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SPECTRUM OF ANTIRETROVIRAL (ART) REGIMEN CHANGE AND CONTRIBUTING FACTOR AMONG ADULT HIV/AIDS PATIENT AT SHAMBU HOSPITAL, SHAMBU TOWN, HORRO GUDURU WOLLEGA ZONE, OROMIA REGIONAL STATE, ETHIOPIA

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ABSTRACT

Background: Human Immune Virus (HIV) is responsible for a worldwide pandemic and it is the cause of Acquired Immune Deficiency Syndrome (AIDS). According to latest statistics 33.4 million individuals worldwide are living with HIV, of which 15.7 million (47%) are women and 2.1 million (6.3%) are children under 15 years. In addition there are 2.7 million new infections and 2.0 million deaths from AIDS worldwide**. Result and Conclusion:** Patients that changed their regimen were included in the study to identify the reasons for change and descriptive statistics were generated by Using SPSS & using excels for figures. Out of patients, % were females and % were in the age group -. % were WHO clinical stage III patients and % of patients had missed their CD4 count. In % of patients initial treatment regimen was modified after six months, while, in % and % of patient's initial regimen was modified less than a month and within two to three month time respectively, the most common initial regimens were D4T/3TC/NVP (%), AZT/3TC/NVP (%) and D4T/3TC/EFV (%) The main reasons for modification of therapy were toxicity (%), new drug (%), treatment failure (%), new TB (%), stock out (%), and pregnancy (%) respectively. The main toxicity observed was peripheral neuropathy (%) followed by rash (%) and anemia (%). Among toxicities observed % were due to D4T/3TC/NVP, and the remaining %, %, %, %, % and % were due to AZT/3TC/NVP, D4T/3TC/EFV, AZT/3TC/EFV, TDF/3TC/EFV, TDF/3TC/NVP, and TDF/3TC/LPVr respectively. D4T containing regimens accounted for % of the peripheral neuropathy observed, while NVP containing regimens accounted for % of the rashes reported and AZT containing regimens accounted for % of the Anemia observed. Toxicity was the main reason for initial regimen modification, D4T based regimens had high incidence of peripheral neuropathy. **Objective:** To determine the reason and contributing factors of anti-retroviral regimen changes among patients on anti-retroviral therapy in ART clinic of Shambu Hospital. **Method:** *A retrospective cross-sectional study was done using patient information sheet and physician diagnosis card from January 1, 2008 to December 31, 2016.*

KEYWORD: *Shambu Hospital, ART Regimen, Regimen change.*

1. INTRODUCTION

1.1 Background

Human Immune Virus (HIV) is responsible for a worldwide pandemic and it is the cause of Acquired Immune Deficiency Syndrome (AIDS).[1] According to latest statistics 33.4 million individuals worldwide are living with HIV, of which 15.7 million (47%) are women and 2.1 million (6.3%) are children under 15 years. In addition there are 2.7 million new infections and

2.0 million deaths from AIDS worldwide, albeit recent improvements in access to Antiretroviral Therapy (ART). About 22 million people have died from the HIV/AIDS worldwide since the beginning of the pandemic in the early 80s The proportion of females infected is becoming increasingly significant, with 55% of the infection from Sub-Sahara Africa in 1999 being attributed to women.[2]

Sub-Sahara Africa remains the region most heavily affected by HIV. 1.9 million people living in sub-Sahara Africa, become newly infected with HIV, bringing the total number of people living with HIV to 22.4 million. Moreover an estimated 1.4 million AIDS related deaths

occur in sub-Sahara Africa. But the rate of new HIV infections and death has slightly declined as a result of improved access to ART.[3]

In Kenya, already more than 2 million people are estimated to have been infected from 1985 when the first case of AIDS was reported.[4]

The HIV/AIDS epidemic in Ethiopia continues to pose a threat to the lives of its people. According to the single point estimate in 2007, 977,394 people are living with the virus in Ethiopia. Resulting, a prevalence rate of 2.1% (1.7% among males and 2.6% among females; 7.7% urban and 0.9% rural areas) for a total estimated population of 73 million. The number of new infections is 125,528 including 14,147 HIV positive births of which females' account 57.4%.[5]

The remarkable increase in access to life-saving ART continued in 2012. Fully 1.6 million more people were receiving ART in low- and middle-income countries at the end of 2012, compared with a year earlier – the largest annual increase ever – with the greatest contribution coming from the WHO African Region. The 300 000 people who were receiving ART in low-and middle-income countries in 2002 increased to 9.7 million in 2012.(22) Since beginning of Highly Active.

Antiretroviral Therapy (HAART) in 1996, there have been dramatic declines in morbidity and mortality due to HIV. But these advancements were not without a cost in terms of drug resistance and side effects.[6]

A concern about these negative effects has lead to a more conservative approach to the timing of initiation of therapy and to clinical trials of intermittent therapy in an attempt to decrease the total exposure to drugs over time. ART brings a complex series of choices; when to initiate therapy, what regimen to use, which class of drugs to use, when to change therapy, and which alternative drugs to use.[7]

According to the Standard Treatment Guideline of Ethiopia; the criteria for initiating ART for adults and adolescents are; 1) if CD4 testing is available (a) WHO stage IV disease irrespective of CD4 cell count. (b) WHO stage III disease with CD4 cell counts below 350/mm3. 2) If CD4 testing unavailable; WHO stage III and IV disease irrespective of total lymphocyte count or WHO stage II diseases with a total lymphocyte count bellow 1200/mm3.[8]

Accordingly, the first line ARV regimen in Ethiopia include a triple therapy, two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Protease Inhibitor (PI), if this is not possible, a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or else a triple therapy of three NRTIs. Based on the guideline, common ART regimens in Ethiopia are;TDF/FTC/EFV, AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/NVP or D4T/3TC/EFV.[9]

There are many factors that lead to the ineffectiveness of Antiretrovirals (ARVs) and change in the combinations. Rationale for treatment switch may be; either pre-emptive (risk of long term toxicity, poor adherence, desire for pregnancy, a sub-optimal regimen, co-morbidity, etc.), when virological suppression is usually retained or reactive to virological rebound or (because of resistance or poor adherence) or an established acute and/or chronic toxicity.[10]

Toxicity or Adverse Drug Reaction (ADR) starting from simple rash up to life threatening adverse effects like hepatotoxicity, mitochondrial damage and bone marrow toxicity, create adherence and compliance problems.[11]

1.2 Statement of the Problem

After the introduction of ART, the overall AIDS related morbidity and mortality have been markedly decreased. But it is still high in sub-saharan Africa. Africa is the region most affected by virus. The HIV/AIDS epidemics spreading through the countries of sub-saharan Africa. Africa's HIV/AIDS epidemic has had important effects on society, economics, and politics in the continent.[3]

According to single point estimate in 2007 based on AIDS in Ethiopia 6th report, it was estimated there were 977,394 people living with the virus, and of these 258,264 require ART. From this data we can understand that how HIV is a major problem.[12]

There are many factors that lead to the ineffectiveness of ARVs and lead to change in the combination. Rational for treatment switch may be; either pre-emptive (because the risk of long term toxicity, poor adherence, a desire for pregnancy, a sub-optimal regimen, co morbidity, etc) when virological suppression is usually retained or reactive to virological rebound or (because of resistance or poor adherence) or an established acute and/or chronic toxicity.[10]

Toxicity or ADR create adherence problems and affect patients` willingness to take drugs. Starting from simple rash up to life threatening adverse effects like hepatptoxicity, mitochondrial damage and bone marrow toxicity.[13]

1.3 Significance of the Study

Except a study conducted in tertiary care Hospital in southern part of Ethiopia (Woldmedhin and Wabe, 2012), the pattern of modification of ART regimen and factors responsible for the modification are not well studied and data on modification of HAART are scarce in Ethiopia. Furthermore, no study focuses on modification of ART regimen in primary care hospitals which are fundamental in the health delivery system, serving a catchment area of 250,000 populations (Meseret Wube and Andualem, 2013).

Thus, ART brings a complex series of choices; when to initiate therapy, what regimen to use, which class of drugs to use, when to change therapy, and which alternative drugs to use. Therefore, the aim of this study was to assess reasons for initial ART regimen change in Shambu Hospital. This study would provide a valuable assistance to the concerned organizations especially for health facilities in handling the causes for switching and making the possible amendment.

This study also can potentially provide a long term strategic approach to initial and subsequent decision regarding ART. Moreover, the result would be of paramount importance for being as a baseline for further study.

2. LITERATURE REVIEW

According to the study conducted in Canada, to assess the rate of discontinuation and modification of HAART, as a result of ARV intolerance, the discontinuation and modification rate of HAART regiment among the cohorts ranged from 8-59% (median 33%). The main reason for HAART modification was ARV toxicity / intolerance, which accounted for 20-78% of all modification, followed by therapeutics failure, which accounted for 9-60% of all modification. In general, modification caused by ARV toxicity /intolerance occurred with in the first three months of initiation, whereas treatment failure led to modification of HAART within six to eight months.[14]

An observational cohort of adults with HIV in the Asia-pacific [on TREAT Asia HIV observational data base (TAHOD)] studied to examine the frequency that doctors changed ART regimen after documenting treatment failure and to find out what factors influenced when switches made, among 2446 patients who started ART, 447 were found to have developed treatment failure, with about eight out of hundred patients failing in the first year on treatment. But only fifty two of hundred patients who failed had their treatment changed with in a year the rest of the patients were continued of a failing regimen. Patients who had a more advanced HIV disease and a lower CD4 count and higher HIV Viral load at failure were more likely to have their ARV drugs changed after failure were documented.[15]

According to a study conducted on reasons for modification and disconfirmation of ARV regimens in association with adverse effect (AE), treatment failure, and cost among patients in Southern India, all previously ARV Naïve patients who initiated HAART (N=1443) and had at least one follow up visit were evaluated and the median CD4 count at the time of initiating HAART was 108 cells micro litter. The most common first line regimens were D4T/3TC/NVP.

(63%), AZT/3TC/NVP (19%), D4T/3TC/EFV (9%) and AZT/3TC//EFV (4%). According to this study 20% of patients modified their first line regimen. The most common reason for modifying therapy was the development of adverse effects (64%), followed by cost (19%) and treatment failure (14%), with the median times to modify therapy being 40,151, and 406 days, respectively. Common AEs were itching, and/or skin rash (66%), hepato toxicity (27%) and anemia (23%).[16]

A Study conducted to assess the prevalence of adverse reaction to generic antiretroviral ,in Colorado, among 300 patients receiving NVP or EFV with 3TC and AZT/D4T, after the time of completion of follow up, of a median of 8 months,235 patients were receiving NVP based regimen and 65 took EFV-based regimen. During follow up period, 47 patients (11.5%) had changed at list one drug from previous regimen, an account of toxicity, example, AZT/D4T, and vice versa. The reason for these changes were lipo dystrophy in 15, skin rash in 10 (including one with Stephen Johnson syndrome), anemia in seven , peripheral neuropathy in six, occurrence of TB soon after starting ART in three, sever dizziness and suicidal thoughts in two each and excessive vomiting in one. Among patients receiving NVP based combination, fifteen had rash, six had peripheral Neuropathy, and five had muscle pain. Among those receiving EFV, five had headache, six had skin and nail pigmentation, and one had mildly deranged liver function. None of these individual can change their regimen as they had no finance and also that the national program did not provide any alternative.[17]

A study conducted on discontinuation and Modification of HAART in Uganda, out of 656 patients, the median CD4 cell count at last measurement was 175 cells/micro liters. The largest proportion of respondents (83.8%) received NNRTI based regimens. According to this study, 94(13.7%) patients had ever discontinued therapy; whereas 175(25.5%) had ever modified their initial HAART regiment. The most frequent cited reason for discontinuing therapy was cost (43%). The second most commonly cited reason was side effect and toxicity (21.1%), whereas the most common reasons for modifying therapy was to avoid side effects (71.8%) and cost (23.3%).[18]

According to study done in cote divore, to determine the rates and causes of first ART changes in HIV infected adults, two thousand and twelve HIV infected adults (73%) women initiated ART. At base line, 9% of all patients were on treatment for TB and 3% women were pregnant. First line ART consisted of two NRTI (58% D4T /3TC, 42% AZT/3TC) and EFV (63%), NVP (32%) or IDV (5%). The median follow up time was 16.9 months. During this time, 205 (10%) patients died and 265 (13%) were lost to follow up. Over all, the rate of treatment modification was 20.7%/100 patients /ears. The most common modification were drug substitution for intolerance (treatment failure, (12.4/100 patients years), pregnancy (14.5/100 patients years) and TB (2.5/100 patients-years). The rate of intolerance related substitution were 17.9/100 patients years for D4T,

6.3/100 patients years for NVP, 3.9% patients years ZDV and 0.1/100 patient years for EFV. Twenty percent of EFV substitution resulted from pregnancy and 18%, NVP substitution was related to TB treatment.[19]

According to research done on Successes, challenges, and limitations of current antiretroviral therapy in low-income and middle-income (LIMC) countries, in Malawi, a recent data from the national ART programmed over 100 000 patients started on standard first-line D4T, 3TC, and NVP from 2004 to 2007 showed that, 64·9% of patients were kept alive on ART; 96·4% on first-line, 2·9% on first-line substitutions, with only 0·3% switching to second-line therapy. Despite this success, switching of first-line ART due to toxic effects and drug interactions (e.g., with ant tuberculosis medications such as rifampin) can occur, potentially limiting the durability of fixed-dose combinations. Comorbidities such as tuberculosis are, therefore, yet another consideration when deciding the best time to initiate ART and the choice of first-line regimen.[20]

A Study conducted to assess determinants of survival in adult HIV patients on antiretroviral therapy in Shashemene and Assela hospitals a total of 290 patients were initiated with ART in both facilities during the study period. Data available for analysis included 272 ART patients, of these, the initial ART regimen was changed for 32 (12%) of the patients during the 2-year follow-up period. The main reasons for regimen change were 'toxicity' in 55% of the cases, followed by 'new TB diagnoses' in 29% of the cases for which NVP-based regimens were switched to EFV-based regimens. The AZT/3TC/NVP regimen was significantly more associated with subsequent regimen change compared to other regimens, for toxicity reasons (p=0.029). The main adverse effect was anemia due to AZT.[6]

According to the study conducted on Factors determinant for change of initial antiretroviral treatment regimen in clinic of Mekele Hospital, 105 patients' records were sampled and studied. Twenty one (20%) of the patients had changed their initial ART regimen and about three-fourth 15 (71.4%) of the reasons for change was attributable to toxicity while 3 and 2 were due to treatment failure and pregnancy respectively.[21]

According to study conducted on The Reason for Regimen Change Among HIV/AIDS Patients Initiated on First Line HAAR Therapy in southern Ethiopia, A total of 340 patient cards were assessed. The majority of the patients (69.29%) were females. The most common first regimen, before the first switch, was stavudine / lamivudine / nevirapine (D4T/3TC/NVP) (54.70%) and stavudine / lamivudine / Efavirenz (D4T/3TC/EFV) (20.88%). The main reasons for modification were toxicity, comorbidity, pregnancy, and treatment failure. The main types of toxicities observed were peripheral neuropathy (36.52%), rash (17.83%), and anemia (17.39%).[22]

A study conducted on causes for antiretroviral regimen change among HIV/AIDS patients in Addis Ababa,(St. Paulo's Hospital, Ethio-Tebib Hospital and Addis Ketema Health Centre) A total of 300 patient information cards were reviewed. Regarding to the initial regimen, 189 (63%) patients were on D4T/3TC/NVP, 53 (18%) were on D4T/3TC/EFV, 39 (13%) were on AZT/ 3TC/NVP and 19 (6%) were on AZT/3TC/EFV. The common reasons reported for modification of initial regimens were toxicity 195 (65%), co-morbidity 75 (25%) and planning pregnancy or being pregnant 15 (5%), treatment failure 9 (3%) and adherence difficulty 6 (2%). From all toxicities 195 (65%) reported, peripheral neuropathy accounting 77 (39%) was the most commonly followed by rash 39 (20%), anaemia 26 (13%) and central nervous system manifestations 22 (11%).[23]

According to the study conducted in Nekemte hospital, to assess ART regimen change among HIV/AIDS patients, the main reasons for modification of therapy were toxicity (80.3%), pregnancy (6.3%), new TB (5.6%), stock out (4.9%) and treatment failure (2.8%). The main toxicity observed was lipoatrophy (58.8%) followed by rash (12.3%) and CNS toxicity (11.4%). Toxicity was the main reason for initial regimen modification. D4T based regimens had high incidence of lipoatrophy.[24]

3. OBJECTIVES

3.1General Objective

The general objective of this study was to determine the spectrums of ART regimen change and contributing factors among patients with HIV/ADS in Shambu Hospital.

3.2 Specific Objectives

- To identify common reason for ART regimen change. To identify the type of regimens mostly changed.
- To asses duration for how long patients take initial regimens. To determine magnitude of ART regimen change.

4. METHODOLOGY

4.1 Study setting

The study was conducted in Shambu Hospital, Shambu town, Horro Guduru Wollega zone, Oromia regional state, North West Ethiopia which is found at 315 km from Addis Ababa. According to the central statistical Agency of 2013 G.C, the current population size of Shambu is 100,330. The dominant ethnic group is Oromo. The town has governmental and private organizations/ service providers to the community such as Government Hospital and Health center, elementary, Junior Secondary and preparatory schools and colleges. Telephone, electric, banks, post office, private pharmacy, clinics, drug vendors, etc are from the most prominent mentionable services provided in Shambu town(Central

statistical authority 2000. Statistical abstract 1999. Addis Ababa Ethiopia CSA).

Shambu Hospital has many departments and wards like Outpatient department (OPD), medical ward, gynecology and obstetrics ward, pediatrics ward and surgical ward. It delivers diversified health services and clinics including the emergency services, eye clinic, dental clinic, mother and child health (MCH), psychiatry clinic, laboratory, X-ray, and follow up of chronic disease like TB and HIV AIDS. The Hospital possesses outpatient, inpatient, emergency and ART pharmacies.

4.2 Study design and period
A retrospective cross sectional study was done by reviewing patient information sheet from January 1, 2008 to December 31, 2016.

4.3 Source Population
All patient information sheets of HIV/AIDS patients who take HAART in Shambu General Hospital from January 1, 2008 to December 31, 2016.

4.4 Study Population
The study population was patient information sheet of HIV/AIDS patients who had undergone switching HAART regimen in Shambu General Hospital.

4.5 Inclusion and Exclusion criteria
4.5.1 Inclusion criteria
- All HIV/AIDS patients who are on ART drugs and are undergone spectrum of therapeutic change in Shambu Hospital.
- Patients change only initial regimen.

4.5.2 Exclusion criteria
Those patients who undergone regimen change more than one times. All HIV/AIDS patients on ART drugs who are less than 18 years old.

4.6 Study variable
4.7.1 Dependant Variables
Change of regimen
Prevalence of regimen change

4.7.2 Independent Variables
- Age Sex
- Type of initial regimen Pregnancy
- Co morbidity

4.7 Sample size and sampling technique
No sampling technique was done because all patients who had changed their initial regimen from January 1, 2008 to December 31, 2016 were included

4.8 Data collection process.
Data was collected using data collection format. A well-structured data collection format containing the variables to be measured are designed, developed and utilized by the principal investigator.

4.9 Data analysis and presentation
The data's were categorized and analyzed manually using calculator for statistical analysis. The result was interpreted and presented using tables and figures.

4.10 Quality assurance
The clarity and completeness checkup of data collection formats was under taken before the actual data collection and data clearing was done every day, formats with insufficient information was excluded from the study to avoid error. Then collected data was processed and retained cautiously in the line of its objective.

4.11 Ethical consideration
A formal letter was written department of pharmacy of Shambu Hospital to Shambu Hospital Medical Director in order to get permission to conduct the study. The confidentiality of patients is secured throughout the study periods without writing full patient names by using codes.

4.12 Operational definition
Anti-Retroviral Therapy: Treatment that suppresses or stops a retrovirus. One of the retrovirus is the human immunodeficiency virus (HIV) that causes AIDS.

Drug Side effect: any unwanted effect of a pharmaciteutical product occurring in doses normally used by a patient which is related to pharmacologic property of the drug.

Highly active antiretroviral therapy: a combination of drugs including NRTIs, NNRTIs and Protease inhibitors.

Regimen: a drug or combination of drug used for one course of treatment.

Regimen change: In this study, regimen change refers to change in either of the following: dose, frequency and/or change or modification of one or more drugs used in the possible combinations of either of first line drugs used in ART. It also includes a change of entire regimen within first line or from first line to second line.

Treatment Failure: can be defined as a suboptimal response to therapy. It is often associated with virologic failure, immunologic failure and/or clinical progression (STG FOR GENERAL HOSPITALS 2014)

Immunological failure: is fall of CD4 count to baseline (or below) or 50% fall from on-treatment peak value or persistent CD4level below 100 cells/mm3 (STG FOR GENERAL HOSPITALS 2014).

Clinical failure: is either occurrence of new or recurrent stage4 condition like TB, candidacies, pneumonia, herpes simplex, toxoplasmosis, etc (STG FOR GENERAL HOSPITALS 2014).

4.14 Limitation of the study

The findings of this study should be interpreted with some limitations. These include, lack of appropriately filled patient information sheet, and the retrospective study might not allow for a direct investigation of causal relationship between the factors studied and the outcome of interest. The study collected the main reasons as reported by physician for modification of treatment, but reasons for modification are often interrelated.

5. RESULTS

Demographic Characteristics

The mean age of patients was 39 years. Majority of the patients (%) were in the age range of 20-39 years majority (%) of the patients were females, as shown in *Table 1*.

Table 1: Age and Sex distribution of the HIV/AIDS patients who changed their initial regimen Shambu Hospital General from January 1, 2008 to December 31, 2016.

Demographic characteristics Age group		Frequency	%
20-24		11	9.5
25-29		24	20.7
30-34		37	31.9
35-39		20	17.2
40-44		12	10.3
45-49		6	5.2
50-54		3	2.6
55-59		2	1.7
≥65		1	0.9
Sex	Female	65	56
	Male	51	44

WHO Clinical Stage and CD4 Count

A majority of the patients % of patients were WHO clinical stage III, while were WHO clinical stage IV as depicted in *Fig- 1*. Most patients (%) the initial CD4 count was not recorded and (%) had CD4 count bellow 350 cells/mm3, illustrated in *Fig-2*

Table 2: Initial WHO clinical stage study population in Shambu General Hospital from January 1, 2008 to December 31, 2016.

WHO stage	Frequency	%
I	34	29.3
II	14	12.1
III	55	47.4
IV	13	11.2

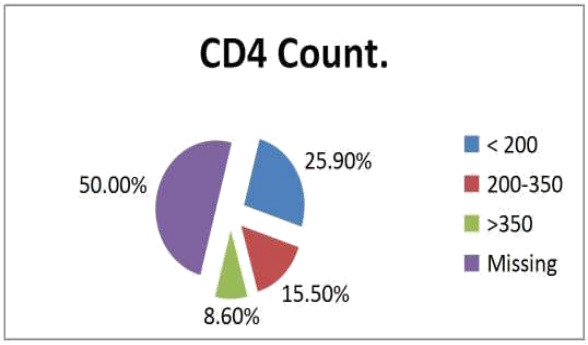

Fig 2: CD4 count of HIV/AIDS patients who changed their initial regimen in Shambu General hospital, January 1, 2008 to December 31, 2012.

Antiretroviral Treatment Regimens and Causes of Change

A majority (50 %) of the patients were on D4T/3TC/NVP at the beginning of the antiretroviral treatment and the rest were on AZT/3TC/NVP (%), D4T/3TC/EFV (%), AZT/3TC/EFV (%), TDF/3TC/EFV (%), TDF/3TC/NVP and TDF/3TC/LPV/r (%) as shown in *Table 3*

The main reasons for modification of treatment regimen were toxicity/side effects (%), new drug available (%), and treatment failure (%) [Clinical %, immunological %], new TB (%), stock out (%), and pregnancy (%) as shown in *Table 3 or Fig-3.*

Table 3: Common reasons for modification by first treatment regimens of HIV/AIDS patients who changed their initial regimen Shambu General Hospital from January 1, 2008 to December 31, 2016.

Initial regimens	Reasons					
	Toxicities N(%)	Pregnancy N(%)	New drug N(%)	Treatment failure N(%)	NewTB N(%)	Stock out N(%)
D4T/3TC/NVP	27 (43.5)	-	29 (90.6)	1(9)	1(12.5)	-
D4T/3TC/EFV	10 (16.1)	-	3(9.4)	2(18.2)	-	-
AZT/3TC/EFV	5 (8.1)	1(100)	-	6(54.5)	-	-
AZT/3TC/NVP	15 (24.2)	-	-	2(18.2)	7(87.5)	1(50)
TDF/3TC/NVP	1 (1.6)	-	-	-	-	-
TDF/3TC/EFV	3 (4.8)	-	-	-	-	1(50)
TDF/3TC/LPV/r	1 (1.6)	-	-	-	-	-

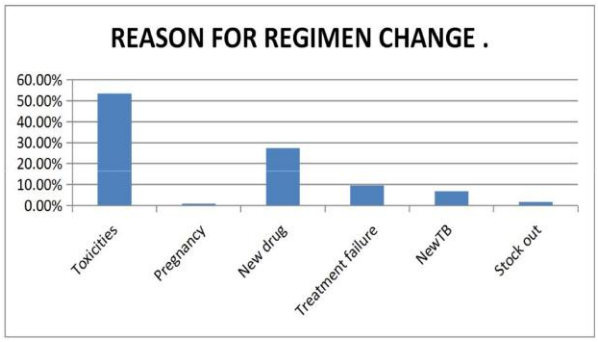

Fig 3: Common reasons for modification by first treatment regimens of HIV/AIDS patients who changed their initial regimen Shambu Hospital from January 1, 2008 to December 31, 2016.

From all toxicity reported, peripheral neuropathy accounted % being the most common followed by rash (%) and Anemia (%) as depicted in *Fig-4.*

Among toxicities observed 43.5% were due to D4T/3TC/NVP, and the remaining %, %, %, %, % and were due to AZT/3TC/NVP, D4T/3TC/EFV, AZT/3TC/EFV, TDF/3TC/EFV, TDF/3TC/NVP, and TDF/3TC/LPVr respectively. D4T containing regimens accounted for % of the peripheral neuropathy observed, while NVP containing regimens accounted for % of the rashes reported and AZT containing regimens accounted for % of the Anemia observed (*Table 3*).

Table 4: Toxicities reported as reason for initial treatment regimen change by first treatment regimen of HIV/AIDS patients who changed their initial regimen Shambu General Hospital from January 1, 2008 to December 31, 2016.

Toxicities	**Initial Regimens**						
	D4T/3TC/NVP N (%)	**D4T/3TC/EFV N (%)**	**AZT/3TC/EFV N (%)**	**AZT/3TC/NVP N (%)**	**TDF/3TC/NVP N (%)**	**TDF/3TC/EFV N (%)**	**TDF/3TC/LPV/r N (%)**
Nausea	-	-	-	2(100)	-	-	-
p.neuropathy	22(68.7)	10(31.3)	-	-	-	-	-
Numbness/ti	3(100)	-	-	-	-	-	-
ngling							
Diarrhea	-	-	-	-	-	1(100)	-
Lipoatrophy	1(100)	-	-	-	-	-	-
Anemia	-	-	4(50)	3(37.5)	-	-	1(12.5)
Rash	1(8.3)	-	-	10(83.3)	1(8.3)	-	-
Jaundice	-	-	-	-	-	-	-
Anxiety/nigh	-	-	1(33.3)	-	-	2(66.6)	-
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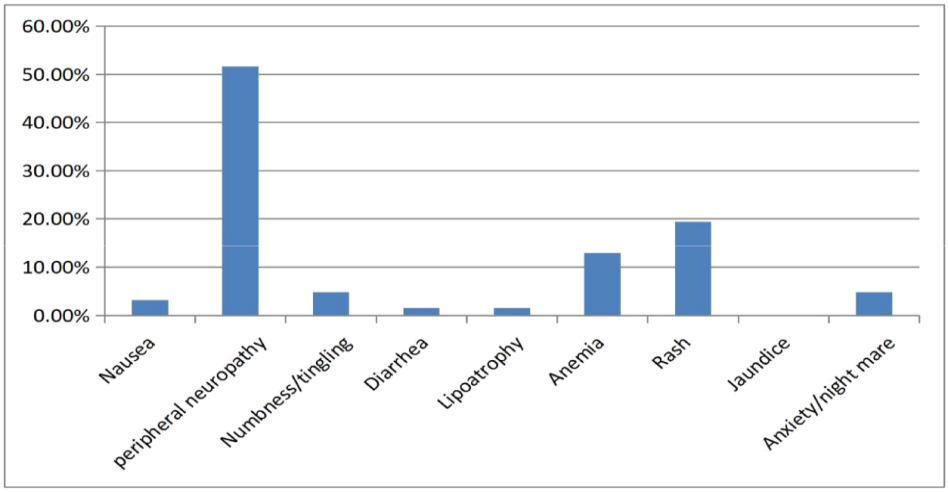

Fig. 4: Toxicities reported as a reason for initial treatment change in Shambu General hospital, January 1, 2008 to December 31, 2016.

Duration of Initial Antiretroviral Treatment before Regimen Change

In 72.4% of patients initial treatment regimen was modified after six months, while, in % and % of patient's initial regimen was modified less than a month and within two to three month time respectively

Table 5: Weeks on initial antiretroviral treatment by treatment regimen of HIV/AIDS patients who changed their initial regimen Shambu Hospital from January 1, 2008 to December 31, 2016.

Initial Regimens	Number of the patient stayed weeks on initial ART regimen					
	< 4	4-8	8-12	12-16	16-20	>24
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
D4T/3TC/NVP	3(30)	1(16.6)	-	-	1(25)	53(63.1)
D4T/3TC/EFV	-	-	-	-	1(25)	14(16.6)
AZT/3TC/EFV	-	1(16.6)	1(14.3)	1(20)	1(25)	8(9.5)
AZT/3TC/NVP	5(50)	3(50)	6(85.7)	3(60)	-	8(9.5)
TDF/3TC/NVP	-	1(16.6)	-	-	-	-
TDF/3TC/EFV	2(20)	-	-	-	1(25)	1(1.2)
TDF/3TC/LPV/r	-	-	-	1(20)	-	-

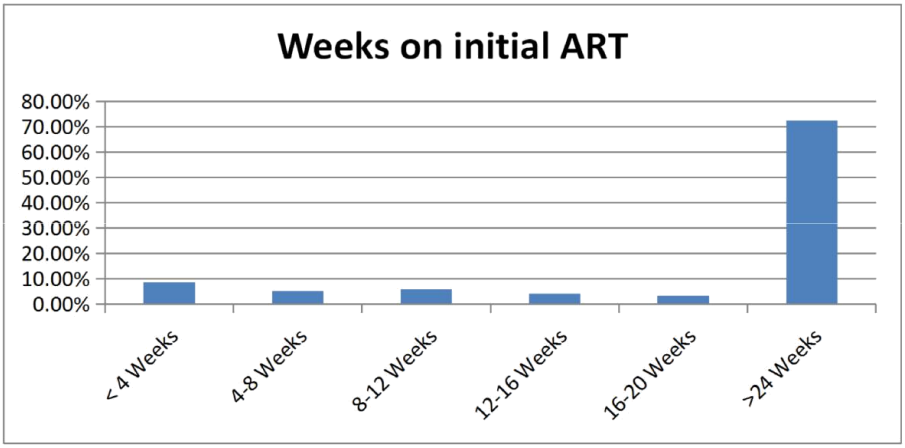

Fig. 5: Percentage of HIV/AIDS patients on initial ART regimen per duration of therapy before switching in Shambu General Hospital, January 1, 2008 to December 31, 2016.

Among the initial regimen changes after six months of therapy % and % were due toxicity and new drug available respectively as shown in Tabel-6.

Table 6: Common reasons for modification by duration of initial regimen of HIV/AIDS patients who changed their initial regimen Shambu Hospital from January 1, 2008 to December 31, 2016.

Reasons	Number of the patient stayed weeks on initial ART regimen					
	< 4	4-8	8-12	12-16	16-20	>24
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Toxicities	9(14.5)	5(8.1)	7(11.2)	-	5(8.1)	36(58.1)
Pregnancy	-	-	-	-	-	1(100)
New drug	-	-	-	-	-	32(100)
Treatment failure	-	-	-	-	-	11(100)
New TB	1(12.5)	1(12.5)	1(12.5)	-	-	5(62.5)
Stock out	-	-	1(50)	-	-	1(50)

6. DISCUSSION

A majority of the patients, 72.9 % of the patients in this study were on D4T based regimens, D4T/3TC/NVP (50 %) and D4T/3TC/EFV (12.9 %) While the rest were on AZT/3TC/NVP (21.5%), AZT/3TC/EFV (10.3 %), TDF/3TC/EFV (3.4 %), TDF/3TC/NVP and TDF/3TC/LPV/r (0.9%) each. The result of this study was not consistent with the studies done in Southern India (Kumarasamy *et al.*, 2006), Malawi (Bartlett and Shao, 2009), Cote d'Ivoire (Mess *et al.*, 2010), southern Ethiopia (Woldmedhin and Wabe, 2012) and Addis Abeba (YOHANNES T. JIMA,2013) where D4T/3TC/NVP accounts for 63%, 64.9%, 58%, 54.70% and 10 % respectively. Difference in WHO clinical stage, contraindications, co morbid situations, drug-drug interaction due to co morbidities and stock status could be the possible factors that might have contributed to the variation.

New drug available (27.5 %), and treatment failure (9.5 %) were the second and the third causes of ART regimen switching, opposite to the studies in Uganda (Kiguba, 2007) and Southern India (Kumarasamy *et al.*, 2006), Addis Abeba (YOHANNES T. JIMA,2013), southern

Ethiopia (Woldmedhin and Wabe, 2012), and Nekemte (Meseret Wube, Andualem,2013).

From all toxicities, peripheral neuropathy was the most common reason for modification, similar to studies in Addis Abeba (YOHANNES T. JIMA, 2013) ,*and* southern Ethiopia (Woldmedhin and Wabe, 2012),but opposite to studies in Southern India (Kumarasamy *et al.*, 2006),Colorado(Wanchu AJ, Pareek S, and Banbery P,2006) ,and Nekemte (Meseret Wube, Andualem,2013). D4T containing regimens accounted for 100% of the peripheral neuropathy observed, This is most probably due to the reason that most of the patients in this study were on D4T-based regimen of D4T/3TC/NVP and D4T/3TC/EFV, were initially with advanced HIV infection, and increased duration of ART are also significantly associated with peripheral neuropathy (van Griensven *et al.*, 2007).

Rash and anemia were second and third most causes for modification. Rash was mainly due NVP containing regimen AZT/3TC/NVP (83.3%), D4T/3TC/NVP (8.3 %),and TDF/3TC/NVP(8.3%) regimens which coincides with a study that stipulates the mechanism of NV P induced skin rash (Popovic *et al.*, 2006).

Anemia were seen in 50%, 37.5%, and 12.5% of the patients on AZT/3TC/EFV, AZT/3TC/NVP and, TDF/3TC/LPV/r respectively. Unlike the Peru's study, Study done in Peru reported anemia as a main reason for discontinuation, and associated this finding with the use of standard 600 mg ZDV in low weight patients (Bangsberg *et al.*, 2006), in this study, was likely to be due to lack of adequate baseline anemia assessment and the fact that no close monitoring of anemia at the study site.

CNS toxicities were the fourth causes for modification. Anxiety/ nightmares and Numbness/tingling were seen in 4.8%, 3.2% and 1.6% of the patients on D4T/3TC/EFV, TDF/3TC/EFV, and AZT/3TC/EFV respectively. Which may be due to EFV and studies show that EFV is associated with CNS toxicity, moreover, a CYP2B6 allelic variant is more common in African-Americans which is associated with significantly greater EFV plasma exposure (Haas *et al.*, 2004).

Availability of new drug was the second major reason for modifying ART drugs in this study, Unlike to the studies in Uganda (Kiguba, 2007) and Southern India (Kumarasamy *et al.*, 2006), Addis Abeba (YOHANNES T. JIMA, 2013), southern Ethiopia (Woldmedhin and Wabe, 2012), and Nekemte (Meseret Wube, Andualem,2013). This was likely to be due to the remarkable increase in access to life-saving ART continued in 2012. Fully 1.6 million more people were receiving ART in low- and middle-income countries at the end of 2012, compared with a year earlier – the largest annual increase ever – with the greatest contribution coming from the WHO African Region(Journal of Glob Health Action. 2010).

9.5% of patients changed their initial regimen due to treatment failure which occurred in patients on AZT/3TC/EFV(54.5%), AZT/3TC/NVP(18.2%), D4T/3TC/EFV(18.2%), and D4T/3TC/NVP(9%). This may be explained by differences in primary resistance to NRTIs or NNRTIs containing regimens (Dorrucci *et al.*, 2001).

Co-morbidities in patients with advanced disease and concurrent treatments for opportunistic diseases may affect antiretroviral tolerance and thereby increase risk of toxicities (Cesar *et al.*, 2010). 6.9% of the patients changed their regimen due to tuberculosis and it was the only co morbidity reported in this study which is consistent with the study in Cote d'Ivoire (Mess *et al.*, 2010) and hospitals in southern Ethiopia (Alemu and Sebastián, 2010; Woldmedhin and Wabe, 2012). 87.5%, 12.5% of the patients on AZT/3TC/NVP and D4T/3TC/NVP were switched. The most probable reason being over lapping drug toxicity of NVP with anti TB drugs and potential for drug interaction as TB drugs like rifampine is enzyme inducers.

Contrary to studies in Southern India (Kumarasamy *et al.*, 2006) and Uganda (Kiguba, 2007) cost was not a major reason for ART regimen change because ARV drugs are provided to patients free of cost.

Despite the cost free service stock out problems accounted 1.7% of the treatment regimen Change which is a result of poor pharmaceutical stock management system either at the hospital or national level.

Unlike the studies in Cote d'Ivoire (Mess *et al*, 2010), Addis Abeba (YOHANNES T.JIMA, 2013), Nekemte (Meseret Wube, Andualem, 2013), and southern Ethiopia (Alemu and Sebastián, 2010; Woldmedhin and Wabe, 2012), Pregnancy didn't account for the lion's share for regimen switch in this study. Only 0.9% of patients changed their initial regimen due to Pregnancy which occurred in patients on AZT/3TC/EFV. This switch was due to the recommendation of the Ethiopian guideline to avoid teratogenic effect of EFV in pregnant women during the first trimester. Contrary to the recommendation of the guideline, current studies reveal no increased risk of overall birth defects in women exposed to EFV during the first trimester of pregnancy (Ford *et al.*, 2010).

A noticeable link was observed between common reasons for Modifications of regimen and initial regimen. Similarly, toxicities like peripheral neuropathy, rash and anemia were associated with respective initial regimen. However, weeks of stay on initial regimen had no important association with initial regimen rather weeks of stay on initial regimen had important association with respect to common reasons for regimen changes because

the longer stay the higher probability of regimen change. This was consistent with the findings reported in the Addis Abeba (YOHANNES T.JIMA, 2013), and southern Ethiopia (Alemu and Sebastián, 2010; Woldmedhin and Wabe, 2012).

7. CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The result of this study indicated toxicity as the main reason for modification of initial ARV drugs among the study population. Peripheral neuropathy was the leading cause for modification of HAART, D4T containing regimens accounted for 100% of the peripheral neuropathy observed, while NVP containing regimens accounted for 99.9% of the rashes reported and AZT containing regimens accounted for 100% of the Anemia observed. While new drug, treatment failure, new TB, stock out and, pregnancy, were the rest reasons for initial antiretroviral regimen changes in this study. Majority (72.4%) of patients their initial treatment regimen was modified after six months, of the patients who changed their initial regimen after six months 63.1% and 16.6% were on D4T/3TC/NVP and D4T/3TC/EFV respectively. Tuberculosis was the only co-morbidity disease reported in this study and all patients who switched were due to occurrence of tuberculosis after starting ARV drugs on NVP based regimen.

7.2 Recommendations

Proper clinical recording, and there had to be sufficient qualitative and well-effective laboratory equipment. Updating ART guidelines as pharmacotherapy is dynamic and improvements in pharmaceutical procurement and stock management systems at hospital or national level, As much as possible, clinicians should stick to the national antiretroviral drug use guidelines for the management and follow up of patients receiving HAART are recommended.

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