Reasons for antiretroviral drug switch among patients attending at the antiretroviral therapy clinic of Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Haftom Niguse, entitled: "*Reasons for antiretroviral drug switch among patients attending at the antiretroviral therapy clinic of Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia*" and submitted in partial fulfillment of the requirements for the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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Abstract

Background: The Human Immunodeficiency Virus (HIV) destroys and impairs the function of immune cells which results in increased susceptibility to a wide range of diseases. HIV continues to be a major global public health issue, having claimed more than 34 million lives so far. Globally there were approximately 37 million people living with HIV and about 15 million (40%) were receiving antiretroviral treatment (ART) at the end of 2014. ART has revolutionized the treatment of HIV and transformed this infection from a fatal to a medically managed disease.

Objective: This study was performed to determine the reasons for anti-retroviral drug changes among patients on follow up at ART clinic, Tikur Anbesa Specialized Hospital.

Methods: The study was a hospital based retrospective cross-sectional study conducted from 10 June to 10 September 2015, using a pre-tested data collecting form and chart review. Among patients who experienced antiretroviral drug switch, 259 were included in the study using systematic random sampling.

Results: The main reasons for initial antiretroviral switches was toxicity (74.1%), undocumented reason (7.3%), adherence difficulty (6.5%), treatment failure (4.2%) and pregnancy (2.3%). The major toxicity types were lipodystrophy (33%) anemia (16.7%), and peripheral neuropathy (15.8%) with Stavudine based regimen being the major (78.5%) toxicity causing anti-retroviral regimen. Among the 259 patients 54 (20.8%) of them switched for the second time 3 (1.2%) for the third time. The main reason for the second switch was toxicity (31.5%), adherence difficulty (20.4%), treatment failure (20.4%) and pregnancy (11.1%).

Conclusion: The reason for initial ARV drug switch was significantly associated to the type of initial ART regimen. The occurrence of second ARV drug switches was associated to the type of ART regimen, clinical stage and duration of stay on firstly switched ART. With few exceptions, almost the entire ART initiation and change pattern was in line with the national and WHO guidelines on the use of antiretroviral drugs.

Key words: *HIV, ARV drug switch, Tikur Anbesa Specialized Hospital, Reason for change*

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Table of contents

List of Acronyms/Abbreviations

AAU	Addis Ababa University
ABC	Abacavir
ADM	Antiretroviral Drug Modifications
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
CD4	Cluster of Difference
ddI	Didanosine
d4T	Satvudine
EFV	Efavirenz
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PI	Protease Inhibitors
PLWHA	People Living With HIV/AIDS

3TC	Lamivudine
TASH	TikurAnbessa Specialized Hospital
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization
VL	Viral Load

List of Tables

List of Figures

1. INTRODUCTION

1.1. Background

The Human Immunodeficiency Virus (HIV) destroys and impairs the function of immune cells. Infected individuals gradually become immune-deficient which results in increased susceptibility to a wide range of infections and diseases. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which can take from 2 to 15 years to develop depending on the individual. AIDS is defined by the development of opportunistic infections, or other severe clinical manifestations and certain cancers [FMHACA, 2014;WHO, 2015].

HIV continues to be a major global public health issue, having claimed more than 34 million lives so far. Globally, 1.2 million people died from HIV-related causes in 2014. There were approximately 36.9 million people living with HIV at the end of 2014 with 2.0 million people becoming newly infected in that same year. About 25.8 million (70%) of People living with HIV are from Sub-Saharan Africa. This region, with only 12% of the global population accounted for 70% of the global new HIV infections in 2014. About 15 million (40%) people living with HIV were receiving ART globally, of which 13.5 million were receiving ART in low- and middle-income countries and about 823 000 were children. The HIV coverage among people with HIV infection eligible for ART in 2012 was 61%. [WHO, 2015]

Ethiopia is among the countries most affected by HIV/AIDS. The existence of HIV infection in Ethiopia was recognized in the early 1980s with the first two AIDS cases reported in 1986. Since then the epidemic has rapidly spread throughout the country. The epidemic peaked in the mid-1990s. Since 2000 the epidemic has declined in major urban areas and stabilized in rural settings [MOH, 2010].

Highly Active Antiretroviral Therapy (HAART) has revolutionized the treatment of HIV and transformed this infection from a fatal to a medically managed disease. But these advancements were not without a cost in terms of drug resistance and side effects [Wilkin et al., 2006]. The advent of potent HAART in 1996 led to a revolution in the care of patients with HIV/AIDS in the developed world. These treatments have dramatically reduced rates of mortality and morbidity and have improved the quality of life of PLWHIV. Most importantly,

through ART, HIV/AIDS which was once an infectious disease with an almost universally fatal outcome has been transformed into a manageable chronic infectious disease. WHO progress report also confirmed increased survival; decreased HIV associated mortality and vastly improved quality of life. ARV drugs give these results by way of suppressing viral replication which then leads to the restoration of number and quality of CD4 cells [Palella et al. 2003; WHO, 2011].

Expanding access to ART is changing the global HIV epidemic in momentous ways. AIDS-related mortality rates are declining rapidly. The scaling up of ART averted an estimated 4.2 million deaths in low- and middle-income countries in 2002–2012.Improved access to ART is resulting in major increases in life expectancy. In South Africa, for example, data from ART programs in three provinces show that the life expectancy of adults receiving ART is about 80% of the normal life expectancy provided they do not start treatment late.[WHO, 2013a]

In Ethiopia, antiretroviral treatment began in 2003 and free ART was launched in January 2005. Since the beginning of HAART, a linear increase has been observed in the number of people living with HIV/AIDS (PLWHA) ever enrolled, ever started and on ART. The number of patients on ART reached 308,860 by the year 2014. As a result of this, there have been dramatic declines in morbidity and mortality due to HIV. Total HIV positive population was 789,960 in 2011 and it is estimated to reduce to 691,073 in 2015. Meanwhile, the new HIV infection was 24,236 in 2011 and declined to 15,073 in 2015. In addition, the annual total AIDS related deaths declined from 13,749 in 2011 to 6,827 in 2015[MOH, 2010;NARC, 2015].

The goal of ART is to attain maximal and durable suppression of the viral replication. Viral suppression enables recovery of the immune response and thereby reduces risk of opportunistic infections (OIs) and death. The effectiveness of ART is assessed by clinical observations, CD4 cell count and determination of plasma viral load. ART initiation should be timed appropriately and not delayed until the immune system is irreversibly damaged. Consideration of the stage of the HIV disease and the degree of immune damage determine the timing of initiation of ART [FMHACA 2014].

Antiretroviral management brings a complex series of choices; when to initiate therapy, what regimen to use, which drugs within each class, when to change therapy, and which

alternative drugs to use [Hammer, 2002]. According to the Standard Treatment Guideline of Ethiopia, 2014; the criteria for initiating ART for adults and adolescents were: WHO stage 3 and 4 disease irrespective of CD4 cell count, CD4 count ≤500cells/mm^3 irrespective of WHO clinical stage and Active TB co-infection with HIV irrespective of CD4 cell count [FMHACA 2014].

Triple combination therapy has been in use for more than two decades globally. Currently, the preferred first regimen triple therapy in Ethiopia is TDF/FTC/EFV or NVP Alternatives are TDF/3TC/EFV or NVP, ZDV/3TC/EFV or NVP. Other options are ABC/3TC/NVP, ABC/3TC/EFV and ABC/3TC/ZDV. The second line regimen consists of ZDV ±3TC +LPV/r (or ATV/r), ZDV+ABC+LPV/r (or ATV/r),TDF/3TC± ZDV + LPV/r (or ATV/r), ABC/ddI /LPV/r (or ATV/r), EFV or NVP / LPV/r (or ATV/r) [FMHACA, 2014].

HAART regimens commonly require changes, which often involve switches of multiple medications simultaneously. A treatment switch may be either because of the risk of acute toxicity, long-term toxicity, treatment failure, poor adherence, a desire for pregnancy, co-morbidity with other chronic diseases or stock out of drugs The approach to switch ART depends on the reason for change, the amount of previous ART experience, and the available treatment options. For example, when patients develop an adverse effect to a drug, effective treatment may be easily accomplished by substituting another agent for the offending drug in the regimen. Patients who have experienced toxicities, treatment failure, and drug resistance during past regimens may require a new treatment regimen [Wilkin et al. 2006; Jima et al., 2013].

Patients should be evaluated after a treatment switch to assess for potential concerns with the new regimen, medication tolerance and conduct targeted laboratory testing. For example, if lipid abnormalities were present and/or were a reason for the ARV change or are a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. If any specific complaints, laboratory abnormalities, or viral rebound are absent at 3-month visit, the patient may resume on a regularly scheduled basis [WHO, 2013a].

The WHO definition treatment failures for the decision to switch ART regimens can be clinical, immunological or virological. Clinical failure is occurrence of new or recurrent clinical event indicating severe immunodeficiency after 6 months of effective treatment. Immunological failure is when CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 ells/mm^3. Finally, a virological failure is when plasma viral load is above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support[WHO 2013b].

There are many factors that may lead to treatment failure such as: inadequate adherence; drug side effects and toxicity leading to poor adherence, drug-drug interaction between the ARVs and other concomitantly administered drugs resulting in sub-therapeutic ARV concentrations, and suboptimal potency of the ARV regimen that will lead to short survival of patient on ART. Virologic failure, immunologic failure and clinical failure have distinct time course and may occur independently or simultaneously. In general, virologic failure occurs first followed by immunologic failure and finally clinical failure. These events may be separated by months to years. The delay between virological and immunological failure carries the risk of exposing HIV to failing regimen. This can lead to development of further cross resistance, which compromises the efficacy of the second line regimen. Thus, viral load monitoring offers the advantages of detecting treatment failure early and preventing accumulation of further resistance mutations. Hence, plasma viral load determination is recommended every six months to identify virological failure early [Katabira& Oelrichs 2007;Petersen et al., 2008].

The value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings. However, most ART programs in resource-limited settings still continue to rely on clinical and immunological monitoring. This limited use of viral load monitoring has been identified as a key reason for the lower than expected rates for switching ART regimens in resource-limited settings [WHO, 2013a].

A patient's changing clinical status often mandates a change in ART. For example, caution should be used with NVP in pregnancy because it has been associated with an increased risk of fatal hepatitis in pregnant women, especially in women with higher CD4 counts. NVP generally should not be initiated in women whose CD4 count is >250 cells/µL. Medications used to treat comorbid illnesses often interact with antiretroviral agents. A prime example is the interaction of

rifampin with both NNRTIs and PIs. This interaction may be avoided by substitution of EFV for NVP, perhaps by dose adjustment of EFV, or by substitution of rifabutin for rifampin in the case of PIs. Other important drug interactions include statins with PIs, oral contraceptives with NNRTIs or PIs, and ergot derivatives with PIs[Wilkin et al., 2006].

Low levels of adherence are associated with drug resistance to medications. The risk of emergence of drug resistance with suboptimal adherence is generally greater in patients taking NNRTIs compared with most PIs. Many patients with stable virologic suppression on more difficult regimens can change to regimens with lower pill burdens and minimal dosing complexity, thus improving adherence and quality of life. In two studies, adherence improved in subjects randomized to switch from a PI to EFV or to ABC compared with those who continued the PI-based regimen. Other investigators have reported improvements in quality of life, as assessed by questionnaires, in two randomized studies in which PIs were switched to NVP or to either NVP or EFV compared with continuing the PI. While changing an ARV regimen for quality-of-life considerations it should be kept in mind the potential for adverse effects of the new regimen [Bangsberg et al., 2006; Wilkin et al. 2006].

1.2. Statement of the problem

The latest advances in ART, regarding both new drugs and fixed-dose co-formulations, have produced significant improvements in adherence and in reducing toxicity. New drug classes (integrase inhibitors) and treatment strategies (protease inhibitor boosting) have made HIV therapy easier for many patients. It may be possible to switch to drugs that are taken less often and/or have a lower pill burden, including fixed dose formulations that combine two or more drugs in a single pill. Treatment simplification usually works best when people are on one of their first regimens and have minimal drug resistance. As a result of the scale-up of antiretroviral treatment (ART) programs and substantial financial support worldwide, an increasing number of HIV-infected individuals in low-income and middle-income countries (LIMCs) now have access to ART. Despite this progress, important questions remain on the best use of ART and how patients should be maintained on a successful regimen.[Bartlett & Shao, 2009]

Antiretroviral treatment change should be done when necessary to spare the future treatment options. The approach to patients who need to switch will differ depending on several issues, including ART experience and available options. Regimen substitution requires adjustment in learning the new medication about the treatment dosing, time of intake and deal with many individual based inconveniences, which might be challenging and reason for non-adherence. Knowing the reasons for ART change may help to minimize the risk factors. These lead to decrease the rate of regimen change, treatment failure, drug resistance, and improve the quality of life the patient [Demessie et al., 2014;Wilkin et al. 2006].

Clinical status, CD4 cell count, and the plasma HIV-1 RNA level can be used in an integrated fashion to determine whether HIV disease is progressing on therapy and whether a change from first-line to second-line therapy should be made. An assessment of adherence to medications should also be made and the remaining treatment options considered. In practice, it is important to assess the adherence level before declaring treatment failure and switch of the drugs. Although virologic, immunologic and clinical non-responses remain even after improving adherence. Clinicians are encouraged to make decisions to change therapy on a case-by-case basis. This is important because a small number of patients may have poor immunologic response despite good virologic suppression and the symptoms of immune reconstitution inflammatory syndrome (IRIS) may be confused with clinical failure[MOH, 2009].

Both early and late switching have advantages and disadvantages. An early switch can preserve treatment options and the patient's ability to effectively respond to second-line ARVs therapy. A late switch allows more patients to stay on first-line therapy, keeping medicine and laboratory monitoring costs down. Moreover, many people only have access to first-line ARVs because of limited availability to second-line drugs. The disadvantages of a late switch are increased risk of accumulating drug resistance and mutations, resulting in fewer choices of active ARVs for second-line therapy. A late switch also increases the possibility of a poor response to the new therapy because the patient may be too ill [WHO 2007].

As a general principle, mild toxicities do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given. Moderate or severe toxicities may require substitution with a drug in the same ARV class but with a different toxicity profile. Example: substitution of Zidovudine (AZT) or Tenofovir(TDF) for Satvudine(d4T) in cases of neuropathy, substitution of TDF or d4T for AZT when anemia occurs and substitution of Nevirapine (NVP) for Efavirenz (EFV) for CNS toxicity. For other toxicities, for which a specific agent cannot be identified as causal, and/or low-grade but intolerable side effects which frequently compromise adherence, a complete regimen switch to the second line drugs is recommended. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved in order to prevent the emergence of drug resistance[MOH, 2009].

Data on modification of ART and factors associated with ARV drug switch are limited among HIV patients in Ethiopia. Most studies in Ethiopia are on small sample of patients who were on ART for less than three years. Tikur Anbesa Specialized Hospital (TASH) is the largest referral hospital in the country. Even though the ART clinic has begun provision of medications since March 2005, as to knowledge of the principal investigator there is no research done regarding pattern of ARV drug switch and the associated reasons for the switch. Thus this study was conducted with an aim to assess the reasons contributing for the change of ART regimen among patients with HIV/AIDS in TASH. As this study included patient data for the past ten years it enables to know the common reasons of ARV drug switch in patients on long period exposure to ART. In addition, this study would identify the extent of second and third time ARV drug switch and the determinant factors associated with these multiple switches. Furthermore, this study elucidates the patterns of ARV drug switches in tertiary hospitals.

1.3. Literature review

Antiretroviral drug modifications (ADM) due to toxicity have been reported to be associated with many factors: demographic characteristics such as female sex, age, ethnicity, genetics, HIV disease status, type of ART, and co-morbidities. It has also been reported that toxicity-related ADM are most frequent within the first 3 months of ART. Majority of the studies, however, have focused on the first event of ADM [Marta, 2013].In a 2010 study of 1318 treatment-naive patients, switches or discontinuations because of drug toxicity occurred at a rate of 22 per 100 person-years. The most frequent adverse effects were gastrointestinal intolerance (29 %), hypersensitivity (18 %), CNS side effects (17 %), and hepatic events (12 %) [Elzi et al., 2010].

A study analyzed 5026 adult HIV infected patients, who were being on ART between 1996 and 2007 in 7 Sites throughout the Caribbean and Latin America. The primary reason for change among HAART initiators were: adverse events (14%), death (5.7%) and failure (1.3%) with specific toxicities varying among sites. After change, most patients remained in first line regimens[Cesar et al. 2010].

A study done in Côte d'Ivoire followed 2012 HIV infected adults initiating ART for a median follow up time of 16.9 months. Overall, the rate of treatment modifications was 20.7/100 patient-years (PY). The most common modifications were drug substitutions for intolerance (12.4/100PY), pregnancy (4.5/100PY) and tuberculosis (2.5/100PY). The rates of intolerance-related substitutions were 17.9/100PY for stavudine, 6.3/100PY for nevirapine, 3.9/100PY for zidovudine and 0.1/100PY for efavirenz[Messou et al. 2010].

In a study done in Mekelle hospital assessed 105 patients' records. About 20 % of the study subjects had changed their initial ART regimen. In 71.4% of the cases the reason for change was attributable to toxicity, with ZDV being the most dominant drug. Treatment failure and pregnancy accounted for14.3% and 9.5%, respectively. Little more than half (54.3%) were initiated on ZDV/3TC/NVP followed by 12.4% TDF/3TC/NVP and 11.4% TDF/3TC/EFV. Anemia and rash were the most commonly reported ADR events [Bayou et al., 2014].

A study done at Bedelle hospital assessed a total of 84 patient cards retrospectively. The most common first line regimen, before the switch, was d4T/3TC/NVP (42.9%) and (d4T/3TC/EFV) (25%). The main reasons for modification were toxicity, comorbidity, pregnancy, and

treatment failure. The main types of toxicities observed were peripheral neuropathy (31%), anemia (27%), and rash (25.4%). d4T-base regimen had the highest hazard for ARV drug switch [Mekonnen & Molla, 2014].

A Hospital based study conducted in Dessie assessed 122 patients who switched initial ART regimen. The most frequent prescribed first regimens before switch were AZT/3TC/EFV (36%),AZT/3TC/NVP (27%), d4T/3TC/EFV (19%) and d4T/3TC/NVP (18%). Toxicity (66%) followed by co-morbidity (14%) and planning pregnancy (11%) were the most common reasons for modification of ART. The main toxicity was anemia (52%) and peripheral neuropathy (9%).Among these patients 8% of the patients had changed their regimen for a second time [Mulugeta & Chane, 2012].

A retrospective cross-sectional study conducted in two primary hospitals and one health center in Addis Ababa reviewed 300 patients in 2010. The most common first regimen before first switch was d4T/3TC/NVP (63%) and d4T/3TC/EFV (18%). The main reasons for modification were toxicity (65%), comorbidity (25%), pregnancy (5%) and treatment failure (3%). The main types of toxicities observed were peripheral neuropathy (39%), rash (20%) and anemia (13.33%)[Jima et al., 2013].

A national review of first treatment change in UK which conducted a case note and questionnaire based audit in 504 patients indicated that virlorogical failure was cited as a reason in 30% of patients with adherence difficulties (14%) treatment simplification (10%), and patient choice (10%)being other reasons given for switching. Among 132 patients for who virological failure was cited as a reason for switching, 72% switched after a resistance test result had been obtained and 9%switched while resistance testing was being performed but before results were available. 3% had a sample stored for future resistance testing, 11%were neither tested for resistance nor had a sample stored, and in 5% the information was unclear[Hart et al., 2007].

An observational cohort study in the Asia and Pacific region indicated that among 2446 patients who initiated ART, 447 were documented to have developed treatment failure(7.8 per 100 person-years). A total of 253 patients changed at least one drug after failure (51.6 per 100 person-years). There was no difference between patients from high- and low-income countries. Advanced disease stage, a lowerCD4 count and a higher HIV viral load were associated with a

higher rate of treatment modification after failure. Compared with patients from low-income countries, patients from high-income countries were more likely to change two or more drugs (67%vs. 49%; P=0.009) and to change to a protease-inhibitor-containing regimen.[Zhou et al., 2010]

A hospital based retrospective cross sectional study done in Raichur, India assessed 3510 patient records and (14.8%) of the patients had changed initial HAART regimen. About one third of the patients (33%) were on AZT/3TC/NVP at the beginning of the ARV treatment and the rest were on d4T/3TC/NVP (25%), TDF/3TC/NVP (23%) and AZT/3TC/EFV (14%), d4T/3TC/EFV (3%), TDF/3TC/EFV (2%).Main reasons for the substitution to HAART regimens were comorbidity (58.26%), followed by adverse drug reactions (ADR) (38.46%) and pregnancy (3.28%).TB was the only major co-morbidity reported in this study. Among this (36.34%) were cured of TB and rest (21.92%) were newly diagnosed with TB [Sandeep et al., 2014]

Longitudinal observational study in Kenya analyzed 1286 patients. The initial ART regimens were primarily d4T/3TC/NVP (62.1%). Median ART duration was 350 days (11.6 months). ART switches occurred in (54.5%) patients. Concurrent ART-related toxicities (40.6%) and tuberculosis treatment interactions (28.1%) were the most frequent reasons for ART switch[Hawkins et al., 2007].

2. OBJECTIVES

2.1. General objective

- To determine reasons that led to switching ARV drugs among adult HIV/ADS patients on ART.

2.2. Specific objectives

- To identify the pattern of initial ART regimens and the subsequent changes
- To determine the proportion of second and third time ART regimen shift among patients whose initial ART regimen had been changed
- To assess practice of ARV drug switch in adhering with the National and WHO guidelines for use of ART
- To assess the relationship between patient characteristics and reasons for initial ART change.
- To assess the relationship between patient characteristics and occurrence of second time ART switch.

3. METHODOLOGY

3.1. Study setting

The study was conducted in ART clinic of Tikur Anbessa Speciaized Hospital (TASH). TASH is located in Lideta Sub-City, Addis Ababa, Ethiopia and established in 1972. Affiliated with Addis Ababa University College of Health Sciences, TASH serves as a training center for undergraduate and postgraduate medical students, dentists, nurses, midwives, pharmacists, medical laboratory technologists and radiology technologists. It is the largest referral hospital in Ethiopia, with 700 beds. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation [AAU, 2015].

TASH has 200 doctors, 379 nurses and 115 other health professionals dedicated to providing health care services. The various departments, faculty members and residents under specialty training in the School of Medicine provide patient care in the hospital. The hospital also has 950 permanent and contract support staff. In addition, almost all regional and federal hospitals in Addis Ababa use TASH as referral unit and training sites [AAU, 2015].

TASH serves about 250,000 patients per year in its outpatient department and about 24,000 in the inpatient and same number in the emergency departments. The major services provided by the hospital are: internal medicine, emergency medicine, surgery, gynecology and obstetrics, pediatrics, oncology/chemo-radiology, radiology, psychiatry and dermatology. The pharmacy services in the TASH are organized for outpatient, emergency and inpatients [TASH, 2012].

The ART clinic in TASH is outpatient department which is organized in to adult ART, pediatric ART and prevention of mother to child transmission (PMTCT) units. The pediatric ART unit was established in March 2005 which enrolled only 40 children by that time. Since then 830 children have been enrolled in this unit. As of October 2015 there were 600 pediatric patients actively on ART. Regarding personnel in this unit it had one monthly rotating resident, one general practitioner, five nurse one adherence supporter and one data clerk.

In the adult ART unit 6,020 patients have been enrolled until October 2015. Among them 5,500 patients were actively on follow up. The personnel in this unit consisted of one monthly rotating resident, 3 consulting internists, 6 nurses, 2 data collectors, 2 adherence supporters and one

patient assistant. It has also a separate ART pharmacy with 3 pharmacists working full time. Since March 2005, 4539 patients have initiated ART in TASH. In October 2015, 2641 patients had been actively following ART therapy. [TASH, 2015].

3.2. Study design and period

The study was a hospital based retrospective cross sectional study. Data collection was conducted from 10June to 10September 2015.

3.3. Source and study population

The source population constituted of all adult HIV infected patients who had been on follow-up at the ART clinic of TASH. The study population included all HIV infected patients initiated ART at TASH that had experienced regimen switching.

3.4. Patient inclusion and exclusion criteria

Inclusion criteria:

- Patients on follow up in the ART clinic who had undergone at least one ART regimen switching until the study period.
- Adult HIV/AIDS patients 18 years old and above
- Patients receiving ARVs for at least 6 months at the beginning of the study period
- Patients receiving ARVs solely from TASH ART pharmacy.

Exclusion criteria:

- Patients with incomplete demographic and clinical information.

3.5. Sample size determination and sampling technique

The sample size was calculated using the standard sample size calculation formula.

$$N = \frac{Z^2 \alpha \, P(1 - P)}{\delta^2}$$

The magnitude of initial ART switch in the study made at Mekelle hospital was 20%. Taking P= 0.2 with 95% confidence level, $Z\alpha$=1.96, and δ=0.05; the calculated sample size was 246.

Taking 5% of contingency 246* 5% = 12.3, the total sample size would therefore come to 259 patients.

Sampling procedures

The recorded list of patients who had changed their regimen was used as a sampling frame. From a total of 1714 patients who changed their initial regimen 259 patients were included by systematic random sampling method. When the total number of sampling frame is divided to sample size (i.e.$1714/259$) it gave 6.6. Therefore every 6^{th} patient from the list was taken as a sample patient.

3.6. Study variables

Independent Variables

Socio-demographic characteristics: Age at initiation, Sex, Marital status, Family size, Educational status.

***Disease related variables*:** Baseline WHO stage, Base line CD4, Baseline viral load, and Baseline weight.

***ART related variables*:** Types of initial regimen

Dependent Variables

Reasons for change

Presence of second ARV drug switch

3.7. Data collection and management

3.7.1. Data abstraction form

Data abstraction form (Annex I) was developed based on the objectives of the study. It contained socio-demographic, clinical information and ART information such as, CD4 count, WHO stage, initial regimen, date on which treatment was started, date of ARV drug switch, duration of initial ARV therapy before first switch, regimen switched to, and reason for changing the ART. The types of toxicity and treatment failure reasons were included. If there was ARV drug switch for the second and third time it was recorded in a similar manner.

3.7.2. Data collectors recruitment and training

Three pharmacists working in the ART pharmacy were recruited and trained for one day each about the methods of data collection prior to the start of actual data collection.

3.7.3. Data Quality Control

To ensure data quality, the data collectors were trained by the principal investigators for one day each. The data abstraction format was pre-tested in 5% of the sample size to check for appropriateness of the data collecting instrument. Confusions and clarity found during the process of pre-test were corrected and modifications were made accordingly.The principal investigator had made frequent checks on the data collection process to ensure the completeness and consistency of the collected data.

3.8. Data analysis procedures

The data was cleaned for inconsistencies and missing values. The cleaned data was then coded and entered into Statistical Package for Social Sciences (SPSS) version 20. Quantitative Descriptive statistics was generated to meet the objective of the study. The categorical variables were described using frequency tables and figures. The continuous variables were stratified into sub groups in order to study associations using binary and multivariate logistic regression. Odds Ratios (OR) and 95% CI were used to look into the strength of association between the dependent and independent variables. Statistical significance was set at p-value <0.05.

3.9. Ethical considerations

Prior to study initiation, ethical clearance was obtained from Addis Ababa University, School of Pharmacy ethical review committee. In addition, permission was sought from the hospital medical director to conduct the study. Only numerical identifications were used as a reference. Confidentiality and anonymity of subject was maintained by not recording identifying details, such as name or any other personal identifiers. No disclosure of any name of the patients, the healthcare provider or drug product was made in relation to the finding.

3.10. Operational definitions

ABC based regimen: regimen containing Abacavir as one of the NRTI backbones and may have different NNRI or PI bases.

Adherence difficulty: it is inability to achieve 95% adherence level to the ART medications due to patient inconveniences in relation to pill burden, frequency of administration and other patient related behaviors.

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

AZT based regimen: regimen containing Zidovudine as one of the NRTI backbones and may have different NNRI or PI bases.

Comorbidity: is defined as the occurrence of one or more additional disorders which are on drug therapy with HIV/AIDS simultaneously (TB, diabetes, hypertension)

d4T based regimen: regimen containing Stavudine as one of the NRTI backbones and may have different NNRI or PI bases.

TDF based regimen: regimen containing Tenofovir as one of the NRTI backbones and may have different NNRI or PI bases.

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

Treatment failure: is defined as either occurrence of new opportunistic infection (TB, candidiasis, pneumonia, herpes simplex, toxoplasmosis, etc.), immunological failure (a drop of CD4 cell count below baseline pretreatment level) or virologic failure (a virological rebound after complete suppression).

4. RESULTS

4.1. Characteristics before ART switches

4.1.1. Baseline characteristics before first ART switch

In this study, a total of 259 patients whose ARV drug switched were included 59% of them were females. The mean (±SD) age of patients during initiation of ART was 36.5 (±8.9) years, with just above half (52.1%) of the patients in the age range of 31-45 years. Nearly half (46.3%) of the patients were married and majority (72.6%) of the patients had a family size of 1-3. With regards to their education level, about 45 % had received secondary education [Table 1].

Table 1Socio-demographics of patients included in the study

Demographic characteristics		Frequency (%)
Sex	Male	106(40.9)
	Female	153(59.1)
Age on initiation (years) Mean±SD (36.5±8.9)	18-30	84 (32.4)
	31-45	135 (52.1)
	46-65	40 (15.5)
Marital status	Single	54 (20.8)
	Married	120 (46.3)
	Divorced	43 (16.6)
	Widowed	42 (16.2)
Family size Mean±SD (2.6±1.5)	1-3	188 (72.6)
	4-6	66 (25.5)
	7-9	5 (1.9)
Educational status	No formal education	27 (10.4)
	Primary school education	71 (27.4)
	Secondary school education	117 (45.2)
	Higher institute education	44 (17.0)

During initiation of ART, about 80% of the patients were on WHO clinical stage III and IV. The mean baseline CD4 count was 138cells/µL, with most (80%) of them having a CD4 count of less

than 200cells/µl. In addition, the mean weight of the patients during initiation of ART was 55.6 kg (SD= 10), with 60% of them had a weight between 45 and 60 kg. Among the patients in this study viral load record during initiation of ART was found in only 1.2% of the patients and the mean value was 3,361 viral copies/µL. Majority (82.6%) of the patients had been on ART for 5-10 years duration. About 16% of the total patients had received TB treatment and 96.6 % were on Cotrimoxazole prophylaxis [Table 2]

Table 2: Clinical characteristics of patients included in the study

Baseline clinical characteristics		Frequency (%)
WHO clinical stage	stage I	14 (5.4)
	stage II	40 (15.4)
	stage III	126 (48.7)
	stage IV	79 (30.5)
CD4 count (cells/ml) (mean ± SD) =138.45±97.2	<200	207 (79.9)
	200-350	38 (14.7)
	>350	14 (5.4)
Weight (kg) (mean ± SD) = 55.6±10.18	<45	38 (14.7)
	45-60	155 (59.8)
	>60	66 (25.5)
OI prophylaxis	Cotrimoxazole	139 (53.7)
	Cotrimoxazole& Isoniazid	111 (42.9)
	Isoniazid	6 (2.3)
	Neither	3 (1.2)
TB treatment	Yes	41 (15.8)
	No	218 (84.2)
Years on ART	<5	7 (2.7)
	5-10	214 (82.6)
	>10	38 (14.7)

4.1.2. Characteristics of patients who switched ART twice

Among the total 259 patients 54 (20.8%) of them had changed their regimen for a second time. Two third (64.8%) of the patients were females. The mean age of patients were 36.5 years (SD = 8.9) and most (92.6%) of them were below 45 years old. Most (81.5%) of the patients had family size between 1 and 3. [Table 3]

Table 3: Socio-demographics of patients who switched for the second time

Demographic characteristics		Frequency (%)
Sex	Male	19 (35.2)
	Female	35 (64.8)
Age on initiation (years)	18-30	22 (40.7)
	31-45	28 (51.9)
	46-65	4 (7.4)
Marital status	Single	15 (27.8)
	Married	21 (38.9)
	Divorced	6 (11.1)
	Widowed	12 (22.2)
Family size	1-3	44(81.5)
	4-6	10 (18.5)
	7-9	-
Educational status	No formal education	5 (9.3)
	Primary school education	17 (31.5)
	Secondary school education	25 (46.3)
	Higher institute education	7 (12.9)

About half (48.2 %) of patients were on WHO stage I prior to second switch. The mean CD4 and weight of the patients were 401.7cells/µl (SD=282) and 61.9kg (SD=12.2), respectively. About 43% had CD4 count above 350 cells/µl. Only a fifth of the patients had a CD4 count below 200 and slightly more than half (51.8%) of the patients had a body weight of > 60 kg. Almost all (98.2%) patients had received Cotrimoxazole prophylaxis and half of the patients were on ART for 3 to 6 years before second time ARV drug switch [Table 4].

Table 4: Clinical characteristics of patients who switched for the second time

Clinical characteristics		Frequency (%)
WHO clinical Stage	stage I	26 (48.2)
	stage II	8 (14.8)
	stage III	11 (20.3)
	stage IV	9 (16.7)
CD4 count (cells/µL)	<200	11 (20.4)
Mean±SD= 401.7±282	200-350	20 (37.0)
	>350	23 (42.6)
Weight (kg)	<45	3 (5.6)
Mean±SD=61.9±12.2	45-60	23 (42.6)
	>60	28 (51.8)
OI prophylaxis	Cotrimoxazole	27 (50.1)
	Cotrimoxazole& Isoniazid	1 (1.8)
	Isoniazid	25 (46.3)
	Neither	1 (1.8)
TB treatment	Yes	9 (16.7)
	No	45 (83.3)
Years firstly switched ART	<3	13 (24.1)
	3-6	27 (50.0)
	>6	14 (25.9)

4.2. Pattern of ART regimen

4.2.1. Pattern of ART regimen during first ART switch

About two third (62%) of the patients started their initial ART on d4T based regimens [Figure 1].

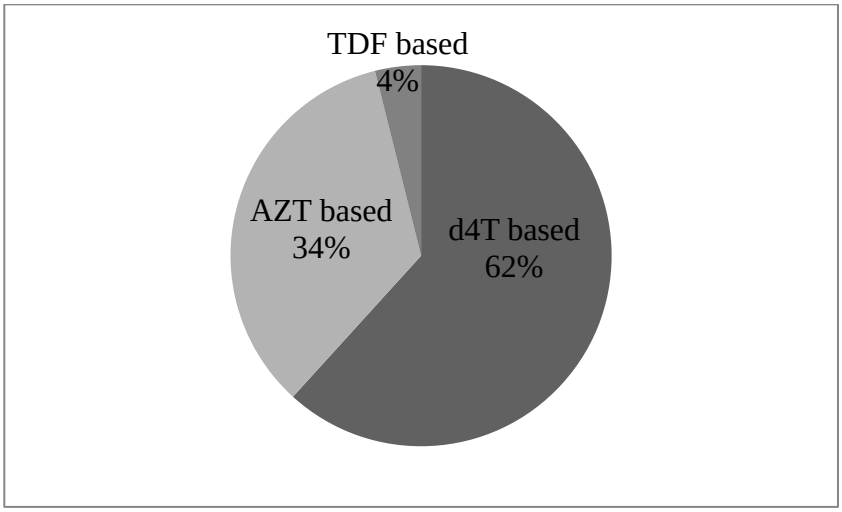

Figure 1: Initial antiretroviral regimen group in patients included in the study

During the first change of ART, 159 (61.4%) patients underwent single drug substitution followed by 99 (38.2%) two drugs substitution and 1 (0.4%) changed the whole regimen. Most (86.2%) of the patients who started on d4T based regimen had changed their initial regimen to TDF based regimen. Similarly, 85.4% of the patients that started on AZT based regimen had changed to TDF based regimen. On the contrary majority (70%) of the patients who started on TDF based regimen had changed to other TDF based regimen containing different NNRTI. Generally most (85.3%) of the patients' initial regimen was changed to TDF based regimen [Table 5].

Table 5: Pattern of first antiretroviral switch by regimen groups

	Initial regimen: frequency (%)			
Changed regimen	d4T based	AZT based	TDF based	Total
d4T based	2 (1.3)	4 (4.5)	-	6
AZT based	18 (11.2)	9 (10.1)	1 (10.0)	28
TDF based	138 (86.2)	76 (85.4)	7 (70.0)	221
ABC based	2(1.3)	-	2 (20.0)	4
Total	160 (100)	89 (100)	10 (100)	259 (100)

On initiation of regimen the d4T based regimen contained NNRTIs of either NVP (d4T/3TC/NVP, 63.8%) or EFV (d4T/3TC/EFV, 36.2 %). Similarly, the AZT based regimen was divided almost equally into AZT/3TC/NVP and AZT/3TC/EFV. On the other hand TDF based regimens consisted of TDF/3TC/EFV (50%), TDF/3TC/NVP (40%) and TDF/3TC/LPV/r (10%) [Table 6].

After initial ART switched, most (85%) of the patients were on TDF based regimen followed by AZT based (11%), d4T based (2%) and ABC based (2%).Among all regimens, 66.4% of the first time changes were to TDF/3TC/EFV. Breaking down this revealed that 53% of patients who started on d4T/3TC/NVP, 86.3% of patients started on d4T/3TC/EFV, 64.5 % of patients started on AZT/3TC/NVP 81.8% of patients who started on AZT/3TC/EFV and 75% of patients who started on TDF/3TC/NVP changed their initial ART into TDF/3TC/EFV[Table 6].

Table 6: Pattern of first antiretroviral switch by individual regimen

Changed regimen	Initial regimen: Frequency (%)							Total
	d4T based		AZT based		TDF based			
	d4T/3TC/ NVP	d4T/3TC/ EFV	AZT/3TC /NVP	AZT/3T C/EFV	TDF/3T C/NVP	TDF/3T C/EFV	TDF/3T C/LPV/r	
d4t based								
d4T/3TC/NVP	-	1(1.7)	1 (2.2)	2 (4.5)	-	-	-	**4**
d4T/3TC/EFV	1 (1.0)	-	1 (2.2)	-	-	-	-	**2**
AZT based								
AZT/3TC/NVP	11 (10.8)	1 (1.7)	-	3 (6.8)	-	-	-	**15**
AZT/3TC/EFV	2 (1.9)	4 (6.9)	3 (6.7)	-	-	-	-	**9**
AZT/3TC/LPVr	-	-	1 (2.2)	2 (4.5)	-	1 (20)	-	**4**
TDF based								
TDF/3TC/NVP	31(30.4)	-	7 (15.6)	-	-	3 (60)	-	**41**
TDF/3TC/EFV	54 (53.0)	50 (86.3)	29 (64.5)	36 (81.8)	3 (75.0)	-	-	**172**
TDF/3TC/LPV/r	2 (1.9)	1 (1.7)	3 (6.7)	1 (2.3)	-	-	-	**7**
TDF/3TC/ABC	-	-	-	-	-	-	1(100)	**1**
ABC based								
ABC/ddI/LPV/r	-	-	-	-	1(25.0)	-	-	**1**
ABC/3TC/LPV/r	1 (1.0)	1 (1.7)	-	-	-	-	-	**2**
ABC/3TC/ATV/r	-	-	-	-	-	1(20.0)	-	**1**
Total	**102 (100)**	**58 (100)**	**45 (100)**	**44 (100)**	**4 (100)**	**5 (100)**	**1 (100)**	**259**

4.2.2. Pattern of ART regimen during second and third switch

Among the total 259 patients, 54 (20.8%) of them had second time ARV drug switch. During second ART change, majority (72.2%) were single drug substitution and 20.4% and 7.4% had undergone two drugs substitution and changed the whole regimen, respectively [Table 7].

Table 7: Pattern ofsecond antiretroviral switch by regimen groups

Second regimen switched to	Regimen before second switch: frequency (%)				
	d4T based	AZT based	TDF based	ABC based	Total
AZT based	-	-	5 (14.7)	-	5
TDF based	5 (100)	14 (100)	28 (82.4)	1 (100)	48
ABC based	-	-	1 (2.9)	-	1
Total	5 (100)	14 (100)	34 (100)	1 (100)	54

Among the 54 patients who changed for the second time, twenty patients who were on d4T, AZT and ABC based regimens had changed to TDF based regimen. The rest were on TDF based regimen and had changed to other TDF based regimen containing different NNRTIs and PIs. Generally, most (88.9 %) of patients' second time ARV drug switch was towards the TDF based regimen [Table 8].

Table 8: Pattern of second antiretroviral switch by individual regimen

Second time switched to	Regimen before second switch: Frequency (%)									
	d4T based		**AZT based**			**TDF based**			**ABC based**	
	d4T/3TC/NVP	d4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	AZT/3TC/LPVr	TDF/3TC/NVP	TDF/3TC/EFV	TDF/3TC/LPV/r	ABC/ddI/LPV/r	**Total**
AZT based										
AZT/3TC/NVP	-	-	-	-	-	-	1(6.3)	-	-	**1**
AZT/3TC/EFV	-	-	-	-	-	-	1(6.3)	-	-	**1**
AZT/3TC/LPVr	-	-	-	-	-	1(6.7)	1(6.3)	-	-	**2**
AZT/3TC/ATV/r	-	-	-	-	-	-	1(6.3)	-	-	**1**
TDF based										
TDF/3TC/NVP	1(33.3)	-	1(25)	-	-	-	5(31.2)	-	-	**7**
TDF/3TC/EFV	2(66.7)	2(100)	4(75)	7(87.5)	-	11(73.3)	-	-	1(100)	**27**
TDF/3TC/LPV/r	-	-	-	1(12.5)	1(100)	2(13.4)	2(12.5)	-	-	**6**
TDF/3TC/ATV/r	-	-	-	-	-	-	3(18.7)	3(100)	-	**6**
TDF/3TC/AZT/LPV/r	-	-	-	-	-	1(6.7)	1(6.3)	-	-	**2**
ABC based										
ABC/3TC/LPV/r	-	-	-	-	-	-	1(6.3)	-	-	**1**
Total	**3(100)**	**2(100)**	**5(100)**	**8(100)**	**1(100)**	**15(100)**	**16(100)**	**3(100)**	**1(100)**	**54**

After second ARV drug switch, most (89%) of the patients were on TDF based regimen followed by AZT based (11%) and ABC based (2%). About half of the second time changes were to TDF/3TC/EFV. Around one third of patients had changed to PI containing second line regimens. Only one patient had changed from TDF/3TC/EFV to the second line ABC/3TC/LPV/r.[Table 8]

Among patients in this study, 3 (1.2%) patients had changed their ART regimen for the third time. Two of the ARV drug switches were single regimen substitution (from TDF/3TC/LPV/r to TDF/3TC/ATV/r and from TDF/3TC/LPV/r to ABC/3TC/LPV/r). One patient changed two drugs (from AZT/3TC/NVP to TDF/3TC/ATV/r).

4.3. Reasons for switching ART

During initial changes toxicity was the most common reason (74.1%) reported followed by adherence difficulty, treatment failure, pregnancy and comorbidity. About 7 % of the patients changed their first regimen without documented reason whereas 4.2% of patients had more than one reasons.

During second time changes about one third of the patients changed regimen due to toxicity followed by adherence difficulty, treatment failure, Pregnancy and stock out constituted. About 15% of the patients changed regimen without documented reason. During third time changes one patient each changed regimen due to treatment failure, stock out and undocumented reasons [Table 9].

Table 9: Reasons for first, second and third antiretroviral switches

	Frequency (%)		
Reason for change	1st change	2nd change	3rd change
Toxicity	192(74.1)	17(31.5)	-
Adherence difficulty	17(6.5)	11(20.4)	-
Treatment failure	11(4.2)	11 (20.4)	1 (33.3)
Pregnancy	6(2.3)	6(11.1)	-
Comorbidity	3(1.2)	-	-
***Combined reasons**	11(4.2)	-	-
Undocumented	19(7.3)	8(14.8)	1 (33.3)
Stock out	-	1(1.8)	1 (33.3)
Total	259 (100)	54 (100)	3 (100)

*combined reasons: Toxicity and Adherence difficulty, Toxicity and Treatment failure

4.3.1. Toxicity

During the first ARV drug switch, lipodystrophy was the most common toxicity reason which accounted for about one third of the cases. Combined toxicity accounted for about one fourth of the toxicity reasons in which combined lipodystrophy and peripheral neuropathy were the most common. The other toxicity reasons were Anemia, Peripheral Neuropathy, CNS toxicities, hepatotoxicity, rash, dyslipidemia respectively in descending order [Table 10].

About two third of the toxicity was caused by d4T containing regimens (63.4% d4T/3TC/NVP and 36.6% d4T/3TC/EFV). About one third of toxicities were due to AZT based regimen (53.2% AZT/3TC/NVP and 46.8% AZT/3TC/EFV). One patient each who was on TDF/3TC/EFV and TDF/3TC/LPV/r changed their initial regimen due to toxicity reason [Table 10].

Stavudine containing regimens were responsible for most of the Peripheral neuropathy and lipodystrophy toxicities. AZT containing regimens were responsible for all of the anemia reasons. The entire Skin rashes and CNS toxicity reasons were due to NVP and EFV containing regimens, respectively. Hepatotoxicity was due to both NVP and EFV containing regimens [Table 10].

Table 10: Types of toxicity reasons for first antiretroviral switch per regimen

Toxicity reasons	Initial regimen: frequency (%)						Total
	d4T based		AZT based		TDF based		
	d4T/3TC /NVP	d4T/3TC /EFV	AZT/3T C/NVP	AZT/3T C/EFV	TDF/3T C/EFV	TDF/3T C/LPV/r	
Lipodystrophy	39(19.2)	20(9.8)	6(3)	2(1)	-	-	**67(33)**
Anemia	-	-	14(6.9)	20(9.8)	-	-	**34(16.7)**
Peripheral Neuropathy	17(8.4)	14(6.9)	1(0.5)	-	-	-	**32(15.8)**
CNS toxicities	-	1(0.5)	-	2(1)	1(0.5)	-	**4(2)**
Hepatotoxicity	1(0.5)	1(0.5)	1(0.5)	1(0.5)	-	-	**4(2)**
Rash	-	-	2(1)	-	-	-	**2(1)**
Dyslipidemia	-	-	-	1(0.5)	-	1(0.5)	**2(1)**
GI irritation	-	-	1(0.5)	-	-	-	**1(0.5)**
Leukopenia	-	-	1(0.5)	-	-	-	**1(0.5)**
lactic acidosis	-	-	1(0.5)	-	-	-	**1(0.5)**
respiratory toxicity	1(0.5)	-	-	-	-	-	**1(0.5)**
*** combined toxicity**	30(14.8)	15(7.4)	2(1.0)	7(3.5)	-	-	**54 (26.7)**
Total	**88**	**51**	**29**	**33**	**1**	**1**	**203(100)**

***combined reasons:**lipodystrophy and peripheral neuropathy; peripheral neuropathy and hepatotoxicity; anemia and lipodystrophy; anemia and mylosuppression; peripheral neuropathy and anemia; anemia and hepatotoxicity; lipodystrophy& dyslipidemia; CNS toxicity and rash; hepatotoxicity and lactic acidosis.

From all the toxicities reported during second time ARV drug switch; anemia was the most common which accounted for 41.2% of the toxicity, followed by lipodystrophy, CNS toxicities renal failure and combined toxicities, respectively in descending order. Most (94 %) of the toxicity reason during second change was caused by TDF based regimen only one patients who were on AZT based regimen changed due to toxicity reason [Table 11].

Table 11: Types of toxicity reasons for second antiretroviral switch per regimen

Toxicity reason	Regimen before second switch					Total
	AZT based	TDF based				
	AZT/3TC/ EFV	TDF/3TC/ NVP	TDF/3TC/ EFV	TDF/3TC/ LPV/r	TDF/3TC/ ATV/r	
Anemia	-	-	7 (41.2)	-	-	**7(41.2)**
Lipodystropy	-	1(5.9)	2(11.8)	-	-	**3(17.6)**
CNS toxicities	-	-	1(5.9)	1(5.9)	1(5.9)	**3(17.6)**
Renal Failure	1(5.9)	-	-	1(5.9)	-	**2(11.8)**
***Combined toxicity**	-	1(5.9)	-	1(5.9)	-	**2 (11.8)**
Total	**1**	**2**	**10**	**3**	**1**	**17(100)**

* Combined toxicity: lipodystrophy& peripheral neuropathy; anemia & peripheral neuropathy

4.3.2. Treatment failure

In the first ARV drug switch, about half of the treatment failure reasons were due to immunologic failure. One third of the patients had changed their regimen due to combined treatment failure reasons. About half of the treatment failure was due to AZT based regimen (AZT/3TC/NVP, 46% and (AZT/3TC/EFV, 7.7%) while d4T based and TDF based regimen were responsible for one fourth of the treatment failure reasons each [Table 12].

Table 12: Types of treatment failure reasons in first antiretroviral switch per regimen

Initial regimen	Treatment failure: Frequency (%)					Total
	Immun-ological	Clinical	Virologic	Immunologic &virologic	Immunologic, clinical &virologic	
d4T/3TC/NVP	2(15.4)	-	-	-	-	**2(15.4)**
d4T/3TC/EFV	1(7.7)	-	-	-	-	**1(7.7)**
AZT/3TC/NVP	4(30.8)	-	-	1(7.7)	1(7.7)	**6(46)**
AZT/3TC/EFV	-	1(7.7)	-	-	-	**1(7.7)**
TDF/3TC/NVP	-	-	-	1(7.7)	-	**1(7.7)**
TDF/3TC/EFV	-	-	1(7.7)	1(7.7)	-	**2(15.4)**
Total	**7 (53.8)**	**1(7.7)**	**1 (7.7)**	**3 (23)**	**1(7.7)**	**13(100)**

Among the patients who switched ART due to immunological failure had mean peak CD4 of 335.4cells/µL but during the time of ART change it declined to 107.2cells/µL. Similarly, half of patients had peak CD4 >350cells/µL but during the time of ART change half of the patients had CD4 count between 50 and 200 cells/µL. [Figure 2].

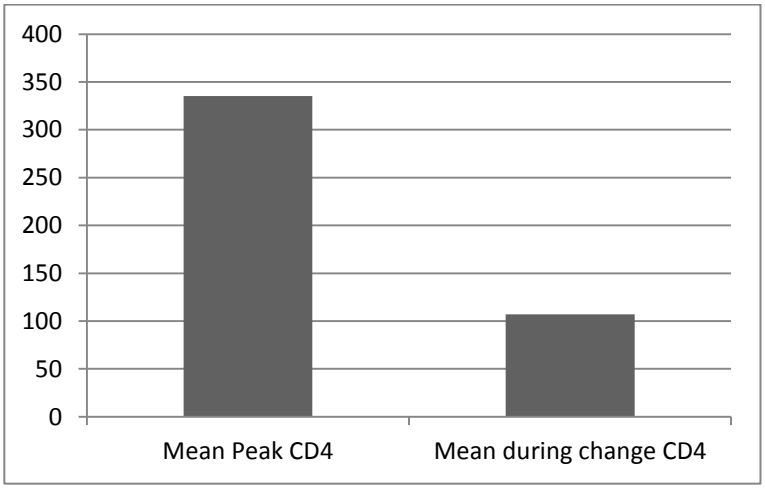

Figure 2: Comparison of CD4 in first antiretroviral switch due to immunological failure

During second time ARV drug switch, about half of the treatment failure reasons were due to virologic failure followed by one third due to immunologic failure. One patient each changed their second regimen due to clinical failure and combined reasons. 10 (91%) of the patients with treatment failure reason were on TDF based regimen. All patients who changed due to treatment failure contain PIs combined with NRTI regimen [Table 13].

Table 13:Types of treatment failure reasons for second antiretroviral switch per regimen

	Treatment failure: Frequency (%)				
ART regimen Before second switch	Immunological	Clinical	Virologic	Immunologic and virologic	**Total**
AZT/3TC/EFV	1 (9.1)	0	0	0	**1**
TDF/3TC/NVP	0	0	3 (27.3)	0	**3**
TDF/3TC/EFV	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)	**7**
Total	**4(36.4)**	**1(9.1)**	**5(45.5)**	**1(9.1)**	**11(100)**

4.3.3. Other reasons

During first ARV drug switch adherence difficulty was commonly reported in AZT and d4T based regimens accounting for 54.2 % and 37.5 %, respectively.57.2% of pregnancy reasons was due to EFV containing regimens [Table 14].

Table 14: Other reasons for first antiretroviral switch per regimen

Initial regimen	Reason: frequency (%)			
	Adherence difficulty	Pregnancy	Comorbidity	Undocumented
d4T/3TC/NVP	6 (25.0)	2 (28.6)	2 (50.0)	8 (42.1)
d4T/3TC/EFV	3 (12.5)	1 (14.3)	-	3 (15.8)
AZT/3TC/NVP	6 (25.0)	-	1 (25.0)	4 (21.0)
AZT/3TC/EFV	7 (29.2)	1 (14.3)	1 (25.0)	4 (21.0)
TDF/3TC/NVP	2 (8.3)	1 (14.3)	-	-
TDF/3TC/EFV	-	2 (28.6)	-	-
Total	24 (100)	7 (100)	4 (100)	19 (100)

During second change adherence difficulty was reported in TDF based and AZT based regimen accounting for 72.7 % and 27.3 %, respectively. 83.3% of the pregnancy reasons were due to TDF/3TC/EFV and 16.7% was due to TDF/3TC/NVP. One patient who was on TDF/3TC/LPV/r changed regimen for second time because of stock out reason.

Table 15: Other reasons for second antiretroviral switch per regimen

ART before 2nd switch	Reasons: frequency (%)			
	Adherence difficulty	Pregnancy	Undocumented	Stock out
d4T/3TC/NVP	-	-	1 (12.5)	-
d4T/3TC/EFV	-	-	2 (25.0)	-
AZT/3TC/NVP	2 (18.2)	-	-	-
AZT/3TC/EFV	1 (9.1)	-	1 (12.5)	-
TDF/3TC/NVP	8 (72.7)	1 (16.7)	1 (12.5)	-
TDF/3TC/EFV	-	5 (83.3)	1 (12.5)	-
TDF/3TC/LPV/r	-	-	2 (25.0)	1 (100)
Total	11 (100)	6 (100)	8 (100)	1 (100)

4.4. Distribution of patients by timeline of switching ART and reason for switch

The mean (±SD) of duration in which patients stay on initial regimen was about 3.5 (±1.95) years with minimum and maximum durations of 0.4 and 9.1 years, respectively. Most (79%) of the patients switched their initial ART regimen after 2 years. only one tenth of patients stayed on their initial regimen for more than 6 years.

6.2%, 4.6% and 4.6% of patients who took d4T/3TC/NVP, d4T/3TC/EFV and AZT/3TC/NVP, respectively remain in their first regimen for less than 2 years while about 18%, 13%, and 5% patients who took d4T/3TC/NVP, d4T/3TC/EFV, and AZT/3TC/NVP remain on their therapy for 2-4 years. About 5% of patients who were on AZT/3TC/EFV and 2% patients on d4T/3TC/NVP stayed on their first regimen for more than 6 years.

Among the patients who had modified due to toxicity, one fifth of the patients changed regimen in the first 2 years, 42%, 28 % and 11% of patients switched in the 2-4, 4-6 years and >6 years, respectively. Majority 69.2% of the treatment failure has been occurred during fewer than 2 years of initiation of ART. About half (53.3%) of the adherence difficulty reasons were after 2-4 years of initial therapy [Table 16].

Table 16:Years on therapy versus regimen and reasons for first antiretroviral switch

	Years on initial ART: frequency (%)				
Initial regimen	<2	2-4	4-6	>6	**Total**
d4T/3TC/NVP	16(6.2)	47(18.1)	33(12.8)	6(2.3)	102(39.4)
d4T/3TC/EFV	12(4.6)	34(13.1)	8(3.1)	4(1.6)	58(22.4)
AZT/3TC/NVP	12(4.6)	14(5.4)	14(5.4)	5(1.9)	45(17.4)
AZT/3TC/EFV	9(3.5)	11(4.2)	12(4.6)	12(4.6)	44(17.0)
TDF/3TC/NVP	3(1.2)	-	1(0.4)	-	4(1.5)
TDF/3TC/EFV	3(1.2)	2(0.8)	-	-	5(1.9)
TDF/3TC/LPV/r	-	1(0.4)	-	-	1(0.4)
Total	55(21.2)	109(42.0)	68(26.3)	27(10.4)	259(100)
Reason for switch					
Toxicity	39(19.2)	85(41.9)	57(28.1)	22(10.8)	203(100)
Treatment failure	9(69.2)	3(23.1)	1(7.7)	-	13(100)
Adherence difficulty	2(13.3)	8(53.3)	3(20.0)	2(13.3)	15(100)
Pregnancy	3(42.9)	4(57.1)	-	-	7(100)
comorbidity	1(25)	3(75)	-	-	4(100)
for patient convenience	1(11.1)	2(22.2)	3(33.3)	3(33.3	9(100)
undocumented	3(15.8)	10(52.6)	4(21.1)	2(10.5)	19(100)

Among the patients who changed for second time, the mean (±SD) duration of stay on the firstly changed regimen before second switch was about 3.1 (±2.04) years with minimum and maximum durations of 0.5 and 7.93 years, respectively. About 37% of them changed their regimen in less than two years after first change followed by 30%, 22%, 11% of patients in 2-4, 4-6 and >6 years duration, respectively. About half (54.5%) of the treatment failure and all the pregnancy reasons were recorded in less than 2 years duration after their first ARV drug switch.

About 19%of patients who have been on TDF/3TC/EFV and 13% patents on TDF/3TC/NVP changed their regimen for a second time in less than 2 years duration. About 4% of patients each who had been on TDF/3TC/LPV/r and AZT/3TC/NVP stayed for more than 6 years on the firstly changed regimens, respectively [Table 17].

Table 17: Years on therapy versus regimen and reasons for second antiretroviral switch

Regimen before second switch	**Years after first switch: frequency (%)**				
	<2	2-4	4-6	>6	**Total**
d4T/3TC/NVP	-	1(1.8)	1(1.8)	1(1.8)	3(5.6)
d4T/3TC/EFV	-	2(3.7)	-	-	2(3.7)
AZT/3TC/NVP	-	2(3.7)	1(1.8)	2(3.7)	5(9.3)
AZT/3TC/EFV	1(1.8)	3(5.6)	3(5.6)	1(1.8)	8 (14.8)
TDF/3TC/NVP	7(13.0)	6(11.1)	2(3.7)	-	15(27.8)
TDF/3TC/EFV	10(18.5)	2(3.7)	4(7.4)	-	16(29.6)
TDF/3TC/LPV/r	-	-	1(1.8)	2(3.7)	3(5.6)
AZT/3TC/LPVr	1(1.8)	-	-	-	1(1.8)
ABC/ddI/LPV/r	1(1.8)	-	-	-	1(1.8)
Total	20(37)	16(29.6)	12(22.2)	6(11.1)	54(100)
Reason for switch					
Toxicity	3(17.6)	6(35.3)	7(41.2)	1(5.9)	17(100)
Treatment failure	6(54.5)	2(18.2)	3(27.3)	-	11(100)
Adherence difficulty	2(50)	1(25)	1(25)	-	4(100)
Pregnancy	6(100)	-	-	-	6(100)
for patient convenience	2(28.6)	3(42.8)	-	2(28.6)	7(100)
Stock out	-	-	-	1(100)	1(100)
undocumented	-	4(50)	2(25)	2(25)	8(100)

4.5. Association between patient characteristics and reasons for first switch

The d4T and AZT based regimens had statistically significant association with toxicity reason for changing ART regimen (AOR=30.89, P=0.00) and (AOR=9.13, p=0.012), respectively as compared to the TDF based regimen. The other demographic and clinical characteristics had no statistically significant association with the toxicity reasons for changing initial ART regimen [Table 11].

Table 18: Binary and multivariate logistic regression for toxicity reason in first antiretroviral switch

Variables		Reason for initial ART change		Crude OR (95% CI)	AOR (95% CI)
		Toxicity	Non toxicity		
Sex	Male	84	22	1.00	
	Female	119	34	0.92(0.50,1.68)	1.15(0.54,2.46)
Age	18-30	65	19	1.00	
	31-45	107	28	1.12(0.58,2.16)	0.84(0.38,1.89)
	46-65	31	9	1.01(0.41,2.48)	0.93(0.30,2.90)
Marital status	Single	41	13	1.00	
	Married	99	21	1.50(0.68,3.27)	1.44(0.55,3.80)
	Divorced	34	9	1.20(0.46,3.14)	1.12(0.35,3.54)
	Widowed	29	13	0.71(0.29,1.75)	0.51(0.17,1.54)
Family size	1-3	145	43	1.00	
	4-6	54	12	1.33(0.65,2.72)	1.22(0.49,3.06)
	7-9	4	1	1.19(0.13,10.89)	1.14(0.09,13.97)
Education	No formal education	21	6	1.00	
	Primary school	55	16	0.98(0.34,2.85)	1.03(0.29,3.66)
	Secondary school	94	23	1.17(0.42,3.22)	1.43(0.41,4.97)
	Tertiary school	33	11	0.86(0.27,2.67)	0.96(0.24,3.78)
CD4 before change 1	<200	54	20	1.00	
	200-350	65	19	1.27(0.61,2.61)	1.10(0.45,2.68)
	>350	84	17	1.83(0.88,3.80)	1.53(0.61,3.84)
stage before change 1	Stage I	39	12	1.00	
	Stage II	29	12	0.74(0.29,1.89)	0.92(0.31,2.77)
	Stage III	82	20	1.26(0.56,2.84)	1.15(0.45,2.97)
	Stage IV	53	12	1.36(0.55,3.34)	1.22(0.41,3.63)
TB treatment	Yes	35	6	1.00	
	No	168	50	0.58(0.23,1.45)	0.78(0.29,2.09)
Regimen before 1st change	TDF based	2	8	1.00	
	d4T based	139	21	26.48(5.26,133.25)	30.89(5.3,179.61)**
	AZT based	62	27	9.18(1.83,46.14)	9.13(1.62,51.49)**
Duration on first regimen	<2 years	39	16	1.00	
	2-4 years	83	24	1.42(0.68,2.97)	0.78(0.31,1.95)
	4-6 years	58	11	2.16(0.91,5.15)	1.36(0.46,4.05)
	>6 years	23	5	1.89(0.61,5.83)	1.53(0.39,5.98)

** Shows statistically significant association

Non toxicity reason= (treatment failure, pregnancy, comorbidity, adherence difficulty and undocumented)

4.6. Association between patient characteristics and second ART switch

The odds for second regimen switch for patients on TDF based regimen were 0.03 (95% CI 0.003, 0.41; P=0.008). This implies that the odds of second switch in patients on TDF based regimen were 97% less than patients on d4T based regimen with the true population effect between 99.7% and 59%. This result was statistically significant.

As compared to patients on WHO clinical stage I, Patients who were on WHO clinical stage II, III and IV before second ARV drug switch had an odds of 7.3, 34.3 and 47.4, respectively, for changing their regimen for the second time.

The odds for second ART switch of patients stayed on the firstly switched ART for 3-6 yearsand > 6 years were 0.048 (95% CI 0.016, 0.14; p=0) and 0.01(95% CI 0.003,0.07; p=0), respectively.This implies that the odds of second switch in patients on firstly changed ART for 3-6 yearsand > 6 years were 95.2% and 99% less than patients on ART for <3years, respectively.

The other demographic and clinical characteristics were not significantly associated with the patients' second time ARV drug switch.

Table 19: Crude and adjusted odds ratio of variables for second antiretroviral switch

Variables		Second time switch		COR (95% CI)	AOR (95% CI)
		yes	No		
Sex	Male	19	87	1.00	
	Female	35	118	1.36 (0.73, 2.53)	0.88(0.34,2.29)
Age	18-30	22	62	1.00	
	31-45	28	107	0.74 (0.39,1.40)	1.32(0.50,3.47)
	46-60	4	33	0.342(0.11,1.07)	0.59(0.12,2.95)
	>60	0	3	0.00	0.00
Marital status	Single	15	39	1.00	
	Married	21	99	0.55(0.26,1.18)	0.68(0.23,2.00)
	Divorced	6	37	0.42(0.15,1.20)	0.55(0.14,2.17)
	Widowed	12	30	1.04(0.42,2.55	1.17(0.29,4.74)
Education	No formal education	5	22	1.00	
	Primary school	17	54	1.38(0.45,4.22)	1.50(0.32,6.94)
	Secondary school	25	92	1.20(0.41,3.47)	1.18(0.28,4.97)
	Tertiary school	7	37	0.83(0.23,2.94)	0.70(0.12,4.00)
CD4 before change 2	<200	26	48	1.00	
	200-350	12	72	0.31(0.14,0.67)	0.39(0.13,1.14)
	>350	16	85	0.35(0.17,0.71)	0.49(0.17,1.37)
Stage before change 2	Stage I	2	49	1.00	
	Stage II	7	34	5.00(0.99,25.78)	7.28(1.04,50.94) **
	Stage III	28	74	9.27(2.11,40.70)	34.26(5.80,202.69) **
	Stage IV	17	48	8.67(1.90,39.6)	47.34(6.85,327.17) **
TB treatment	Yes	9	32	1.00	
	No	45	173	0.92(0.412,2.08)	1.40(0.43,4.57)
Regimen before 2nd change	d4T based regimen	5	1	1.00	
	AZT based regimen	14	14	0.20(0.21,1.940	0.26(0.02,3.60)
	TDF based regimen	34	186	0.04(0.004,0.32)	0.03(0.003,0.41) **
	ABC based regimen	1	4	0.05(0.002,1.07)	0.024(0.00,1.67)
Duration on firstly switched ART	<3 years	29	37	1.00	
	3-6 years	19	120	0.20(0.10,0.40)	0.048(0.016.0.14) **
	>6 years	6	48	0.16(0.06,042)	0.01(0.003,0.07) **

** Shows statistically significant association

5. DISCUSSION

This retrospective cross sectional study of HIV/AIDS patients on ART which is the first study in TASH gives an insight on the reasons for ARV drug switch in patients on tertiary hospitals on the country. In doing so it described the pattern of ART regimen, the rate of ARV drug switch, and the common reasons for ARV drug switch. Such studies would be helpful in understanding the complexity of ART use in patients on referral hospitals which might have different comorbidities.

In this study the demographic characteristics of patients who changed their ART regimen once, is almost similar to those who change for second time. However the clinical characteristics of patients who changed for second time is less advanced when compared with to those who only change regimen once. For example almost half (49%) of patients on initial regimen were on WHO stage III with mean CD4 of 138cells/µL and weight of 55.6kg.On the contrary in patients with second switch 48% of them were on WHO stage I with mean CD4 of 402cells/µL and weight of 62kg.

Most (82.6%) of the patients had been on ART for 5-10 years. The patients in this study had a longer duration as compared to the patients on most other studies such as: Bedelle[Mekonnen & Molla, 2014]all patients stayed on ART for less than 3 years, Addis Ababa [Jima et al. 2013] about 98% of patients stayed on ART for less than 1.4 years and Dessie[Mulugeta & Chane, 2012] only 6% patients stayed on ART for more than 2 years. The higher rate of second and third time switches could be due to the patients in this study had been on ART for longer duration. This higher rate of immunologic failure and adherence difficulty during second time ARV drug switch could be resulted from this longer duration on ART and Higher rate of second switches.

Among the total 259 patients who changed their initial ART regimen 20.8% of them had switched regimen for a second time and 1.2% switched for a third time. This is higher than the studies done in Mekelle[Gebremedhin & Birhane, 2014] (10.2% and 0.6% for twice and third time change, respectively) and Dessie [Mulugeta& Chane, 2012]5.7% for twice change. The higher rate of second and third time switches could be due to patients in this study had been on ART for longer duration as compared to patients in the other studies. The other possible reasons include the advanced stage and higher immune-suppression of patients in this study and variation in monitoring after ARV drug switches.

Almost all patients in this study initiated ART regimen according to the Ethiopian and WHO antiretroviral guidelines at the time of initiation. Accordingly they started on d4T/3TC/NVP or EFV, AZT/3TC/NVP or EFV and TDF/3TC/NVP or EFV. However, there was one patient who started on TDF/3TC/LPV/r which is a second line regimen according to the national and WHO guideline. This may limit the patient's future options of ART drug regimens when the patient is in need of changing regimen.

The main reason for initial ARV drug switch in this study was toxicity (74.1%) which was much higher than the studies done in UK [Hart et al. 2007] (35%) and India [Sivadasan et al., 2009] (27%). However, it is quite similar with studies done in Ethiopia in which it was 75.8% in Mekelle [Gebremedhin& Birhane 2014], 66% in Dessie [Mulugeta & Chane, 2012] 65.58% in Nekemte [Wube et al. 2013] and 67.65% in Southern Ethiopia[Woldemedhin & Wabe, 2012].It is also similar to study done in Southern India [Kumarasamy et al., 2006] where 64% of patients modified initial ART regimen due to adverse effect. But there was a significant heterogeneity on the type of toxicities in these studies.

From all toxicities reported in this study, lipodystrophy was the most common accounting for 33% of all toxicities followed by combined toxicities 26.7% and Peripheral Neuropathy 15.8%. Literatures highlighted that Stavudine is a drug most often associated with mitochondrial toxicity, which results in high rate of lipoatrophy, peripheral neurophathy, lactic acidosis and pancreatitis. d4T containing regimens were responsible for most (88%) of the liopodystrophy and almost all of peripheral neuropathy reasons. This could be due to two third (61.8%) of the patients were started on d4T based regimen. Similarly, majority (75.58%) of the patients in southern Ethiopia[Woldemedhin &Wabe, 2012]and 80.3% of patients in Nekemte [Wube et al. 2013]were started with d4T based regimens. This resulted peripheral neuropathy as main reason for ARV drug switch which was 36.5% & 43.33% in Southern Ethiopia and Nekemte, respectively. Furthermore A study in U.K showed that lipoatrophy accounted for 18.8% of toxicities ,and about 15% of patients were on d4T based regimen[Hart et al. 2007].On the contrary in the studies done in Dessieand Mekelle anemia was the major reason for modification with 77.1% and 39.5% of the toxicity reasons, respectively. But in this study anemia accounted for 16.7% of all the toxicity reasons. This variation was due to the fact that

majority of the patients in Mekelle (48.2%) and Dessie (63%) were started on AZT based regimen compared to this study (34.4%)[Mulgeta & Chane, 2012, Bayou et al.2014].

The major toxicity causing initial regimen was d4T based (68.5%) followed by AZT based (30.5%) and TDF (1%). This was similar to the cohort study done in Uganda [Castelnuovo et al. 2011] where d4T accounted for the most (84%) of the toxicities that led to drug substitution. Several researches indicated toxicity of d4T as a reason for ARV drug switch, as the result of this d4T was removed from the first line and second line recommendations of the WHO and national guidelines.In TASH, currently new patients with HIV/AIDS are not starting with d4T containing regimens and all patients who have been on d4T are now moved to other regimen. The entire anemia and skin rash reasons were due to AZT and NVP containing regimens, respectively. CNS toxicity was due to EFV containing regimens. Of four patients who switched because of hepatotoxicity, two were on NVP and the other two were on EFV.

Almost the entire initial ART regimen switch due to toxicity was according to the WHO recommendation for changing regimen. However, one patient had changed from TDF/3TC/LPV/r to TDF/3TC/ABC due to dyslipidemia. If patients have toxicity in using LPV/r it is recommended to change to NNRTIs or to use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, integrase inhibitors are considered. Another patient also changed from d4T/3TC/EFV to ABC/3TC/LPV/r due to lipodystrophy and dyslipidemia. It is recommended to change the d4T to ABC but changing EFV to LPV/r could aggravate the dyslipidemia as it is the common adverse effect of LPV/r [WHO, 2013b].

During second ART switch, the common type of toxicity was anemia (41.2%), followed by lipodystrophy (17.6%), CNS toxicities (17.6%) and renal failure (11.8%). As the toxicity reasons in the initial ARV drug switches were majorly due to d4T and AZT regimens, this toxicity could have been avoided had the patients were on different regimen than d4T and AZT based regimen for the second time. The higher rate of anemia during second switch may be due lack of adequate baseline anemia assessment while a patient was changing to AZT based regimen during first switch.

During second time switch of ART regimen due to toxicity reasons most of the ARV drug switches were in line with the WHO recommendations. However, one patient who was on a second line regimen (ABC/ddI/LPV/r) changed to a first line regimen (TDF/3TC/EFV) due to anemia. Once a patient has toxicity due to ART regimen, it is recommended to identify the causative agent and substitute it with another agent rather than changing the whole regimen. The anemia may not be associated with the ART regimen and it could be treated without changing the ART regimen. Another patient changed from TDF/3TC/NVP to TDF/3TC/EFV due to CNS toxicity. Changing NVP to EFV could aggravate the CNS toxicity as it is the common adverse effects of EFV [FMHACA, 2014].

Treatment failure accounted for 4.2% patient's first ART change similar with studies done in Nekemte[Wube et al. 2013] (3%) and Southern Ethiopia [Woldemedhin & Wabe, 2012] (2.65%). But in other studies such as Mekelle [Gebremedhin& Birhane 2014] (9.6%) and Dessie [Mulgeta& Chane, 2012] (8%), higher proportion of patients changed their first regimen due to treatment failure. In U.K 30% of the treatment switch was due to virological failure [Hart et al., 2007].This variation may be associated with access to the laboratory facilities such as viral load test. There were very few patients with viral load monitoring in patients on this study. Immunologic failure accounted for about half (53.8%) of the treatment failure reasons. An observational study conducted in Asia indicated similar result as 54% of the treatment failure was immunological failure [Zhou et al., 2010].

In case of treatment failure, it is recommended to change the entire regimen from first-line to second-line. The new second-line regimen should involve drugs that retain activity against the patient's virus strain and should preferably include at least three new drugs, one or more from a new class, in order to increase likelihood of treatment success and minimize the risk of cross-resistance [MOH, 2007]. Using a boosted PI and two NRTI combinations is recommended as the preferred strategy for second-line ART for adults when NNRTI-containing regimens were used in first-line ART [WHO, 2013b].Compared with patients from low-income countries, patients from high-income countries were more likely to change two or more drugs and to change to a protease-inhibitor-containing regimen [Zhou et al., 2010]

The initial ART switch due to treatment failure in this study deviates from the guidelines. Out of the 13 patients who changed initial regimen due to treatment failure, only 38.5 % of them

changed to second line regimens (AZT or TDF/3TC/LPV/r, ABC/3TC/ATV/r and ABC/ddI/LPV/r) but majority of the patients changed to other first line regimens (TDF/3TC/EFV, and AZT/3TC/NVP) despite treatment failure in the initial regimen. After failure on a TDF + 3TCbased first-line regimen it is recommended to use AZT + 3TC as the NRTI backbone in second-line regimens. Similarly after failure on an AZT or d4T + 3TC based first-line regimen it is recommended to use TDF + 3TC as the NRTI backbone in second-line regimens. If a patient continued using the already failed regimen it might increase the virological resistance so that the continued regimen would be ineffective [WHO, 2013b; FMHACA, 2014].

Immunologic failure is defined as fall of CD4 count to pre-therapy baseline (or below); 50% fall from the on-treatment peak value and persistent CD4 levels below 100 cells/μL [FMHACA, 2014].In patients who changed initial regimen due to immunologic failure the mean peak and CD4 counts during change were 335 and 107 cells/μL. This indicated that the definition of immunological failure is in accordance with WHO and National guideline. The mean CD4 count near ART changes had fallen by 68% from the mean peak CD4 count.

During second time switch due to treatment failure all of the 11 patients changed to second line drugs. However, only 45.5% switched to the correct regimen according to national and WHO guideline. The other four patients had only one drug substitution of NNRI into PIs (from TDF/3TC/NVP or EFV to TDF/3TC/LPV/r or ATV/r). In addition two patients had changed into four drug regimen containing the already failed regimen (from TDF/3TC/EFV or NVP to TDF/3TC/AZT/LPV/r).The TDF/3TC/AZT/LPV/r regimen is recommended for patients who have HIV and HBV confections. However there was no information about this comorbidity in the patients' medical chart. Continuation of failed first line regimen despite treatment failure may predispose for development of drug resistance which may result in poor immunological, clinical and virological responses that lead to poor patient outcomes.

Adherence difficulty (6.5 %) is another reason which was comparable to the study done in Mekelle[Gebremedhin & Birhane 2014] (4.8%) but lower than UKs study [Hart et al. 2007] (14.4%). It is higher as compared with studies done in Dessie [Mulgeta& Chane, 2012] (2%) Addis Ababa [Jima et al., 2013] (2%). These variations could be due to difference of the facilities in the involvement of patient on decision making regarding regimen selection and associated difference in the rate of adherence.

When pregnancy related switches were compared, this study had lesser (2.3%) switches as compared to the studies in southern Ethiopia [Woldemedhin & Wabe, 2012] (10.5%), Dessie [Mulgeta& Chane, 2012] (11%), Nekemte [Wube et al., 2013] 6.7% and U.K [Hart et al., 2007] (4.3%). EFV based regimens were the main reasons for switch due to pregnancy that was because these regimens were considered to be teratogenic but recent studies have shown that EFV has similar safety during pregnancy like the other ARTs. In this study there was no pregnancy reason recorded in the patients since December 2011. This showed that the current study setting is implementing the new researches on EFV's safety to use during pregnancy [Ford et al.2010].

Comorbidity accounted for 1.2% of patient's treatment modification which was due to TB treatment. This was similar to U.K [Hart et al., 2007] study in which 2.2% switched their regimen due to anti TB, antiepileptic and hepatitis B virus comorbidity. But it is low compared to the studies conducted in other areas of the country in which it was 19.11% in Southern Ethiopia [Woldemedhin & Wabe, 2012], 14% in Mekelle [Gebremedhin& Birhane, 2014], 14% in Dessie [Mulugeta& Chane, 2012] and 8.7% in Nekemte [Wube et al., 2013].This showed that compared to other areas there is low prevalence of T.B in this study area as 45.2 % of the patients have received isoniazid prophylaxis and only 15.8% of the patients have been treated for TB. NVP containing regimens were responsible for TB related switches. The probable suggestion for this NVP switch to EFV is the drug-drug interaction that exists between NVP and Rifampin. Rifampin is a strong liver enzyme (CYP 3A4) inducer and it decreases the therapeutic level of NVP up to 40% and some studies have also demonstrated the additive hepatotoxicity effects when the two drugs were used together so it's preferable to switch to Efavirenz based regimens which have lesser interaction with rifampin [Hoffmann CJ et al., 2007].

Among patients with first switch about 7% of the patients changed regimen without documented reason. This may be due to change in guideline as majority of the initial regimen was in d4T based regimen. This could also be due to patient's request for simpler once daily dosing regimens instead of complex frequent dosing regimen. All the initial regimens changed without documented reason were d4T (58%) and AZT (42%) based regimens that are given as twice daily dosing and most (95%) of them changed to TDF based regimen which is given as once daily dosing. Otherwise it may be forgetting to record the reason for change by the practitioners.

When the reason for second switch was compared with the reasons for first time switch the toxicity reasons have significantly declined (74.1% vs 31.5%). This could be due to majority of patients having been on TDF based regimen before second switches. But the treatment failure and pregnancy reasons have dramatically increased in the second time switches (4.2% vs. 20.4%) and (2.3% vs. 11.1%), respectively. This could be due to less frequent follow up and monitoring parameters such as viral load were not done once the patients had changed their initial regimen. Adherence difficulty was higher in patients who changed regimen for second time (6.5% vs. 20.4%).This increase could be due to less patient involvement in decision making during selection of regimen for change. There were 2 patients (one during second change and one during third change) who changed regimen due to stock out of drugs. This could be due to national or hospital based problem in keeping appropriate stock level of ART drugs.

Unlike other studies there was combined reasons reported for changing ART regimen. Majority of the combined reason were due to d4T induced toxicity and associated adherence difficulty and treatment failure. After changes of the initial ART regimen, most of the patients were on TDF (85.3%) based regimen; (TDF/3TC/EFV, TDF/3TC/NVP and TDF/3TC/LPV/r) which are considered to be the safest and have low rate of ARV drug switches.

The odds of second switch in patients on TDF based regimen were 97% less than patients on d4T based regimen. This may indicate that the TDF based regimen is more tolerable in patients at TASH. On the other hand people with advanced WHO clinical stage had higher odds for switching their ART for the second time. This may be due to poor tolerability of patients on advanced WHO clinical stage. the odds of second switch in patients stayed on firstly changed ART for 3-6 yearsand > 6 years were 95.2% and 99% less than patients on ART for <3years, respectively. This may imply that patients were tolerating the drugs if they stay longer on the ART.

6. LIMITATIONS OF THE STUDY

This study is a cross sectional retrospective type. It included patients which are on follow up at ART clinic of TASH. As patients who lost follow up due to changing to other facilities, drug discontinuation or death were not included, omission of these patients might affect the results significantly.

The patients in the study might not be completely representative of HIV infected patients in Ethiopia. It studied patients who were on follow-up at ART clinic. Therefore care should be taken in extrapolating these results.

The study collected the main reasons as reported by physician for switch of treatment, but reasons for ART switch are often interrelated.

There was illegibility of some information on patient's information sheets and physician diagnostic cards that might create bias.

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7. CONCLUSION

The proportions of patients who switched ARV drug in our resource constrained setting present a challenge to the limited treatment options that we currently have. The main reasons for ART switch were toxicity, adherence difficulty and treatment failure, lipodystrophy and anemia were among the leading toxicity causes for ART switch. Furthermore, most of the toxicity are incurred from Stavudine based regimen. The reason for initial ART switch was related to the type of initial ART regimen. Similarly the clinical stage and type of ART regimen were associated with the rate of second ARV drug switches. Although most of the patients had improved clinical and immunological outcomes, there was no correlation between their duration on ART regimen and their change in CD4 count and body weight from baseline. With few exceptions, almost all of The ART initiation and changes of TASH is in line with the national and WHO guideline for the use of antiretroviral drugs.

8. RECOMMENDATIONS

- Less toxic and better-tolerated HIV treatment options should be available and used more frequently in TASH.
- Patient should be evaluated regularly after a treatment change to assess for potential concerns with the new regimen, medication tolerance and to assess the effectiveness.
- Since, most of ARV drug switches require laboratory result monitoring; there should be regular laboratory monitoring in TADH.
- For any modification of ART regimen in this setup the reason for change should be well recorded and documented. In addition, there should be updated guideline for switching regimen based on benefit-risk ratio. ART clinics should also establish switch meetings of experts to review cases and utilize all available information before a switch to second-line therapy are made.
- Improvements in pharmaceutical procurement and stock management systems at hospital or national level are recommended. The supply of ART should be based on well updated data and demands based.
- Information is needed on patterns of resistance across the population to recommend future therapy options. Therefore national and Hospital based surveillance of antiretroviral drug resistance should be conducted. It helps to know the resistance pattern and select the locally effective treatments.
- National level study on reasons for regimen change should be done that can help for drug suppliers and policy makers to improve and solve the problem. The reasons of ARV drug switch observed in this cross sectional study should be investigated further in longitudinal multicenter studies of ART utilization.

REFERENCES

Addis Ababa University (AAU). (2015). *Tikur Anbessa Hospital Background*. [online] avalable from:, http://www.aau.edu.et/aaubeta/chs/[Acessed: 23January 2015]

Bangsberg, D., Acosta, E., Gupta, R., Guzman, D., Riley, E., Harrigan, P.et al. (2006). Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS (London, England)*, *January 9*(20(2)), 223–31.

Bartlett, J. A., & Shao, J. F. (2009). Successes , challenges , and limitations of current antiretroviral therapy in low-income and middle-income countries Barriers to ART. *The Lancet Infectious Diseases*, *9*(10), 637–649.

Bayou, T., Woldu, M., G.Meskel, G., & Mezgebe, H. (2014). Factors determinant for change of initial antiretroviral treatment regimen among patients on ART follow-up clinic of Mekelle Hospital, Mekelle, Ethiopia. *International Journal of Basic & Clinical Pharmacology*, *3*(1), 44.

Cesar, C., Shepherd, B. E., Krolewiecki, A. J., Fink, V. I., Schechter, M., Tuboi, S. H. et al. (2010). Rates and reasons for early change of first HAART in HIV-1-infected patients in 7 sites throughout the Caribbean and Latin America. *PloS One*, *5*(6),

Demessie, R., Mekonnen, A., Amogne, W., & Shibeshi, W. (2014). Knowledge and adherence to antiretroviral therapy among adult people living with HIV / AIDS at Tikur Anbessa Specialized Hospital , Ethiopia.*International Journal of Basic & Clinical Pharmacology*,*3*(2), 320–330.

Drug and therapeutics committee (DTC).(2012).. *List of pharmaceuticals for Tikur Anbessa specialized Hospital*. 1st edition.Addis Ababa, Ethiopia:Tikur anbessa specialized hospital in collaboration with PFSA and MSH/SIAPS.

Elzi, L., Marzolini, C., Furrer, H., Ledergerber, H., Cavassin, M., Hirschel, B.et al. (2010). Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arkives of Internal Medicine*, 11(170(1)), 55–65.

Food, Medicine and Health Care Administration and Control Authority (FMHACA). (2014). Standard Treatment Guidelines For General Hospital. 3rd edtion.Addis Ababa.Ethiopia.FMHACA.

Ford, N., Mofenson, L., Kranzer, K., Medu, L., Frigati, L., Mills, E. J., & Calmy, A. (2010). Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS*, *24*(10), 1461–1470.

Gebremedhin, L., & Birhane, A. (2014). Reasons for Anti-Retroviral Regimen Changes in HIV / AIDS patients of Ayder Referral Hospital ART clinic , Mekelle.*International Journal of Pharma Sciences and Research* , *5*(10), 693–700.

Hammer, S. M. (2002). Increasong Choices for HIV Therapy. *The New England Journal of Medicine*, *363*(22), 2090.

Hart, E., Curtis, H., Wilkins, E., & Johnson, M. (2007). National review of first treatment change after starting highly active antiretroviral therapy in antiretroviral-naïve patients. *HIV Medicine*, *8*(3), 186–91.

Hawkins, C., Achenbach, C., Fryda, W., Ngare, D., & Murphy, R. (2007). Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. *Journal of Acquired Immune Deficiency Syndromes* , *45*(3), 304–310.

Hoffmann CJ, Charalambous, S., Thio, C., Martin, D., Pemba, L., Fielding, K.et al. (2007). Hepatotoxicity in an African antiretroviral therapy cohort_ the effect of tuberculosis and hepatitis B.*AIDS (London, England),*21(10),1301-8

Jima, Y. T., Angamo, M., & Wabe, N.-R. (2013). Causes for antiretroviral regimen change among HIV/AIDS patients in Addis Ababa, Ethiopia. *Tanzania Journal of Health Research*, *15*(1), 1–9.

Katabira, E., & Oelrichs, R. (2007). Scaling up antiretroviral treatment in resource-limited settings: successes and challenges. *AIDS (London, England)*, (21 Suppl 4), s5–10.

Kumarasamy, N., Vallabhaneni, S., Cecelia, A. J., Yepthomi, T., Balakrishnan, P., Saghayam, S. et al. (2006). Reasons for Modification of Generic Highly Active Antiretroviral Therapeutic Regimens Among Patients in. *Journal of Acquired Immune Deficiency Syndromes*, *41*(1), 53–58.

Mekonnen, K. Y., & Molla, K. G. (2014). Reason for Regimen Change Among HIV Patients on Initial Highly Active Antiretroviral Therapy in Bedele. *Journal of Biotechnology and Biosafety*, *2*(4), 116–122.

Messou, E., Anglaret, X., Duvignac, J., Konan-N'dri, E., Komena, E., Gnokoro, J.et al. (2010). Antiretroviral treatment changes in adults from Côte d'Ivoire: the roles of tuberculosis and pregnancy. *AIDS (London, England)*, *24*(1), 93–9.

Federal Ministry of Health (MOH). (2007). G*uidelines for Management of Opportunistic Infections and Anti-Retroviral Treatment in Adolescents and Adults in Ethiopia*.Addis Ababa, Ethiopia: Federal HIV/AIDS prevention and control office, MOH.

Ministry of Health of the republic of Uganda (MOH). (2009). *National Antiretroviral Treatment Guidelines for Adults , Adolescents , and Children.*Second edition. Kampala, Uganda:STD/AIDS Control Programme MOH

Federal Ministry of Health (MOH). (2010). *Health Sector Development Program IV: 2010/11 -2014/15*,Final draft.Addis Ababa, Ethiopia:MOH,

Mulugeta, A., & Chane, T. (2012). Cause of Antiretroviral Drug Changes Among Patients on Antiretroviral Therapy At the Art. *International Journal of Pharmaceutical Sciences and Research*, *3*(1), 120–125.

National AIDS Resource Center (NARC). (2015).*HIV / AIDS Estimates and Projections in Ethiopia , 2011-2016*.[online] available from: http://www.etharc.org/index.php/resources/healthstat/[Accessed: 6January2015]

Palella, F. J., Deloria-Knoll, M., Chmiel, J. S., Moorman, A. C., Wood, K. C., Greenberg, A. E., & Holmberg, S. D. (2003). Survival Benefit of Initiating Antiretroviral Therapy in HIV-Infected persons in different CD4+ cell strata. *Annals of Internal Medicine*, *April 15*(138(8)), 620–6.

AIDSinfo.Panel on Antiretroviral Guidelines for Adults and Adolescents.(2014).*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.*Department of Health and Human Services.[online] available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 8 February 2015]

Petersen, M. L., Laan, M. J. van der, Napravnik, S., Eron, J. J., Moore, R. D., & Deeks, S. G. (2008). Long term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. *AIDS, October 18*(22(16)), 2097–2106.

Sandeep, B., Vansant, R. C., Raghunandan, M., Arshad, M., & Suresh, B. S. (2014). Factors influencing the substitution of antiretroviral therapy in human immunodeficiency virus/acquired immunodeficiency syndrome patients on first line highly active antiretroviral therapy. *Asian Journal of Pharmaceutical and Clinical Research, 7*(5), 117–120.

Sivadasan, A., Abraham, O. C., Rupali, P., Pulimood, S. a., Rajan, J., Rajkumar, S.et al. (2009). High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment. *Journal of Association of Physicians of India*, *57*(5), 384–388.

Tikur Anbessa Specialized Hospital (TASH). (2015). *ART clinic monthly report for October 2015.*Addis Ababa, Ethiopia:TASH.

World Health organization (WHO). (2007). *ART failure and strategies for switching ART regimens in the WHO European Region*. Copenhagen, Denmark:WHO Europe.

World Health organization (WHO). (2013a). *Global update on hiv treatment:results, impact and opportunities,breif summary*.Kuala Lumpur ,Malaysia:WHO

World Health organization (WHO). (2013b). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.*Geneva, Switzerland:WHO.

World Health organization (WHO). (2015). *WHO Fact Sheet*. [online]available from: http://www.who.int/mediacentre/factsheets/fs211/en/[Accessed : 9September 2015]

Wilkin, T., Marshall Glesby, & Gulick, R. M. (2006). Switching Antiretroviral Therapy Why, When and How. *Journal of Acquired Immune Deficiency Syndromes*, (12), 782–9.

Woldemedhin, B., & Wabe, N. (2012). The reason for regimen change among HIV/AIDS patients initiated on first line highly active antiretroviral therapy in Southern Ethiopia. *North American Journal of Medical Sciences, 4*(1), 19.

Wube, M., Tesfaye, A., & Hawaze, S. (2013). Antiretroviral therapy regimen change among

HIV/AIDS patients in Nekemt hospital: A primary care hospital in Oromia regional state, Ethiopia. *Journal of Applied Pharmaceutical Science*, *3*(8), 36–40.

Zhou, J., Li, P. C. K., Kumarasamy, N., Boyd, M., Chen, Y. M. a, Sirisanthana, T.et al.(2010). Deferred modification of antiretroviral regimen following documented treatment failure in Asia: Results from the TREAT Asia HIV Observational Database (TAHOD). *HIV Medicine*, *11*(1), 31–39.

Annex

1. **Data Abstraction sheet**

Socio demographic characteristics

Code No _____ Age on initiation (years)_____Months on ART_____

Sex Male ☐ Female ☐ **Family size _____**

Marital status single ☐ married ☐ divorced ☐ widowed ☐

Educational status No formal education ☐ Secondary school education ☐

Primary school education ☐ Hig her institute education ☐

Clinical and immunological characteristics

Weight during initiation of ART_____ before ART switch_____ latest weight _____

WHO clinical stage on initiation of ART ____before ART switch_____ latest stage_____

Base line CD4 count on initiation of ART _____ Date _____

Baseline viral load (VL)_____ Date _____

CD4 count before initial ART switch _____ Date _____

VL before initial ART switch _____ Date _____

Latest CD4 count _____ Date_____

Latest viral load (VL)_____ Date _____

Initial ART regimen_____ Date of ART initiation _____

Regimen switched to _____ Date of initial ART switch_____

Reason(s) for ART switch

Toxicity

Anemia	☐	Peripheral neuropathy	☐	Lipodystrophy	☐
Rash	☐	Hepatotoxicity	☐	Abdominal-pain	☐
Nausea	☐	Diarrhea	☐	GI irritation	☐
Headache	☐	CNS toxicities	☐	Fatigue	☐
Amenorrhea	☐	Renal failure	☐	Dyslipidemia	☐
Jaundice	☐	Other toxicity (specify) _____			

Treatment failure

Immunologic failure ☐ Peak CD4_____ CD4 during change_____

Clinical failure ☐ Clinical finding(s) _____

Virologic failure ☐ Baseline VL _____VL during change _____

Pregnancy ☐ **Adherence difficulty** ☐ **Stock out** ☐

Co morbidity ☐ Type of comorbidity _____

Other reason (specify) _____

TB treatment Yes ☐ No ☐

OI prophylaxis Co-trimoxazole ☐ Isoniazid ☐

Other Medications_____

Patient changed ART regimen for second time **Yes** ☐ **No** ☐

<u>If yes fill the following questionnaire</u>

WHO treatment stage prior to second ART ART switch _____ current treatment stage _____

Second time Regimen switched to _____ Date of second ART switch_____

Weight before second ART switch Date_____

CD4 before second ART switch Date_____

VL before second ART switch Date_____

Reason(s) for ART switch

Toxicity

Anemia	☐	Peripheral neuropathy	☐	Lipodystrophy	☐
Rash	☐	Hepatotoxicity	☐	Abdominal-pain	☐
Nausea	☐	Diarrhea	☐	GI irritation	☐
Headache	☐	CNS toxicities	☐	Fatigue	☐
Amenorrhea	☐	Renal failure	☐	Dyslipidemia	☐
Jaundice	☐	Other toxicity (specify)_____			

Treatment failure

Immunologic failure ☐ Peak CD4_____ CD4 during change_____

Clinical failure ☐ Clinical finding(s) _____

Virologic failure ☐ Baseline VL _____VL during change _____

Pregnancy ☐ **Adherence difficulty** ☐ **Stock out** ☐

Co morbidity ☐ Type of comorbidity _____

Other reason (specify) _____

Other Medications_____