist in the patient. Two NRTIs generally forming the backbone of most combination antiretroviral therapy, the third drug NNRTI or if it is not possible, PIs are used as alternative second line therapy.[2,3,4]

The NRTI class of drugs commonly includes - Zidovudine (AZT), Stavudine (d4T), Lamivudine (3TC), Didanosine (ddi), Abacavir (ABC), and the newly released nucleotide analogue Tenofovir (TDF). The NNRTIs include Efavirenz (EFZ), Nevirapine (NVP), and the protease inhibitors (PIs) are Nelfinavir (NFV), Indinavir (IDV), Ritonavir (RTV), Lopinavir (LPV), and Saquinavir (SQV). Even though not currently available, two drugs, bevirimat and vivecon,

Which are grouped under the newly emerging class called mutation inhibitors, are under intensive investigation,[4]

Current ART regimens are capable of reducing viral load to undetectable level, with consequent increase in T-lymphocyte, $CD4^+$ counts and reduction in development of opportunistic infections. Hence, a substantial reduction in HIV associated morbidity and mortality can be attained,[2,5]

In recent years, excitement about the benefits of combination antiretroviral therapy has been tempered by the growing awareness of the problems that accompany the use of these drugs. In addition to the resistance and difficulty of adhering to complex regimens, adverse effects associated with HAART have become a major concern.[5] In spite of the ART benefits, adverse reactions to these drugs have been pointed to as one of the major reasons for the discontinuation, switch and non-adherence to ART.[5,9,10]

Adverse effects due to antiretroviral drugs (ART drugs) are not new. Since the late 1980s, the earliest drug used to treat HIV infection AZT (Zidovudine), and other nucleoside analogues were at higher doses than currently used doses which were associated with several adverse effects including nausea, diarrhea, muscle disease (myopathy), and hematological effects(e.g. bone marrow suppression leading to anemia and low white blood cell count). However, the most recently approved class of anti-HIV drugs, the PIs, has been associated a new set of strange adverse effects including metabolic abnormalities and changes in body fat distribution.[6]

All antiretroviral drugs can have both short and long-term adverse effects. The risk of specific side effects vary from drug to drug, from drug class to drug class, and from patient to patient. Several strategies have been implemented to improve treatment duration, while development of new antiretroviral drugs continues. Efforts to maximize the effectiveness of currently available treatments include attempts to better understand and manage adverse effects. Research to improve current treatments include decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance.[6,10]

LITERATURE REVIEW

More recently, a result of prospective study on the adherence to initial ART have demonstrated that patients reporting higher numbers of adverse reactions were more likely to be non-adherent to their ART regimens. This indicates that adverse reactions can interfere with every day activities of the patient, thereby leading to the interruption of the treatment as well as switches in the regimens.[8] Similarly, the cross sectional interview of 2,765 HIV positive adults who were on ART therapies in four US cities, respondents with less than 90% adherence reported greater number and severity of adverse effects over all. In addition, the study found that there was no gender difference in rate or severity of adverse effects reported. Latino respondents report more adverse effects than either white does or African Americans. Those taking protease inhibitors (PIs) report higher rate and severity of adverse effects. Older participants reported fewer adverse effects despite being more likely to be on regimen containing PIs.[9]

As management strategies, many studies have reported high rate of adverse effect associated regimen change or switch and discontinuation. In pivotal clinical trials, more than 50% of patients taking EFV based therapy experienced some CNS side effects although few patients discontinued treatment as a result.[2]

In the study of 48 patients designed to decrease EFV associated CNS side effects, EFV was titrated up over two weeks period to a maximum dose of 600 mg (taken once daily at bed time) interim result revealed that 17 patients (35%) experienced at least one moderate or severe CNS side effect. Another 12 patients (25%) reported mild side effects. Two patients discontinued treatment because of CNS side effects.[2]

Several cohort studies have suggested that adverse effects are common reasons for changing ART. Investigators monitoring an Italian cohort of HIV-infected patients whose ART regimens were NNRTIs based found that, clinical drug adverse effects, which occurred in 18% of patients starting NVP based regimen and in 10% of patients starting an EFV based regimen, was the most common reasons for changing the initial ART regimen.

In contrast to gastrointestinal disturbances with PI based regimen, hypersensitivity (rash and hepatitis) was the most common reason for discontinuing a NVP based regimen (12%) and CNS toxicity was the most common reason for discontinuing EFV-based regimen (5%). In addition to adverse effects mentioned above, rash, headache, fatigue and hematological and liver function abnormalities were common adverse effects leading to a change in ART.[10]

A concurrent prospective study conducted to assess factors associated with adverse reactions among individuals initiating ART in two public referral HIV/AIDS centers, Brazil, showed that among 397 charts reviewed, 377 (95%) had precise information on adverse effects and initial antiretroviral treatment. Most patients received triple combination therapy including NRTIs, NNRTIs, and PIs. At least one adverse effect was recorded on 34.50% (N=130) of medical charts (0.17 adverse reactions/100 person/day), while nausea (14.50%) and vomiting (13.10%) were the most common ones. Variables independently associated adverse reactions were regimens with NVP, IDV/RTV combinations, female patients, more outpatient visits, and non-adherences to ART and $CD4^+$ counts of 200-500 cells/mm^3.

An independent and negative association was also found for alcohol use. Adverse reactions were substantial among participants initiating ART. On its conclusion, special elaborated protocols in HIV/AIDS referral centers may improve the diagnosis, management prevention of adverse reactions, thus contributing to improving adherence to ART among HIV-infected patients.[6]

Similar study was conducted in Brazil to describe adverse reactions to ART and to verify its association with selected variables at least one adverse effect was reported by (92.20%) of participants, while (56.20%) reported four or more adverse effects. Antiretroviral regimens including IDV/RTV, irregular use of antiretroviral and switch in regimen were independently associated with four or more adverse reactions (7.92%), (5.73%), and (2.03%) respectively).

In addition, there was no record of hospitalization or death due to the adverse effects, while among the 144 (30.30%) participants who had their ARV regimen switched at least once during the follow-up period, the switch was caused by the adverse effect in 40 (35.10%). Dose adjustment was registered only in two patients.[8]

A retrospective study conducted on adverse effects of ART and associated factors in a total of 43 children, in a Tertiary General Hospital showed that 30% developed adverse effect related to ART i.e. 16% hepatotoxicity, 5% increase serum amylase (without symptom of pancriatitis), 12% AZT induced abdominal pain.

Hepatotoxicity was seen in high viral load (mean=118,608 copies/ml), whereas increased serum amylase was seen at low viral load (mean=3,763 copies/ml) statistically significant. Serum amylase abnormalities were at mean interval of 0.9 year after starting therapy. Hepatotoxicity was seen at mean interval of 1.7 years and AZT induced anemia was seen at mean interval of 2 years of therapy. Hepatotoxicity was the commonest adverse effect of ART followed by increased serum amylase and AZT induced anemia according to the study.[11]

A prospective cohort study in a teaching referral hospital involving all patients who were prescribed a NVP containing antiretroviral regimen released that of total 610 patients 82 (13.4%) were antiretroviral naïve which commencing NVP and (46.20%) and (8.90%) were co-infected with hepatitis C and B virus respectively. Mean duration exposure to NVP was 8.7 months (interquartile range 3.4-14.3). Hepatotoxicity developed in 76 (12.5%), an incidence of 13.1 per 100 persons per year. Estimated incidence of hepatotoxicity at 3, 6 and 12 months was (3.70%), (9.70%), and (20.10%) respectively. In seven patients (1.10%), hepatotoxicity was associated with clinical hepatitis, which was reversible up on discontinuation of therapy. Multivariate analysis identified the duration of prior exposure to ARV drugs, hepatitis C virus and high base line level of alanine aminotransferase as independent risk factor for hepatotoxicity.[12]

Adverse effect was the single most important reason (35%) for ARV regimen change and was the only of a contributory cause in over half of the patients in a study conducted in North Manchester General Hospital, London.[13]

Similarly in a retrospective study conducted in north Italy (1999-2005), the most frequent reason for treatment discontinuation was resistance (17.50%) followed by reduced tolerability to side effects (16.30%). The risk for drug-induced toxicity was low but the study recommended that nevirapine should be used with caution in patients co-infected with hepatitis C virus or with elevated liver function tests.[14]

In a study conducted in outpatient clinic in Kenya, ART switches occurred in 701(54.50%) patients. The commutative incidence of ART switches at 12 months (78.40%). Concurrent ART related side effects (40.60%) and tuberculosis treatment interactions (28%) were the most frequent reasons for ART switch. Baseline AIDS symptoms and $CD4^+$ count of less than 100cells/mm^3 were independent predictors of ART switch. Switching was itself an important predictor of a subsequent toxicity, a new opportunistic infections, or withdrawal from the program.[15]

ART related clinical toxicity was found in 341(26.5%) patients, peripheral neuropathy was reported most

frequently (20.70%). A $CD4^+$ count of less than 100cells/mm^3 and being older than 40 years were independent predictors of clinical toxicity. Unlike to the other studies, no ART related laboratory liver toxicity was observed.[15] Study findings presented recently at the 2007, HIV implements meeting in Rwanda, showed high rate of drug switch, primarily attributable to stavudine related toxicity. "Because of likelihood of stavudine toxicity affecting initial ART regimen durability in this setting, future HIV programs should consider using stavudine as a part of front line therapy" the authors concluded.[15]

Statement of the problem

Effective treatment of HIV-infection requires the use of three or more drug regimens that are complicated and commonly associated with adverse effects and adverse drug interactions. This makes compliance difficult and can result in treatment failure, development of resistance and loss of future treatment options. In addition, some adverse effects may lead to an increase in morbidity and represent additional risk factor for future complications. Serious adverse effects after the initiation of highly active antiretro viral therapy (HAART) are related to both the patient and treatment characteristics. Some patients experience frequent and severe adverse effects that necessitate dose reduction or discontinuation of treatment. Others have adverse effects that are uncomfortable or annoying and can interfere with daily quality of life, still others experience few or no adverse reactions associated with it.[16]

Generally, adverse effects vary with age, sex, race, genetic, nutritional status, stage of the disease, existing concomitant opportunistic infections or other related diseases, duration of treatment and the type of regimen the patient is taking. Side effects resolve in most patients within 6-10 weeks of initiating therapy but for some patients symptoms seen to persist for longer term.[2]

It is also important to note that many parts of symptoms associated with anti-HIV drugs including peripheral neuropathy, gastrointestinal symptoms, mental symptoms and certain metabolic changes are also found in people with HIV-infection who are not taking ART, especially those with advanced stage disease. Thus, it is difficult to determine whether a symptom is related to HIV/AIDS infection or drug adverse effect.[7]

Common but mild adverse effects occurring early in most antiretroviral regimens induce gastrointestinal effects such as vomiting (3-15%), nausea (4-26%), and diarrhea (4-32%), which may be transient or persist throughout therapy. Other common naissance adverse effects are fatigue (2-7%) and headache (12-18%) caused by AZT and nightmares associated with EFV (52%).

Several uncommon but more serious adverse effects associated with ART include AZT associated anemia (1-7%), d4T associated peripheral neuropathy (13-24%), PI associated retinoid toxicity (exemplified by pruritis and ingrown to nails, PI and NNRTI associated hypersensitivity reaction (5-24%). Other subtle and serious adverse effects include lactic acidosis, hepatotoxicity, hepatic steatosis, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders and bone abnormalities including osteoporosis, osteonecrosis and osteopenia.[17]

No absolute guideline exists for the management of adverse effects. It may include pharmacological and non-pharmacological interventions. Clinically, managements include treatment interruptions, switching to another drug or regimen, dose adjustment (therapeutic drug monitoring) and adjustment of possible drug and disease interactions. Supportive medications for the specific symptoms may be also recommended.[16,17]

Furthermore, there were no studies done in Shambu hospital concerning antiretroviral adverse effects and on the existing, ART related toxicity management strategies. Thus, detailed understanding of the existing HIV treatment strategy is important to assure the efficacy and safety of antiretroviral treatment so that patient adherence and quality of life be improved.

Significance of the study

It is important to health professionals and patients to have knowledge on the existing adverse effects of ART and management strategies that can be undertaken. It also provide information on the existing prevalence of adverse effects, factors associated with the occurrence of adverse effects and assess on monitoring and management steps being undertaken for the existing adverse effects. It can serve as a baseline for further studies in the area.

The most challenging in our world today is the development of adverse effects to most ART drugs which may lead to treatment failure and difficulty to control different infectious diseases. To decrease such problems drug adverse effect management is the most important.

In dealing with problem like HIV/AIDS that has impact on economy of the country, implement or accomplishment of ART drug adverse effect management strategies is useful based on guideline to monitor in health care system of the country.

Therefore, the result of this study is helpful as a base line data to assess ART drugs adverse effects and management strategies undertaken in our country for further study. Also the result will be useful to manage ART adverse effects in Shambu Hospital and it will encourage researchers who conduct ART drug adverse effects and management on the group of drugs in the future.

OBJECTIVES

General objective

To assess antiretroviral adverse effects and potential management strategies undertaken in patients taking ART in Shambu Hospital/ART clinic.

Specific objectives

- To identify factors that contributed for the occurrence of adverse effects.
- To assess potential management strategies undertaken for the observed adverse effects.
- To determine the prevalence of adverse effects in patients taking ART.

METHODOLOGY

Study area and period

The study was conducted in Shambu Hospital/ART clinic, which is in Shambu town located at 315km away from Addis Ababa, Horro Guduru Wollega Zone, and Oromia region at an elevation of 2088 meters. The area is at high altitude with lower temperature and high rainfall. The hospital has different department and delivers different health services. . It was 1st founded in 1978 E.C. The hospital has a total of 185 staffs with 87 administration staffs and 68 health professionals. It delivers different services with different specialists. The hospital gives ophthalmological service, dental services . Pharmaceutical and laboratory services are also among the common services given in the hospital. The study was conducted from July 15 to October 15, 2016.

Study design

A cross-sectional retrospective review of patient record charts (from 2013-2016) was done to assess ART associated adverse effects and potential management strategies undertaken for the adverse effects in patients taking ART in Shambu Hospital/ART clinic.

Population

Source population

All HIV positive individuals in Shambu Hospital/ART clinic who started ART follow-up.

Study population

All HIV positive individuals who have started ART in this clinic and have duration of follow-up of six months and above.

Inclusion and exclusion criteria

Inclusion criteria

The study include HIV positive individuals with ART follow-up of more than or equal to six months.

Exclusion criteria

HIV positive individuals on ART follow-up who were transferred to other health centers were not included.

Sample size determination

The sample size was determined by using the following formula:-

$$No = \frac{z^2 p(1-p)}{d^2}$$

Where,
n_o = minimum sample size required
p = estimate of the prevalence rate
d = margin of sampling error tolerated
z = 1.96 at confidence interval of 95%.

Since there is no estimate for the prevalence rate of adverse effects, it is assumed to be 50%, to get the minimum sample size with confidence interval of 95% and marginal error of 5%.

$$No = \frac{z^2 p(1-p)}{d^2}$$

$$= \frac{(1.96)^2 0.5(1-0.5)}{(0.05)^2}$$

$$= 384$$

Hence, the minimum sample size required is 384.

Since the source population is less than 10,000 (1,873), the sample population is adjusted as:

$$NF = \frac{no}{1+\frac{no}{N}}$$

Where, **NF** = required sample size

N = total number of population

$$nf = \frac{384}{1+\frac{384}{1873}}$$

$$= 320$$

A sample of 320 HIV positive individuals record charts were selected since these would allow for a 50% prevalence estimate with 95% confidence interval.

Sampling technique

The sample population was withdrawn from the total study population using random cluster sampling technique by grouping patient record charts into different clusters and then a required amount of sample was taken.

Study variables

Independent variables

The independent variables include the following:

- Age
- Sex

- Weight
- CD4+ count
- Types of ART regimen
- Presence of non-ART drugs
- Non-adherence
- ART switch
- Co-morbid illness

Dependent variables
The dependent variables include variables under study and they are:-

- Adverse effects of ART drugs
- Management strategies undertaken

Pre-testing
Before starting the actual data collection, a small-scale trial test was done on the data collection format for having all required information for the study and to maintain the quality of the study.

Data processing and analysis
Once all necessary data were obtained, data were checked for completeness, sorted and categorized accordingly. Data was analyzed and finally the result was presented by using tables and figures.

Data quality assurance
The clarity and completeness checking of data collection format was under taken before the actual data collection and data clearing was done every day, format without full information was excluded from the study to avoid error.

Data collection process
A well-structured data collection format was designed and relevant data were transferred from available patient record charts to the designed data collection format. The format was designed to contain two major parts which are:-

- Part I:- socio-demographic characteristics of patients
- Part II:- clinical variables

Ethical consideration
Written permission for conducting the study on patients' records was obtained from the hospital director and confidentiality of the records was maintained.

RESULTS

Socio-demographic characteristics of patients
From a total of 320 study population, the majority 194 (60.63%) were females. About 273(85.32%) of the patients were found in the age group of 16-49 years, the rest 19(5.94%) and 28(8.75%) were found in the age range of below 15 and above or equal to 50 years respectively. Out of 320 patients, 273(85.32%) have weight in the range of 40-59kg when weighed at initiation of ART. Orthodox accounted to the majority 121(37.81%), Protestants 115(35.94%), while Muslims and others accounted only for 78(24.37%) and 6(1.88%) respectively. Considering the marital status, 117(36.56%) were married, 98(30.63%) were single, 49(15.31%) were widowed, 43(13.44%) were divorced, and the rest 13 (4.06%) were separated.

Educational level data showed that (38.44%) were in the primary level, (35.31%) were in the secondary, (14.69%) were in the tertiary level of education and the rest (11.56%) of the patients were illiterate. Individuals in almost all occupation are vulnerable to the disease regardless of what job they are performing. From this, house wives are more affected accounting 87(27.19%), merchants were 85(26.56%), daily laborers' 53(16.56%) students 38(11.87%), farmers 35(10.94%), teachers 15(4.69%) and others account the rest of the population.

Regarding patient sources, the majority of the patients were obtained from general voluntary counseling and testing (VCT) 251(78.44%), 33(10.31%) were outpatients, 11(3.44%) were from inpatient, 6(1.87%) were from prevention of mother to child transmission (PMTCT) and the others 14(4.37%) were self-referred, from TB clinic, public health centers, and private hospitals [table-1].

Table 1: Patient characteristic distribution among HIV- patients taking ART in Shambu Hospital/ART clinic, September, 2016.

Patient characteristics		Frequency (n=320)	Percentage (%)
Sex	Male	126	39.37
	Female	194	60.63
Age (years)	≤15	19	5.94
	16-49	273	85.32
	≥50	28	8.75
Weight (Kg)	≤39	26	8.12
	40-59	273	85.32
	≥60	21	6.56
Religion	Orthodox	121	37.81
	Muslim	78	24.37
	Protestant	115	35.94
	Other*	6	1.88
Level of education	Illiterate	37	11.56
	Primary	123	38.44
	Secondary	113	35.31
	Tertiary	47	14.69
Occupation	Farmers	35	10.94
	House wives	87	27.19
	Merchants	85	26.56
	Teachers	15	4.69
	Students	38	11.87
	Daily Labourers	53	16.56
	Others**	7	2.19
Marital status	Single	98	30.63
	Married	117	36.56
	Divorced	43	13.44
	Widowed	49	15.31
	Separated	13	4.06
Patient source	General VCT	251	78.44
	Outpatient	33	10.31
	Inpatient	11	3.44
	PMTCT	6	1.87
	Higher private clinic	5	1.56
	Others***	14	4.37

Other*:- Adventist, Chatolic
Others**:-
Secretary, soldiers, retired, electricians
Others***:- Public health centers, TB clinics

Clinical variables

History of adverse effects

Drug adverse effects have been seen in 82(25.63%) of the patients on ART follow-up, whereas the majority 238(74.37%) did not show drug adverse effects.

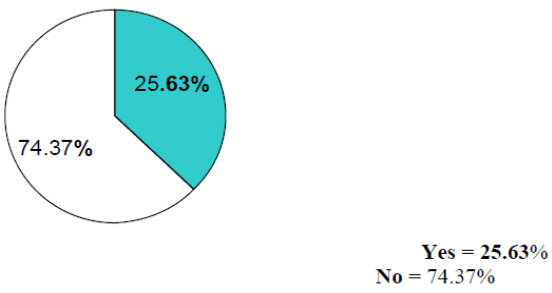

Fig. 1: History of adverse effects in patients taking ART in Shambu Hospital/ART clinic, September, 2016.

Among adverse effects encountered by patients in Shambu Hospital, dyspepsia, Lipodystrophy and peripheral neuropathy (PN) are the leading, accounting for 25(15.06%), 18(10.84%) and 17(10.24%) respectively. The rest include mucocutaneous manifestations like [skin rash 13(7.83%), itching 4(2.41%) and skin lesion 2(1.20%)], CNS manifestations [headache 13(7.83%), insomnia 7(4.22%), confusion 5(3.01%) and anxiety and nightmares 9(5.41%)], other gastrointestinal manifestations [diarrhea 5(3.01%), nausea 10(6.02%) and vomiting 11(6.62%)] and others [hepatotoxicity 5(3.01%), pancreatitis 2(1.20%), and fatigue 4(2.41%).[table-2].

Table 2: Drug adverse effects in patients on ART follow-up in Shambu Hospital/ART clinic, September, 2016.

ART adverse effects		Frequency (n=166)	Percentage (%)
Gastrointestinal	Dyspepsia	25	15.06
	Vomiting	11	6.62
	Diarrhea	5	3.01
	Nausea	10	6.02
	Total	51	30.72
Neurological	PN	17	10.24
	Headache	13	7.83
	Anxiety	6	3.61
	Confusion	5	3.01
	Insomnia	7	4.22
	Total	48	28.92
Skin reactions	Rash	13	7.83
	Itching	4	2.41
	Lesion	2	1.20
	Total	19	11.44
Hematological	Anemia	12	7.23
	Total		
Others	Lipodystrophy	18	10.84
	Hepatotoxicity	5	3.01
	Fatigue	4	2.41
	Pancreatitis	2	1.20
	Nightmares	3	1.80
	Others*	4	2.41
	Total	36	21.68

Others*: - anorexia, dizziness, epilepsy, neuralgia

Factors associated with adverse effects

From 82 patients who experienced ART-adverse effects, 29 (35.36%) were male while 53(64.64%) were female. Most of the patients were found in the age group between 16-49 years 71(86.59%). Couples accounted for the majority 117 (36.56%), while others are single 98 (30.63%), divorced 43 (13.44%), widowed 49 (15.31%) and separated 13(4.06%). Among 82 patients, 7 (8.54%) experienced adverse effect due to adverse drug interaction, 23(28.05%) have had co-morbid illness along with HIV/AIDS and 14 (17%) were non-adherent to their ART regimen.

In 19 patients (23.17%), adverse drug reactions occurred after ART switch was done. The regimens associated with development of adverse drug reaction include, d4T/3TC/NVP 5 (6.10%), AZT/3TC/EFV 4 (4.88%), d4T/3TC/EFV 4 (4.88%) and AZT/3TC/NVP 3 (3.65%) [table-3].

Table 3: Distribution of factors related with adverse effects in patients taking ART in Shambu Hospital/ART clinic, September, 2016.

	Factors associated	Frequency (n=82)	Percentage (%)
Sex	Male	29	35.36
	Female	53	64.64
	Total	82	
Age	≤15	5	6.10
	16-49	71	86.59
	≥50	6	7.32
	Total	82	
Adverse drug-drug interaction	Yes	7	8.54
	No	75	91.46
	Total	82	
Co-morbid illness	Yes	23	28.05
	No	59	71.95
	Total	82	
Non-adherence	Yes	14	17
	No	78	83
	Total	82	
ART switch	Yes	19	23.17
	No	63	76.83
	Total	82	
ART regimen	d4T/3TC/NVP	5	6.10
	d4T/3TC/EFV	4	4.88
	AZT/3TC/NVP	3	3.65
	AZT/3TC/EFV	4	4.88
	TDF/3TC/NVP	1	1.22
	TDF/3TC/EFV	2	2.44
	Total	19	23.17

Laboratory tests during development of adverse effects

From 82 patients who experienced adverse effects, laboratory test was done for 82 (100%) patients like CD4, Hgb and WBC. From this data, $CD4^+$ count between 200-399 cells/mm^3 accounted for 45 (54.88%) while $CD4^+$ count less than 200 cells/mm^3 and more than 400 cells/mm^3 accounted for 9(10.97%) and 28 (34.5%) respectively. Other laboratory values except Hct were mostly in their normal range. Accordingly, Hgb (74.39%), WBC (65.82%) and Sr.cr. (82.32%) were in their normal range, but Hct (66.66%) was below its normal range [Table-4]. (See annex-2 for normal ranges).

Table 4: Retrospective study of adverse effects and laboratory findings obtained during the development of adverse reactions in patients taking ART in Shambu Hospital, September, 2016.

Laboratory values		Frequency (n)	Percentage (%)
$CD4^+$ count	≥400	28	34.15
	200-399	45	54.88
	≤200	9	10.97
	Total	82	
Hgb	Low	21	25.61
	Normal	61	74.39
	Total	82	
WBC	Low	27	34.18
	Normal	52	65.82
	Total	79	
Sr.cr.	Elevated	9	17.65
	Normal	42	82.35
	Total	51	
Hct	Elevated	11	22.92
	Normal	5	10.42
	Low	32	66.66
	Total	48	

Management strategies undertaken

Management strategies were undertaken in 65 (79.26%) patients out of 82 patients. Switching ART and giving palliative medicines were the two management undertaken accounting for (23.17%) and (41.01%) respectively. While the others were discontinuation of ART (4.88%), cessation of non-ART drugs (6.24%) and dose reduction of ART (3.96%).

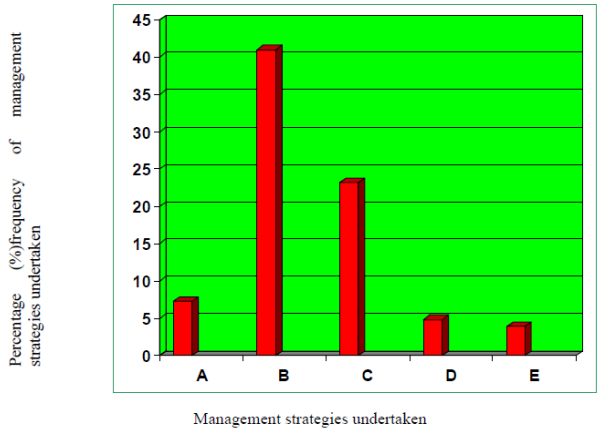

Fig 2: Clinical management of adverse effects of ART in patients taking ART in Shambu Hospital/ART clinic, September, 2016.

Keys

A…Cessation of non-ART drugs
B… Palliative medications given
C…ART switch
D…ART discontinuation
E…Dose reduction

Palliative medications given

Dyspepsia that occurred due to antiretroviral drugs was managed by giving drugs like antacid suspension (11.11%), omeprazole (7.41) and cimetidine (7.41%). Stavudine associated with PN was alleviated by administering pyridoxine (25.92%). Moreover, hematological adverse effects (anemia) was managed by giving iron folate (11.11%) while headache, skin rash, anxiety, nausea and vomiting were managed by drugs like analgesics (11.10%), antihistamines (11.11%), amitryptiline (7.41%) and metoclopramide (7.41%) respectively [table-6].

Table 5: Palliative medications given to alleviate adverse effects of ART in patients taking the medication in Shambu Hospital/ART clinic, September, 2016.

Adverse effects	Palliative medicine	Frequency (N=27)	Percentage (%)
Dyspepsia	Antacid suspension	3	11.11
	Omeprazole	2	7.41
	Cimetidine	2	7.41
PN	Pyridoxine	7	25.92
Anemia	Iron foliate	3	11.11
Headache	Ibuprofen	1	3.70
	Diclofenac	1	3.70
	Paracetamol	1	3.70
Skin rash	Antihistamine	3	11.11
Anxiety	Amitryptiline	2	7.41
Nausea & vomiting	Metoclopramide	2	7.41

DISCUSSION

ART adverse effects are among the challenges encountered by patients, where management to these adverse effects is highly required. In this study, among 320 patients whose cards were reviewed, less than one-third 82(25.62%) of them experienced adverse effects ranging from mild to severe which led to switch of the drug responsible, reduction in dose and using of palliative medications.

The study conducted in outpatient clinic in Kenya showed that ART-related adverse effects were found in 341(26.50%) patients.[15] This similarity can be due to similarity in nutritional status and the drug regimens employed.

In the current study most common adverse reactions observed were gastrointestinal upsets that accounted for 51(30.72%) of which the most common was dyspepsia 25(15.06%) mainly associated with AZT. Nausea, vomiting and diarrhea were 10(6.02%), 11(6.62%), and 5(3.01%) respectively. This figure is lesser when compared with the study done in Brazil, which showed that nausea (14.5%) and vomiting were (13.1%).[6]

In addition, other adverse effects were neurological problem 48(28.92%), from these peripheral neuropathy 17(10.24%) was mainly observed in patients taking d4T containing regimen. This is less than the study conducted in Kenya in which peripheral neuropathy accounted for (20.70%).[15] These might have occurred because of difference in gene and races. Headache 13(7.83%),

anxiety and nightmares 9(5.41%), confusion 5(3.01%) and insomnia 7(4.22%) were the other CNS adverse effects observed mainly due to EFV-based regimen. Lip dystrophy 18(10.84%), hepatotoxicity 5(3.01%), fatigue 4(2.41%) and pancreatitis 2(1.20%) were other adverse effects observed in this study. Lip dystrophy was observed in patients taking d4T containing regimen, hepatotoxicity was mainly due to NVP while fatigue is due to AZT, Pancreatitis that occurs because of 3TC was reported by two patients.

Anemia was seen in 12(7.23%) patients, which was contributed by AZT. Long-term use of AZT causes bone marrow suppression, which leads to decreased production of red blood cells that result in development of anemia.

Adverse effects vary with many variables like age, sex, race, gene, nutritional status and types of regimens patients are taking, disease conditions, opportunistic infections and duration of treatment. Adverse drug interactions, ART switches and irregular use of ART are also other factors that result in the development of adverse effects.

In this study, 82 patients who developed adverse effects 53(64.64%) were female and the rest 29(35.36%) were male. This is supported by the study conducted in Brazil, which showed that female patients were more associated with adverse drug interaction.[6] Majority of the patients who experienced adverse effects were found in the age range of 16-49 years 71(86.58%) and the elderly were 6(7.32%). In this study, among six elderly patients (age ≥50 years) reviewed 5(83.33%) of them developed adverse effects. This contrasted to the study carried out in US, which showed that older patients reported few adverse effects on regimen containing PI-based as adverse effects observed in the current study associated with NVP and EFV-based regimen instead of PIs.

From 82 patients, development of adverse effect was associated with drug interactions in 7(8.54%) patients. This drug interaction was mainly between antiretroviral drugs and anti-tubercular drugs. For example, adverse effects of d4T with isoniazid and NVP with rifampicin overlap and caused peripheral neuropathy and rash respectively.

Switching of drugs may also be associated with occurrence of other types of adverse effects. When the initial regimen is associated with adverse effect, physicians replace the drug responsible with its alternative. The newly administered regimen may cause another form of adverse effect. Accordingly, for 19 patients, ART switch was done as management strategy for the occurred adverse effects. From this, 3(15.78%) of them developed adverse effect due to the switched drugs. The study done in Kenya showed ART switch due trelated adverse effect was (40.60%) that is greater than what is indicated in the current study's result.[6]

Non-adherence is also associated with the occurrence of adverse effects. Fourten (17%) were identified to be non-adherent to their medication, this means that reduced tolerance to the adverse effects resulted in the interruption of the medication follow-up i.e. adverse effects can interfere with the everyday activity of patients thereby leading to the interruption of the treatment. Twenty seven (28.05%) patients who developed adverse reaction also had co-morbid illnesses along with HIV-infection. Common co-morbid illnesses assessed were TB, hepatitis, URTIs, pneumonia, candidiasis and some other bacterial and fungal infections.

ART-regimen types are one of the most important variables associated with development of adverse effects. According to the finding of this study, d4T/3TC/NVP, d4T/3TC/EVF and AZT/3TC/EVF were the regimens mainly associated with the occurrence of adverse drug reactions accounting for 5(6.10%), 4(4.88%) and 4(4.88%) respectively. AZT/3TC/NVP (3.65%) and TDF/3EC/EFV 2(2.44%) were the fourth and the fifth causes for development of adverse effects. In three patients, TDF containing regimen resulted in occurrence of adverse reaction. As a result, this study showed, d4T was the main cause for PN and lip dystrophy. NVP caused hypersensitivity (rash) and hepatotoxicity in most patients, EFV was mainly associated with CNS adverse effects like anxiety, nightmares and confusions and AZT caused anemia and GI upsets in most patients. TDF was not given as initial regimen but replace AZT and d4T in case of adverse effects.

In three patients, TDF resulted in renal insufficiency after switch has been made. Finally, it may be concluded that: NVP-based regimen is more associated with adverse effects than EFV-based. EFV-based regimen resulted in switch in (4.57%) of patients due to CNS-toxicity and hypersensitivity (rash) was the reason for switching of NVP-based regimen in (7.83%) patients. This is comparable with several cohort studies in Italy in which the reason for discontinuing EFV based regimen was (5%) and NVP based regimen was (12%).[10]

A number of laboratory tests were done to relate the result obtained with different adverse effects directly or indirectly. The majority of laboratory values were in their normal range even though some had values below or above the normal range. In this study, in 9(10.97%) of patients $CD4^+$ counts was found to be below 200cells/mm^3 and 45(54.88%) of the $CD4^+$ count fall in the range of 200-400cells/mm^3. This was supported by the study done in Brazil that showed $CD4^+$ count of 200-500cells/mm^3 independently associated with adverse effects.[6]

Laboratory tests for Hgb and Hct have been done when anemia was suspected for patients taking AZT-containing regimen. Accordingly, Hgb (25.61%) and Hct (66.66%) values were below the normal range

respectively indicating the presence of anemia a test for level of sr.cr. has also been done and majority of the values were in their normal range (82.35%) while (17.65%) had elevated value, which is directly related to TDF toxicity resulting in renal impairment requiring serious interventions and monitoring.

Even though the treatment for HIV is modified worldwide, the side effects are worsening the treatment outcome. To overcome these complexities, there should be potential management strategies to be undertaken to limit the side effects. These potential management strategies include switching of the particular drug responsible for the side effect of the total regimen, giving palliative medications for the symptoms, discontinuation of the drug or the regimen, cessation of non-ART drugs and reducing the doses of the drugs. This study showed that switch (23.17%) due to serious adverse effects was the most important management strategies undertaken against ART side effects. Study conducted in London showed that adverse effect was the most important reason for ART switch (35%).[13] Similarly, the study conducted in Brazil supported this statement as it indicated ART switch was done because of adverse effect in 40 (35.10%).[8]

As it has been seen in this study, whenever d4T adverse effect was observed, switch was made to AZT and vice versa. NVP and EFV are used interchangeably whenever adverse effect is seen in one of the two. In few cases, AZT and d4T were switched to TDF. NVP and EFV were switched to ABC as management for the adverse effects of these drugs. In this study, there were no data that reports ABC related adverse effect after switch was done.

Giving palliative medicines (41.01%) was undertaken as management strategies next to switch in Shambu hospital. It was given to relieve symptoms and other worsening conditions from side effects of ART drugs. For instance, NVP-based regimens cause cutaneous problems, mainly rash, which was managed by giving antihistamines such as promethazine. Similarly, peripheral neuropathy, anemia, headache and GI disturbances were managed by pyridoxine, iron foliate, analgesics and antacid suspensions plus omeprazole respectively.

Treatment discontinuation (4.88%) was done for 3-5 days mainly due to adverse drug interaction of ART with other drugs (anti-TB) and some serious adverse effects of ART such as PN and EFV toxicity. Cessation of non-ART drugs (6.24%) was also undertaken as management since they potentiate adverse effects of ART drugs. For example, isoniazid (INH) was reported to cause peripheral neuropathy like NVP in few patients.

Sometimes dose reduction (3.96%) was applied as management strategy. This was in agreement with the study conducted in Brazil in which dose adjustment was undertaken in only two patients.[6] In this study, dose reduction was made particularly for the regimens containing d4T in which a patient experienced peripheral neuropathy and weight gain.

CONCLUSION

The most common adverse effects occurred in patients taking ART in Shambu Hospital/ART clinic were gastrointestinal upsets of which dyspepsia and lipodystrophy was the leading; neurological from which peripheral neurophathy was the most frequent; skin reactions; hematological (anemia), and others like, hepatotoxicity and fatigue.

The ART drug regimen type patients were taking also the main factor with which adverse effect varied in both frequency and severity. Accordingly, patients who were taking NVP-based regimen manifested adverse effects frequently while d4T/AZT showed more adverse effects that required management. Opportunistic infections and adverse drug-drug interactions were also other factors that contributed to an increase in development of adverse effects.

The most commonly applied management strategy was ART switch, which was done when severe adverse effects like Dyspepsia, PN, anemia, lipodystrophy and hepatotoxicity were developed. In addition to ART switch, giving palliative medicine was applied to treat the symptoms and complications of developed adverse effects. Discontinuation of ART and cessation of non-ART drugs was used in some patients while dose reduction was done for a few numbers of patients.

Generally, adverse effect was the main challenge encountered by patients taking ART and in few patients treatment failure because of non-adherence. Thus, to optimize the treatment success and adherence, clinicians must focus on preventing adverse effects whenever possible.

RECOMMENDATIONS

- Health professionals who are responsible to record information of patients on medical charts are highly recommended to write full information.
- The health professionals dealing with HIV patients should work hard in minimizing adverse effects of ART and maximizing the success of ART.
- Clinicians should identify drugs responsible for the occurrence of adverse effects as in some cases, adverse effects are reported without identifying the drugs caused them.
- Health professionals who deal with ART patients should follow the laboratory investigations of their clients routinely with necessary recordings.
- Allied health professionals should keep patient cards in a way that is easy to take off and return back to the specified place on the shelf provided.

LIMITATION OF THE STUDY

- The data source does not give more information about patients of age less than 15 years.
- Retrospective review of the medical records of patients might not give as much information as prospective studies.
- The data source doesn't cover adverse effects of all ART drugs; rather it explains the adverse effects of drugs, which patients are taking in this hospital.
- Some laboratory investigation was not done to get reliable information.

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Operational Definitions

Adverse effect:- response to a drug that is noxious and unintended and that occurs at the doses used in humans for prophylaxis, diagnosis, therapy of diseases, or for modification of physiologic functions.

Antiretroviral drugs:- are medications for the treatment of infections by retroviruses, primarily HIV. Include different classes of drugs that act at different stages of the HIV cycles.

Palliative medicine:- also called "supportive therapy" is a drug or treatment given to relieve symptoms of a condition resulted due to adverse effects of antiretroviral medications.

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