Reasons for Modification or Discontinuation of First Highly Active Antiretroviral Therapy among Human Immunodeficiency Virus Infected adult Patients at Jimma University Specialized Hospital, South West Ethiopia.

By

Endalkachew Mekonnen Eticha

Research Thesis to be submitted to Department of Pharmacy, College of Public Health and Medical Sciences, Jimma University; in Partial Fulfilment of the Requirements for the Degree of Master of Science (MSc) in Clinical Pharmacy.

September 2013

Jimma, Ethiopia

Reasons for Modification or Discontinuation of First Highly Active Antiretroviral Therapy among Human Immunodeficiency Virus Infected adult Patients at Jimma University Specialized Hospital, South West Ethiopia.

By

Endalkachew Mekonnen Eticha

Advisors:

Mr. Nezif Hussien (B.Pharm, MSc in clinical Pharmacy)

Mr. Abdulalik Workicho(BSc, MPHE)

Abstract

Background: Highly active antiretroviral therapy has markedly decreased the morbidity and mortality due to HIV disease. However, toxicities and new TB drug treatment would result in frequent modification or discontinuation of antiretroviral drugs.

Objective: To assess reasons for modification or discontinuation of first highly active antiretroviral therapy and risk factors among HIV infected adult patients at Jimma University Specialized Hospital, South West Ethiopia.

Methods and materials: Retrospective general cohort study was conducted on 1533 of HIV infected adult naïve patients with ≥ 15 years and on highly active antiretroviral therapy from 2006 to 2010 at ART clinic of Jimma University Specialized Hospital. Kaplan-Meier was used to estimate probability of highly active antiretroviral therapy discontinuation or modification as well as Cox-regression models the associations between modification or discontinuation and toxicities with baseline factors. Cox-proportional hazard regression also used to evaluate effect of early modification or discontinuation of highly active antiretroviral therapy on treatment failure.

Result: High prevalence (47.7%) of modification and discontinuation was found. Estimated probability of modification or discontinuation within one year of HAART start was 16.6% (15.6– 17.6%). Toxicities were the most frequent 431(71.9%), reason for modification; however, no documented reason for discontinuation. Efavirenz and non-stavudine had lower risk of modification or discontinuation (Hazard ratio (HR) of 95% CI = 0.573(0.465 - 0.707) and 0.397(O.323 – 0.487)) when compared with nevirapine and stavudine based regimens respectively. Positive for tuberculosis screen and bedridden patients had higher hazard of modification or discontinuation (Hazard ratio (HR) = 1.411(1.162-1.714) and 1.485(1.054-2.093)). Early modification or discontinuation had associated [(HR) = 2.29(1.56 - 23.36)] with treatment failure. Age ≥ 35 years and positive for Tuberculosis had high hazard of toxicities ((HR) =1.326(1.091-1.612) and 1.473(1.120-1.938)) where efavirenz and non- stavudine containing regimens had lower hazard ((HR= 0.570(0.425-0.765) and 0.298(0.217-0.411)) for toxicities.

Conclusions: High prevalence of modification and discontinuation of highly active antiretroviral therapy, particularly due to toxicities. Positive for TB screen and the use of stavudine and nevirapine containing regimen had high risk of modification or discontinuation and also for toxicities. Close monitoring and management of toxicities are crucial for durability of highly active antiretroviral therapy.

Key words: Ethiopia, initial HAART, modification or discontinuation, risk factors

Table of Contents

List of figures

List of tables

Acknowledgment

First and foremost, I thank The Lord for giving me the strength and wisdom to do this thesis. I would like to acknowledge my advisors Mr. Nezif Hussein (B.Pharm, MSc in clinical pharmacy) and Mr. Abdulalik Workicho (BSc, MPHE) for their guidance and support throughout my work. At end I would like to give my appreciation to Jimma University for their financial support and services for our thesis and Jimma university Specialized hospital and staffs for their all support and services.

List of acronyms and abbreviations

AE	Adverse effects
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy/treatment
ZDV	Zidovudine
3TC	Lamivudine
CD4	T-cells (T-lymphocytes bearing CD4 receptor)
D4T	Stavudine
EFV	Efavirenz
FMHACA	Food, medicine and healthcare administration and control authority
HAART	Highly active antiretroviral therapy
HAPCO	HIV/AIDS prevention & control office
HIV	Human immunodeficiency virus
HR	Hazards ratio
IND	Indinavir
IQR	Inter quartile range
RVI	Retroviral infection
cART	Combined antiretroviral therapy
EPA	Ethiopian pharmaceutical association
MOD	Modification or discontinuation
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine

OIs	Opportunistic infections
PIs	Protease inhibitors
PLHIV	Peoples living with human immunodeficiency virus
PMTCT	Prevention of Mother to Child Transmission
SPSS	Stastical package for the social sciences
TB	Tuberculosis
TF	Treatment failure
UNAIDs	Joint United Nations Programme on HIV and AIDS
WHO	World health organization

1. Introduction

1.1 Background information

The emergence of the HIV (Human Immunodeficiency Virus) epidemic is one of the biggest public health challenges the world has ever seen in recent history. Globally, it is estimated to be 2.7 million people were newly infected with HIV in 2010. Of those newly infected individuals, about 1.9 million (70%) were living in Sub-Sahara Africa. Fifty percent (50%) of those that are HIV positive are women globally, where as in Sub-Saharan Africa women make up 60% of the HIV positive population.(1-2)

Ethiopia is one of the Sub-Saharan countries with hard hit by the HIV epidemic which probably began in the late 1970s or early 1980s with the first AIDS (Acquired immunodeficiency syndrome) cases reported in 1986. There were 789,900 people currently living with HIV and 952,700 AIDS orphans in 2012. Similar to other Sub-Saharan African countries spread through unprotected heterosexual intercourse(2-3). Antiretroviral Treatment (ART) programme was launched in 2003. There were a total of 333,434 people had ever started ART and 249,174 adults and 16,000 children currently on treatment by the end of 2011. (3-5)

Highly active antiretroviral therapy (HAART) has led to a major reduction of AIDS-related morbidity and mortality both in observational studies and clinical trials. Indeed, survival has steadily increased throughout the different eras of antiretroviral therapy.(6-8) Since 2001, the World Health Organization (WHO) has advocated a public health approach to HAART to rapidly improve access to this life-saving intervention in resource-poor settings.(9) This approach focuses on maximizing survival at the population level through standardized sequencing of available antiretroviral drugs, delivered to individuals by means of simplified approaches to clinical decision making and basic laboratory monitoring.(10) Similar to other countries in the world, HAART is universally available in Ethiopia and has been shown to prolong survival.(2-3)

Modification of the HAART regimen within 1 or 2 months of its initiation is mostly due to intolerance or toxicity, because immunological or virological failure is not easy to evaluate within the first 3 months.(11) Patients' early experience of toxicity of the initial HAART or modification in the antiretroviral regimen may reduce later

adherence to HAART.(12) In resource limited countries, serious toxicities of the drug, treatment failure and others complicate the whole management of antiretroviral therapy and lead to treatment modification or discontinuation.(11, 13-15)

Risk factors for discontinuation or modification of initial antiretroviral drugs can be grouped into three categories: (1) patient-related factors: Socio-demography and educational level; (2) disease-related factors: CD_4, plasma viral load, WHO clinical stage; (3) treatment-related factors: treatment failure and toxicities.(11, 13-16) Our cohort study done in Jimma University Specialized hospital, Southwest Ethiopia, has provided an important insight into the rate and reasons for modification or discontinuation (MOD) of HAART and risk factors among 1533 patients who started HAART as part of routine clinical care.

1.2 Statement of the problem

Studies from developed world states that 36–44% of patients may modify their first HAART regimen and 25% might discontinue therapy in the first 12 months of treatment.(17-19) Cross sectional study done in Ethiopia at Shashemene and Hawassa referral hospitals showed up to 67% of initial regimen modification within six months period.(20) Treatment toxicities, adherence problems, and treatment failures were major reasons of treatment MOD. High initial regimen MOD could expose patients to second regimen options. Second regimen options are less likely successful than first regimen (21-22) and may lead to suboptimal therapy and treatment failure.(13, 17, 21)

Treatment discontinuation was the main cause for treatment failure and staying on a failing first-line therapy was associated with increased mortality risk.(23-25) Monitoring efficacy of treatment in countries with limited resources is difficult because of inadequate laboratory facilities, shortage of trained staff and cost reagents which implies prevention is more economical than monitoring.(10)

Despite increasing access to antiretroviral drugs in resource poor settings; knowledge on long-term success, safety and tolerability of treatment programs was poor.(26-27) In addition, now a day's HIV related complications are declining and patients' survival is approaching to normal population in many patients (10, 21) and the future challenge of HAART treatment expected to be around minimizing drug toxicities.(28) Challenge in identifying factors associated with MOD are important for initial selection of regimens and when to modify regimens. Poor initial drug selection could increase the rate of initial regimen modification or discontinuation that may complicate future HAART management especially in developing countries.(26)

Data showing rate, reasons and risk factors for first HAART modification or discontinuation in Ethiopia is limited. Lack of these data may make physicians or ART expertise difficult to differentiate risky patients, appropriate regimen selection for specific patients and to identify reasons. Observational Studies done at Dasseie and Hawassa referral hospital, Ethiopia,(20, 29) identified major reason for regimen modification or discontinuation; however both did not determine any risk factors associated with MOD and drug toxicities.

2. Literature review

Determining rate and reason to modify or discontinue HAART and associated risk factors is very important for long-term effectiveness of treatment.(21) Toxicities, treatment failure and adherence problems are major reasons. Different observational studies showed that demographic factors, baseline CD_4, and WHO clinical stages were major risk factors associated with HAART discontinuation or modifications.(11, 14, 16, 18, 22, 30)

The rate and reasons for MOD initial HAART regimen have been assessed by different cohort studies from resource-rich and poor settings. A Multi-cohort study done from Latin America and the Caribbean's shows high rate of early modification or discontinuation after treatment initiation ranging from 8–28% in the first 3 months and 18–41% in the first 12 months with substantial variation across sites.(11) Similarly, other cohort studies report high rate of early initial regimen modification.(11, 14-15, 22, 30-31) Two cross sectional studies done in Ethiopia at Shashemene and Hawassa and Dassie referral hospitals showed high prevalence (up to 67%) of regimen modification or discontinuation with variation of reason to change in two sites.(20, 29)

Different cohort studies (11, 14, 20, 29, 32) identified drug toxicities as the most common reasons for modifying or discontinuing therapy. Study conducted in India and Uganda (16, 30)shows that cost was one of the major reasons for discontinuation or modification of drug, unlike other cohorts. Multi cohort studies from seven Latin America and the Caribbean's and study done on data report from 12 eastern European countries shows significant heterogeneity in the distribution of adverse events across sites or centres.(11, 16, 33)

Haematological toxicities (e.g. Anaemia), gastrointestinal toxicities and fat changes like lipodystrophy were the main toxicities reported for MOD.(11, 13, 15, 28, 34-36) Most previous and current studies have not evaluated the differences between short and long-term toxicities, but a cohort study done in Brazil (15) indicated gastrointestinal toxicities associated with short term toxicities and metabolic toxicity particularly dyslipidemia and lipodystrophy was the most frequent reason for long term toxicities. Other cohort studies also showed gastrointestinal abnormalities as the most common reason for early HAART modification.(31, 33) Unlike the above studies haematological

adverse events, 70% of which were anaemia, were most common for early change in Peru with prevalence of 67%.(11) Final result from different observational studies indicates that toxicities can compromise adherence and thus impact future treatment options; which especially relevant in the context of limited access to second and third line treatment regimens.(11, 15, 20, 30)

Most observational studies (11, 15, 20, 29-30) agree that peoples living with HIV and on HAART were less likely to modify or discontinue their therapy shortly after HAART initiation because of treatment failure than drug toxicities. Cohorts from seven Latin America and Caribbean countries, southern India and Brazil (11, 15-16) indicate that treatment failure was given as the reason for modification or discontinuation at 5%, 14%, and 20% respectively.

Socio-demographic and clinical factors were associated with HAART modification or discontinuation in different cohorts.(10, 13-14) The UK Collaborative HIV Cohort (UK CHIC) study demonstrated that those aged < 30 years and those aged > 50 years were at higher risk of HAART discontinuation for reasons other than virological failure.(25) Unlike UK CHI cohort, other cohort from UK found that older patients were less likely to modify or discontinue HAART.(13) A multi cohort study from Latin America and Caribbean's failed to identify consistent associations between gender or age and risk of antiretroviral change.(11) But, Brazilian cohort and Italian cohort (I.Co.N.A) demonstrates that being women had a higher hazard for Short term toxicities and poor adherence.(15, 25) One cross sectional study from Uganda demonstrated that modification of HAART was associated with marital status, being unmarried had more risk to modify or discontinue ARV than married individuals.(16)

ART regimen has been associated with initial regimen MOD in some studies. Anaemia was the most common side effect that causes modification of regimen from AZT-based regimens.(11, 13, 29) AZT-based use was associated with an increased risk of discontinuation in the first four months of therapy and this early toxicity was associated with low baseline body weight in Latin American cohort.(11) Another study (29) from Ethiopia at Dasseie referral hospital indicates 50% toxicity was due to AZT /3TC/ EFV-regimen in which anaemia was the only adverse effect resulted from these regimen.

Efavirenz-based regimens had the lower hazard for change than NVP-based regimen in Peru.(29)

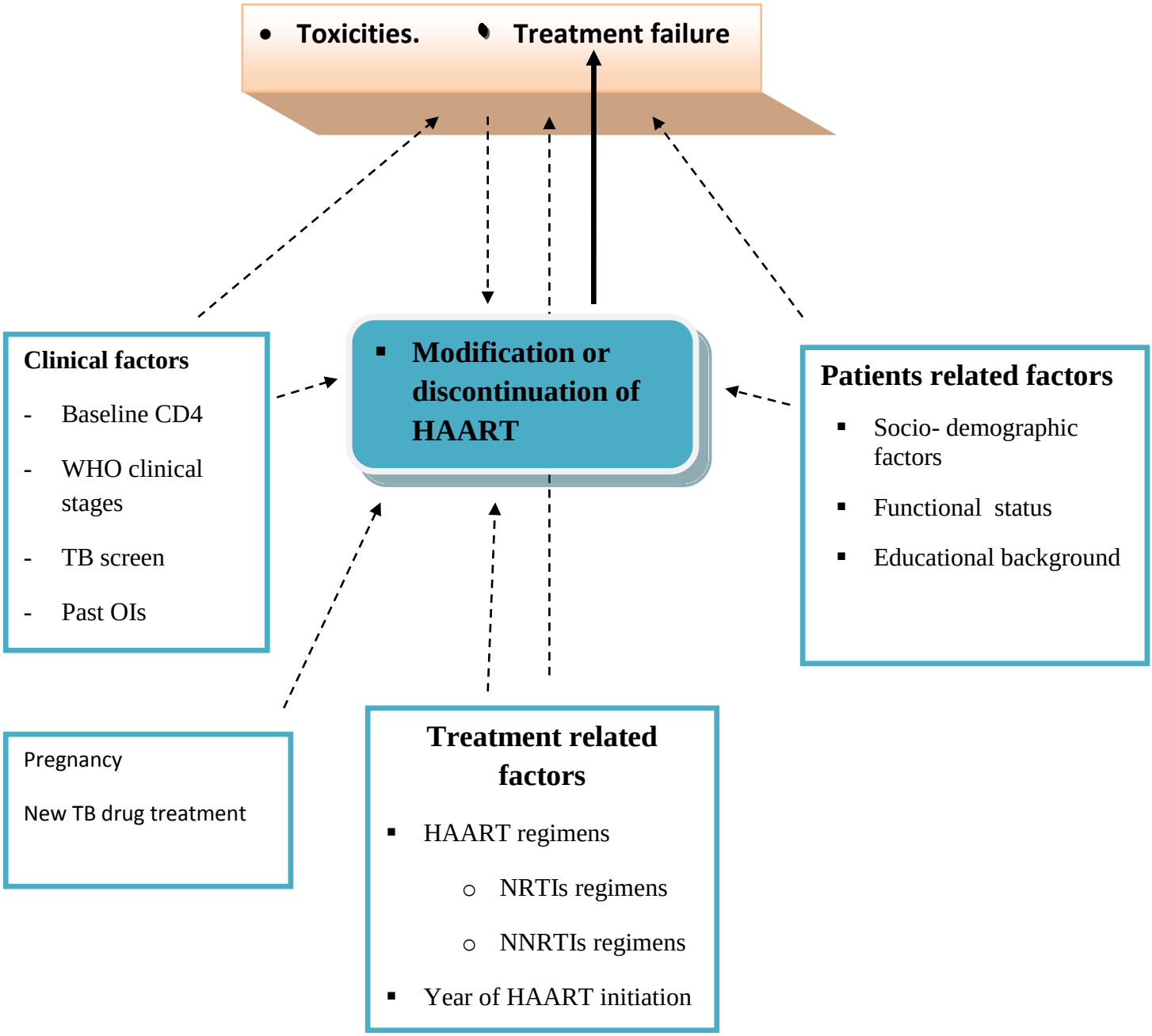
Cohort studies from Brazil found that HAART regimen containing lamivudine and efavirenz associated with significantly lower hazard of Treatment failure.(15) The use of zidovudine, lamivudine, and efavirenz was also associated with a significant reduction in the hazard of treatment failure. Based on their findings, they highlighted this combination as well-tolerated antiretroviral drug combinations. In contrast, didanosine (ddi) use was independently associated with almost three fold higher hazard for treatment failure when compared to regimens without this drug.(15)

Studies from developed and developing countries indicated that AIDS-defining illness at treatment initiation increased the probability of discontinuation. Two studies from UK(22) and Ethiopia(29) show tuberculosis was the only co-morbid disease reported. In contrast to this, in Haiti patients having advanced disease at baseline had unexpectedly lower rates of modification/discontinuation due to adverse events than other sites in Latin America.(11)

The Swiss HIV Cohort Study indicated that higher baseline CD4 cell count was associated with highest risk of gastrointestinal tract intolerance that may compromise quality of life and poor treatment adherence and lead to treatment modification.(22) This is in contrast to other New Orleans cohort study in which gastrointestinal tract adverse events tended to be more common in people with lower CD4cell counts.(31) Lower CD4 lymphocyte counts (<200 cells/mm3) was associated with increased hazard of treatment failure.(15)

As a summary; toxicities, treatment failure and new TB drug treatment were the main reason for treatment modification and discontinuation. Toxicities were the major cause of modification and discontinuation in both resource rich and poor countries and have impact in future success of treatment. ART regimen, lower CD4 count, age, gender and AIDS defining illness at treatment initiation increased the probabilities of discontinuation or modification.(11, 15, 30)

2.1 Conceptual framework



3. Significance of the study

Determining rate, reasons and risk factors for HAART MOD is required for understanding of long term success, safety and convenience of HAART regimens in resource-limited and rich settings. It is also important for improving patient care and increasing adherence. Minimizing drug toxicities has a significant role in HAART success as HIV related complications are declining and patients' survival is approaching to normal population in many patients. These data can potentially provide a long term strategic approach to initial and subsequent decisions regarding ART.

As shown in above literature review, drug toxicities were the most common reason for MOD. In resource limiting settings old drugs has been in use due to their low cost and availability although less toxic and tolerable rugs were available. In Ethiopia (also to JUSH), current formulary restrictions appear to be unlikely to modify quickly as treatment options are limited. Identifying reasons and risk factors of HAART MOD and toxicities could make physicians understand and manage them with what is available locally. This could make patients to stay on safe and tolerable first regimen drugs. If not, it makes patients to lose the possible treatment regimen options for future and also make the nation or providers to shift their funding toward buying cost drugs. Generally it could have great impact on pharmacoeconimic aspects of HAART related to availability, funding and cost of alternative drugs.

Finding of this study may support or contribute to initiate update of guidelines on HIV/AIDS management as one source. It may also initiate the Federal HIV/AIDS prevention and control office and other researchers to carry out a national and regional study to determine rate and assess reason of modification and discontinuation of highly active antiretroviral therapy with their risk factors.

4. Objective of the study

4.1 General objective of the study

- To assess reasons of modification or discontinuation of first HAART and risk factors among HIV Infected adult Patients in Jimma University Specialized Hospital, South West Ethiopia.

4.2 Specific objective of the study

- ✓ To determine prevalence of initial HAART regimen MOD. .
- ✓ To identify reasons for MOD of HAART.
- ✓ To evaluate the effect of early MOD on treatment failure.
- ✓ To assess risk factors associated with ART drugs toxicities.
- ✓ To assess risk factors associated with MOD.

5. Methods and materials

5.1 Study area and settings

The study was conducted at ART clinic of Jimma university specialized hospital (JUSH). It is one of the teaching hospital found in southwest of Ethiopia in Jimma town which is 365 Km from capital city, Addis Ababa. It is referral Hospital which provides fee free services for HIV virus infected patients in Jimma zone and around regions, including transfer in patients. Patients infected with HIV and confirmed with diagnosis are enrolled into pre-ART care. Those patients eligible to start treatment according to clinical (CD4 below 200, WHO stage IV, WHO stage II and III with TLC less than or equal 200) and social criteria (resident of catchment area, no identified barrier for adherence) will start HAART. Patient adherence value will be estimated on appointment day and those with poor (> 6 doses out of 30 doses) and fair (3-5 doses out of 30 doses) adherence will be asked for reasons. The reasons for poor and fair adherence will be evaluated accordingly.

In our settings, 2776 patients live with HIV and 1664 were on HAART from January 2006 to December 2010. From these patients our study was conducted on 1533 patients. For 131 individual we couldn't get their follow up record. The study was conducted from January 1, 2013 to August 30, 2013.

5.2 Study design

Retrospective general cohort study was employed.

5.3 Selection of participants

5.3.1 Source population

Peoples living with HIV (PLHIV) and on ART clinic of JUSH

5.3.2 Study population

Naïve HAART initiators from 2006-2010 at ART clinic of JUSH fulfilling inclusion criteria were studied. PLHIV and on HAART before 2006 when ART started in our settings (i.e. study area) were not included due to fear of incomplete information on records, limited access due to cost and less availability of treatment options.

5.3.3 Inclusion and exclusion criteria

Inclusion criteria

Human immunodeficiency virus infected patients ≥ 15 years who were naïve HAART initiators from 2006-2010 and had at least one follow-up visit were included. HAART experienced patients from 2010 to 2012 who started treatment during 2006 to 2010 were also included to evaluate effect of early modification or discontinuation on treatment failure.

Exclusion criteria

Women with HIV who received HAART for PMTCT were excluded. Transfers in patients were also excluded.

5.4 Sample size determination

All naïve HAART initiators from 2006 -2010 calendar year with inclusion criteria were included.

5.5 Instrument and data collection procedures

Tools for data collection was prepared from baseline socio-demographic, clinical and treatment related factors collected from different articles done previously and modified to match with ART follow-up record of our setting. We classified the factors into three categories: (1) patient-related factors; (2) clinical related factors and (3) treatment-related factors. Trained nurses and database clerk workers collected the data using data collection tool from ART follow-up record (medical record). The following information were collected: socio-demographic factors, baseline and consecutive CD4 count, baseline WHO clinical stage, initial HAART, time HAART started, first ART modified, time at modification or discontinuation of HAART, second regimen, reasons for modification of HAART, past opportunistic infections, TB screen result and death report. Occurrence of new opportunistic infection, treatment failure and death reports were also collected from ART follow up record.

Patients ART follow up records were reviewed from year of HAART initiation until occurrence of the event (modification or discontinuation). Censoring was done for those who never had modification or discontinuation of HAART. Lost to follow and drop

outs were recorded as treatment discontinuation. Individuals who died and transfer out while on their first regimen were censored at the time of death and transfer at analyses. Time was measured from the start of HAART and ended at the earliest of regimen modification, death and last visit before lost to follow and transfer out. Reason for occurrence of an event was filled on data collection format for analysis. Clinical and immunological information were collected to evaluate the effect of modification or discontinuation on treatment failure.

5.6 Study variables

Independent variables

- **Patients related variables**
  - Socio-demographic variables
  - Functional status
  - Educational background
  - Pregnancy
- **Treatment related variables**
  - HAART regimens
  - Time of HAART initiation
  - New TB drug treatment
- **Clinical related variables**
  - Baseline CD4 cell counts
  - Baseline WHO clinical stages
  - Past opportunistic infections
  - TB screening

Dependent variable

- Time to modification or discontinuation of HAART

- ❖ Reason for modification (toxicities, Treatment failure)

5.7 Data analysis

The collected data was cleaned, categorized, coded, entered and analysed by using stastical package for the social sciences (SPSS) version 16. Rate was estimated and reported as the number of occurrences per 100 persons-years (PY). Probability of HAART regimen MOD was estimated using Kaplan-Meier techniques.

Cox proportional hazard regression models the associations between independent variables with the outcomes (MOD, toxicities and treatment failure). Factors found to be associated with the outcome in the univariate analysis assuming a significance threshold of 20% were included in the multivariate model. The multivariate model was tested for each factor in order to evaluate its impact on outcome. Antiretroviral drugs regimens in different classes having common antiretroviral drug were not analyzed in the same model. The multivariate models that showed a significant effect on the outcome considering the significance threshold of 5% are described. The hazard of early regimen MOD on the occurrence of new opportunistic infection or death and immunological outcome was estimated using Cox's regression model**.** Variables in the Cox models included all available demographic, treatment and clinical characteristics, as well as early modification of the initial regimen.

5.8 Data quality assurance

To maintain quality of data, data collection tool was prepared for this specific study and pre-tested for its completeness of variables on randomly selected patients' card. After a format had filled, it was cross checked with computer database. For data collection, two first degree nurses and one ART database clerk supervisor were involved. The supervisor and principal investigator checked and supervised for completeness of the tool with appropriate information and cross check with both computer databases. Cross cheeking with computer database was performed by database clerk.

5.9 Ethical consideration

Ethical approval to conduct this study was asked and obtained from ethical review board of College of Public Health and Medical Sciences, Jimma University. Permission to conduct the study was secured from the medical director of Jimma university

specialized hospital. All the required data was collected from secondary data sources, patients' medical card, without any contact with the patients. The confidentiality of the information was kept and no disclosure of the patients name (only ART follow up record was used), the health care provider or drug product in relation to the findings during data collection and analysis. All patients name, reasons for change and drug regimen was coded.

5.10 Dissemination Plan

The final findings and full detail of the article will be disseminated and/ or presented to Jimma university community, EPA (Ethiopian pharmaceutical association) and finally will be tried to be publish on peer-reviewed journal.

5.11 Operational definition and definitions of terms

- HAART - as combination of two NRTIs and at least one PI or one NNRTI.
- First HAART Regimen – initial HAART regimen naïve patient had started.
- Second HAART regimen –regimen MOD
- HAART discontinuation was defined as stopping of antiretroviral therapy with no documented regimen resumed for at least one month (lost to follow up and drop out were also included as HAART discontinuation).
- HAART modification was defined as substitution of at least one antiretroviral drug in the regimen. Dosage adjustments of the regimen were not considered as modifications.
- Early modification and discontinuation was defined as less than 7months of therapy from HAART initiation.
- Treatment failure is either:
    - Immunological (Fall of CD4 count to below baseline or 50% fall from on-treatment peak value or Persistent CD4 levels below 100 cells/mm3) and/ or

- Clinical failures (occurrence of new opportunistic infections or death).

- Toxicities is defined as the occurrence of adverse events such as diarrheal, vomiting, nausea, anaemia, rash, fatigue, peripheral neuropathy, lipodystrophy, metabolic disturbances, or any other related to HAART which were confirmed clinically or with laboratory test when available..

    - Short-term toxicity - any toxicity occurring up to one year after HAART initiation.

    - Long-term toxicity - any toxicity occurring more than one year after HAART initiation.

- Baseline CD4 count was defined as CD4 count measurement at HAART initiation or closest to initiation date with $\pm$ 1 month.

- Lost to follow-up - patient left for treatment less than or equal to three months.

- Drop out- lost for treatment for greater than three months.

- Functional status

    - Working (W) – able to perform usual work in or out of the house, harvest, go to school, for children, normal activities and playing.

    - Ambulatory (A) – able to perform activities of daily living.

    - Bedridden (B) – not able to perform daily activities.

- Advanced immunosuppression - when patients are in advanced WHO clinical stages (stage III and IV).

- Primary level school education – up to grade eight.

6. Results

A total of 1533 naive patients starting HAART with at least one follow-up visit were included, of which 963 (62.8%) were females. Socio-demographic and clinical characteristics are given in table 1. The median age and CD4 cell count of patients were 30 (inter-quartile range (IQR) 26 – 38) years in age) and 144 (IQR; 79-210) cells/mm^3 respectively. More than two thirds of the patients, 1102(71.8), started ART with a CD4 cell count of ≤ 200 cells/mm3 and 61.9% of these were females.

Table 1: Baseline Socio-demographic and clinical characteristics of the Patients on HAART at the ART clinic of JUSH from 2006-2010, Ethiopia 2013

Baseline characteristics	**N (%)**
Age group	
<= 35	1055(68.8)
>35	478(31.2)
Sex	
Female	963(62.8)
Male	570(37.2)
Marital status	
In relationship	733(47.8)
Not in relationship	798(52.0)
Missing values	2
Religion	
Orthodox	862(56.2)
Muslim	479(31.2)
Protestant	180(11.7)
Catholic	10(0.7)
Others	2(0.1)
Primary level education	
Below	835(54.5)
Above	698(45.5)
Functional status	
Working	1058(69.0)

Table 1: continued ……	
Ambulatory	394(25.7)
Bedridden	63(4.1)
Missing values	18(1.2)
Eligibility code	
Code II (CD4 based)	1319(86)
Code I (clinical only)	197(12.9)
TLC	17(1.1)
Year of HAART initiation	
Before Sep. 2008	801(52.3)
After Sep. 2008	732(47.7)
Initial CD4	
<=200	1102(71.8)
>200	429(28)
Missing values	2
WHO clinical stages	
Stage I	290(18.9)
Stage II	436(28.4)
Stage III	648(42.3)
Stage IV	159(10.4)
Past opportunistic infections	
Yes	1183(77.2)
No	342(22.3)
Missing values	8
TB screen	
Negative	1207(78.7)
Positive	281(18.3)
Missing values	45(2.9)

Near to half of the patients, 733(47.8), were in relationship and orthodox was the most common religion, 862(56.2%), found in HAART initiators. With regard to educational background greater than half, 835(54.5), of the patients were below primary level school (< 8 grade). At the time of HAART initiation 1183 (77.2%) patients had past opportunistic infection before HAART initiation. Herpes zoster was the most frequent opportunistic infection (41%). For majority of the patients, 1319 (86%), CD4 count was the eligible criteria for HAART initiation; while 197(12.9%) naïve patients were started on HAART based on clinical eligibility criteria. At HAART initiation half of patients were in advanced disease stage (clinical stage III and IV). Initiation of treatment was started at WHO clinical stage III for majority of the patients, 648 (42.3%).

Table 2: First HAART regimens prescribed for HIV virus infected adult patients at ART clinic of JUSH from 2006 to 2010, Ethiopia 2013.

	N (%)
Initial HAART regimen	
D4T + 3TC + NVP	855(55.8)
TDF + 3TC + EFV	302(19.7)
ZDV + 3TC + NVP	165(10.8)
ZDV + 3TC + EFV	88(5.7)
D4T + 3TC + EFV	87(5.7)
TDF + 3TC + NVP	36(2.3)
NNRTI-based	
NVP based	1056(68.9)
EFV based	477(31.1)
NRTI-based regimen	
D4T based	942(61.4)
TDF based	338(22.0)
ZDV based	253(16.5)

More than half of patients, 855 (55.8%), were started initial regimen of D4T-3TC-NVP combination followed by 302 (19.7%) of TDF-3TC-EFV as shown in table 2.

Nevirapine based regimens were the most frequently, 1056(68.9%), used NNRTIs. All combination regimens contain 3TC as NRTIs backbone. NVP was less commonly, 36(10.7%), initiated with TDF. Among patients started HAART before September 2008, 91.8% of them were on D4T containing regimen. In contrast to this, TDF was not used during this period because TDF started in our setting after 2008

Patients were followed for a total of 6,898.5 person years (PY) with a median follow up of 54.20 (95% CI: 51.012 – 57.388) months. A total of 731 modification and discontinuation were observed corresponding to an overall incidence rate of 10.59 per 100 PY with a median follow up of 24.37 months (95% CI: 21.463 – 27.204).

Table 3: Reasons for modification of first HAART regimens prescribed for HIV infected patients from 2006 to 2010 at ART clinic of JUSH, Ethiopia 2013.

Reasons for modification	N (%)
Toxicities	431(71.9)
Unspecified toxicities	297
Specified toxicities	134
Fat changes	82
Peripheral neuropathy	30
Anaemia	14
CNS manifestation	5
Rash	2
Hepato-toxicities	1
New TB drug treatment	120(19.9)
Pregnancy	29(4.8)
Treatment failure	24(4.0)

Six hundred forty (41.75%) patients had ever modified their initial HAART regimen and 91 (5.94%) patients discontinued their therapy and overall MOD was 47.7%. From those MOD their regimen near to two thirds of patients, 465(63.6%), were females.

Three fourth of patients, 74.9% and 79.6%, MOD their initial regimen had CD4 count <=200cells/mm^3 and past opportunistic infection before HAART initiation respectively.

Kaplan-Meier estimates of the overall probability of MOD at 3-month and 1-year for the cohort was 8.1% (7.4– 8.8%) and 16.6% (15.6– 17.6%) respectively. The next 2-year and 3-year probabilities of MOD were 24.2% (23.1 – 25.3%) and 31.2% (30% - 32.4%) at 95% CI respectively.

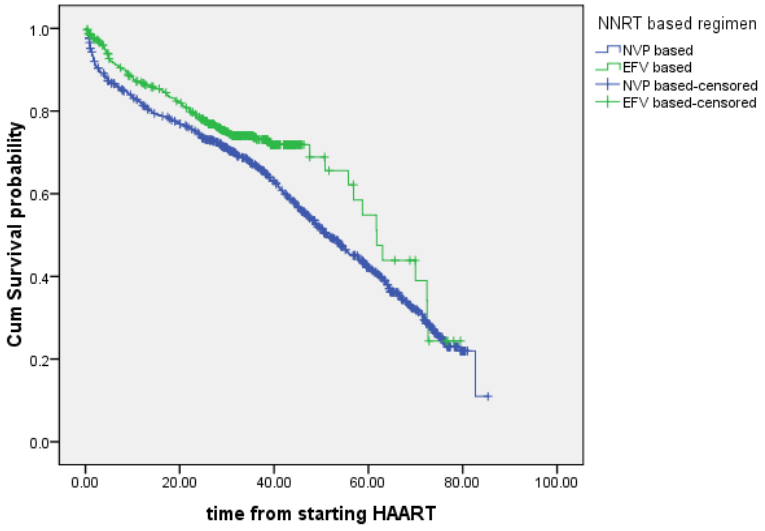


Figure 1: *Kaplan-Meier plot of time to HAART modification stratified by NNRTIs: p = 0.057*

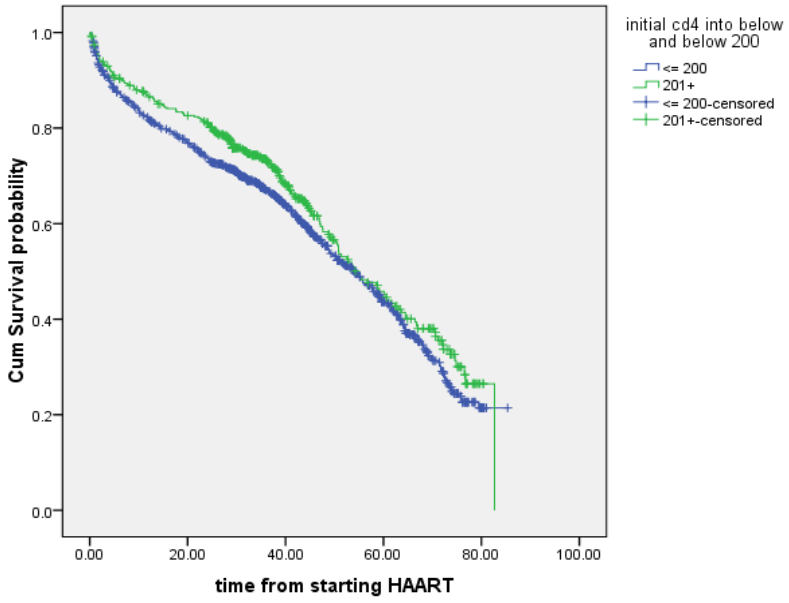


Figure 2: *Kaplan-Meier plot of time to HAART modification stratified by CD4 count. P = 0.002*

The above two Kaplan-Meier plots showed that patients on nevirapine based regimen and had baseline CD4 count less than or equal to 200 had high probability of modification or discontinuation.

Drug toxicities or adverse events (ADE) were the predominant reason for modification of HAARTs as shown in table 3. It prompted modification in 431 (71.9%) of HAART initiators with a median follow up of 38.367(95% CI: 34.870-41.863) months and were the most common reason. New TB treatment, 120(20%), planning pregnancy or being pregnant, 29(4.8%), and treatment failure, 24(4%), were other causes for modification of initial HAART regimens. There was no documented reason for 36(5.63%) patients among those modifying their regimen and for all those discontinued their HAART regimen. Fat changes, 82(13.6%), peripheral neuropathy, 30(5%), and anaemia, 14(2.3%), were the most common toxicities among specified toxicities.

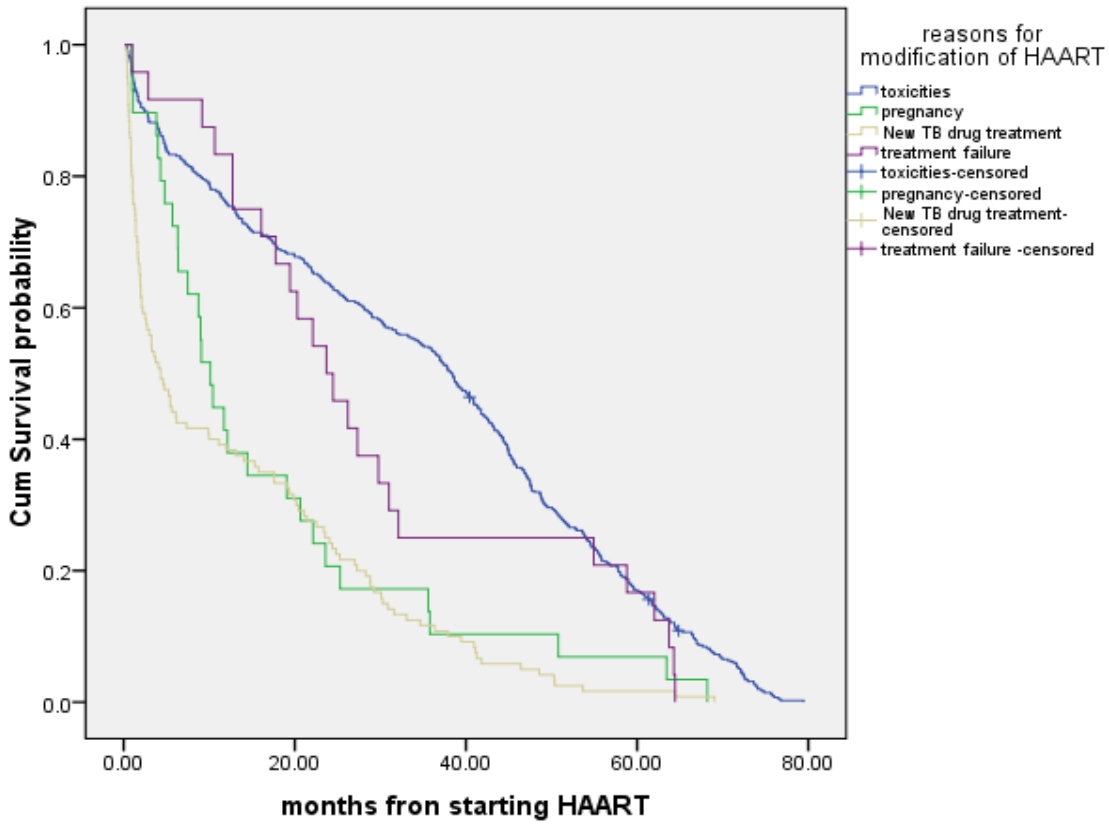


Figure 3: *Kaplan-Meier plot of HAART modification stratified by reasons: toxicities, pregnancy, new TB drug treatment and treatment failure.*

Of 731 individuals MOD their initial HAART regimen 253 (34.6%) of them experience the events within 12 months of which near to half of them experience the events within the first three months. Toxicity was the main reason for 50(11.6%) and 104(24.13%) of patients modifying their treatment during 3 and 12 months respectively. Anaemia, peripheral neuropathy, and rash were the most common toxicities within the first three months.

From all patients who modified their initial treatment, 616 (96.25%) modified to first line regimen; while 24(3.75%) of patients started second line treatment. Among 731 patients MOD their regimen 543(74.3%) patients had been on D4T-3TC-NVP combination as initial regimen. New TB treatment and Fat changes (lipodystrophy and lipoatrophy) were the main reason for D4T-3TC-NVP regimen modification at 103(22.1%) and 67(14.4%) respectively. Unlike patients on D4T-3TC-NVP, patients on TDF-3TC-NVP had the lowest prevalence, 6(0.9%), of modify their regimen. Among 4,599 first line ART drugs prescribed D4T was the most common, 413(8.98%), ART modified followed by NVP, 163(3.54%).

Table 4: NNRTIs and NRTIs class based reasons for modification of HAART among PLHIV at the ART clinic of JUSH from 2006-2010, Ethiopia, 2013.

HAART classes	**Toxicities N (%)**	**Pregnancy N (%)**	**New TB drug treatment N (%)**	**Treatment failure N (%)**
NNRTIs classes				
NVP	374(86.8)	8(27.6)	118(98.3)	13(54.2)
EFV	57(13.2)	21(72.4)	2(1.7)	11(45.8)
NRTIs classes				
D4T	385(89.3)	12(41.4)	104(86.7)	12(50)
AZT	38(8.8)	3(10.3)	13(10.8)	3(12.5)
TDF	8(1.9)	14(48.3)	3(2.5)	9(37.5)

Fat changes and peripheral neuropathy in 78(95.1%) and 28(93.3%) of patients respectively were the main reason for D4T-based modification. Unlike D4T it was anemia which was a majorly responsible for modification of ZDV, 10(71.4%).

Drug toxicities were the main reason for modification of NNRTIs although type of toxicities varied according to treatment regimen as shown in table 4. Three of five reported CNS toxicities were from EFV containing regimens and two specified skin rashes were from NVP and both reported early.

As shown by table 5, univariate analysis of baseline factors showed that older than 35 age, above primary level education, less advanced WHO clinical stages, no opportunistic infection and positive for TB screen at HAART initiation were associated with hazard of toxicities. When transferred to multivariate analysis and modelled they had also association with hazard of toxicities, except patients with past opportunistic infection.

Table 5: Unadjusted and adjusted hazard ratios (95% CI) for ART toxicities among 1533 naïve adult patients at the ART clinic of JUSH from 2006-2010, Ethiopia, 2013.

Variables (characteristic)	**Toxicities (%)**	**No toxicities (%)**	**Unadjusted HR(95% CI)**	**Adjusted HR (95% CI)**
Age				
<= 35	281(18.33)	774(50.48)	1	1
>35	150(9.78)	328(21.39)	1.298(1.073- 1.570)*	1.326(1.091 -1.612)*
Primal level school				
Below	206(13.44)	629(41.03)	1	1
Above	225(14.68)	473(30.85)	1.357(1.123- 1.640)**	1.261(1.039 -1.531)**
WHO clinical stages				
Less advanced	201(13.11)	525(34.25)	1	1
Advanced	230(15.00)	577(37.64)	0.823(0.679- 0.998)*	0.775(0.624- 0.962)*

Table 5: continued……

Past OIs				
No	94(6.13)	248(16.17)	1	1
Yes	335(21.85)	848(55.31)	0.807(0.640 -1.018)*	0.787(0.611- 1.014)
TB screen				
Negative	342(22.30)	865(56.42)	1	1
Positive	75(4.89)	206(13.43)	1.281(0.997-1.645)*	1.473(1.120 -1.938)*
First regimen				
D4t-3Tc-Nvp	347(22.63)	508(33.13)	1	1
D4t-3Tc-Efv	38(2.47)	49(31.96)	1.446(1.033- 2.022)*	1.319(0.925- 1.881)
Azt-3Tc-Nvp	25(1.63)	140(9.13)	0.438(0.289 -0.663)**	0.441(0.287 -0.675)**
Azt-3Tc-Efv	13(0.84)	75(4.89)	0.794(0.453 -1.394)	0.697(0.396- 1.227)
Tdf-3Tc-Efv	6(0.39)	296(19.31)	0.100(0.044- 0.224)**	0.091(0.040- 0.206)**
Tdf-3Tc-Nvp	2	34(2.22)	0.289(0.072- 1.1630)	0.270(0.067- 1.088)
NRTIs based				
D4-based	385	557	1	1
Non-D4t based	46	545	0.316(0.231- 0.433)*	0.298(0.217- 0.411)*
NNRTIs based				
Nvp-based	374	682	1	1
Efv-based	57	420	0.635(0.476- 0.847)*	0.570(0.425- 0.765)*

**- statically significant at p<0.05 and ** -significant at p<0.001*

Patients in advanced disease state at HAART initiation had lower risk (HR=0.775 (95% CI: 0.624-0.962)) for ART toxicities than patients with less advanced HIV disease. Multivariate analysis showed age $\geq$ 35 years to be associated with a statistically significant hazard of toxicities [HR=1.326 (95% CI: 1.091-1.612]. Although not statistical significant at multivariate analysis, patients having past opportunistic infection at HAART initiation had lower risk for toxicities, [HR; 0.787(95% CI: 0.611-1.014)]; P=0.064. We did not observe association of CD4 count with ART toxicities.

Efavirenz and non-D4T based regimens were the most tolerable regimens than NVP-based and D4T containing regimens with HR of 0.635(95% CI: 0.476-0.847) and

0.298(95% CI: 0.217-0.411) respectively. Among first line regimens prescribed in our settings from January 2006 to December 2010, TDF-3TC-EFV combination had lowest risk [HR; 0.091(95% CI: 0.040-0.206)] of toxicities compared with D4T-3TC-NVP.

Next to ART toxicities, new TB treatment and being pregnant or planning pregnancy were reasons for HAART modification at 19.9% and 4.8% with 4.30[95% CI: 2.291-6.309] and 10.133(95% CI: 7.613-12.653) median follow-up months respectively. New TB treatment was the main reason for early modification even within the first three months with incidence rate of 3.145 per 100 person year and estimated to be 7.83% of HAART initiators. 98.3% of NVP and 72.4% of EFV-based regimens were modified due to new TB treatment and being or planning pregnancy respectively.

Treatment failure (TF) was also another reason for HAART treatment modification. Twenty four patients (4%) had their HAART regimen modified due to treatment failure in which 7 patients due to clinical failure and 17 due to immunological failure. This corresponds to incidence rate of 0.6 per 100 PY and estimated to be 1.4% of HAART initiators. The median follow-up time for TF was 23.7(95% CI: 3.613 – 30.781) months. From these patients greater than half of them (13 patients) were on NVP- based regimens; while the rest 11 patients were on EFV-based regimens. Individuals treated with ZDV-3TC-NVP as initial regimen showed the highest rate, 41.7%, of treatment failure followed by TDF-3TC-EFV based regimens, 33.3%.

We observed 169 (11.9%) patients had treatment failure with a median follow up period of 20 (95% CI: 16.930-23.070) months from subsequent CD4 cell counts from follow up record and death reports. One hundred thirty eight patients were due to immunological failure and the rest 31 patients were due to clinical failure. Two third of patients, 113(66.9%), on treatment failure were on NVP-based regimens. Among 191 individuals modified or discontinued their initial regimen early (< 7 months) of HAART initiation, only 2 patients had treatment failure. Multivariate analyses showed that hazard of treatment failure in early modifying or discontinuing of the initial HAART regimen is 2.29 times late modifying or discontinuing [HR, 2.29(95% CI: 1.56 - 23.36); P< 0.001].

Table 6: Unadjusted and adjusted hazard ratios (95% CI) for treatment failure among 1533 naïve adult patients at ART clinic of JUSH from 2006-2010, Ethiopia, 2013

Variables (characterstics)	Unadjusted HR (95% CI :)	Adjusted HR (95% CI :)
Year of start		
Before Sep. 2008	1	1
After Sep. 2008	3.05(2.07 – 4.48)*	3.33(2.22 - 5.00)*
Clinical WHO stag		
WHO stage I	1	1
WHO stage II	0.506(0.301 – 0.850)*	0.71(0.42 -1.21)
WHO stage III	0.546(0.340 – 0.877)*	0.63(0.39 – 1.02)
WHO stage IV	0.458(0.242 – 0.867)*	0.61(0.32 – 1.16)
CD4 count		
≤ 200	1	1
>200	1.31(0.91 – 1.88)	1.08(0.74 – 1.57)
Early MOD		
No	1	1
Yes	2.19(1.51 – 3.18)*	2.29(1.56 - 23.36)*

*- *statically significant at p<0.05 and ** -significant at p<0.001*

Univariate analysis of our study showed, patients above primary level education, initiating of HAART after or on 2008, positive in TB screen, ambulatory and bedridden patients at HAART initiation, low initial CD4 count, D4T and/or NVP containing regimen had association with hazard of MOD as shown in table 7. The results from the multivariate model indicate that the hazard of MOD for Ambulatory and bedridden patients at HAART initiation is 1.2 and 1.485 times the hazard for working patients with HR of 1.200(95% CI: 1.013-1.422) and 1.485(1.054-2.093) respectively. Hazard of MOD for Positive in TB screening at HAART initiation is 1.4 times negative for TB. This cohort also showed that patients started treatment after September 2008 had high risk [HR, 1.522(95% CI: 1.279-1.810) for MOD than those started before.

Table 7: Hazard ratios (95% CI) for modification or discontinuation among 1533 naïve adult patients at the ART clinic of JUSH from 2006-2010, Ethiopia, 2013.

Variables	MOD (%)	No MOD (%)	Unadjusted HR (95% CI :)	Adjusted HR (95% CI)
Primary level school				
Below	370(24.14)	337(21.98)	1	1
Above	361(23.55)	465(30.33)	1.209(1.046- 1.398)*	1.263(1.088-1.465)*
Year of HAART Initiation				
Before September 2008	501(32.68)	300(19.57)	1	1
After September 2008	230(15.00)	502(32.75)	1.281(1.008- 1.508)*	1.522(1.279-1.810)*
TB screening				
Negative	569(37.12)	638(41.62)	1	1
Positive	139(9.1)	142(9.26)	1.356(1.126-1.633)**	1.411(1.162-1.714)**
Patients status				
Working	478(31.18)	580(37.83)	1	1
Ambulatory	209(13.63)	185(12.06)	1.196(1.017- 1.408)*	1.200(1.013-1.422)*
Bedridden	37(2.41)	26(1.69)	1.428(1.020- 1.998)*	1.485(1.054-2.093)*
Initial CD4				
< 200	547(35.68)	555(36.20)	1	1
≥200	183(11.94)	246(16.05)	0.850(0.719- 1.005)	0.937(0.788-1.114)
First regimen				
D4T-3TC- NVP	543(35.42)	312(20.35)	1	1

Table 7.continued…….

D4T-3TC-EFV	57(37.18)	30(1.95)	1.318(1.002 -1.732)	0.994(0.742 -1.332)
AZT-3TC-NVP	51(3.32)	114(7.43)	0.577(0.433-0.770)**	0.493(0.367 -0.662)**
AZT-3TC-EFV	23(1.50)	65(4.24)	0.709(0.465 -1.080)	0.502(0.326 -0.772)*
TDF-3TC -EFV	50(3.26)	252(16.43)	0.423(0.315-0.568)**	0.300(0.221 -0.408)**
TDF -TC -NVP	7(0.45)	29(1.89)	0.516(0.244 -1.090)	0.386(0.182 -0.819)*
NNRTIs regimen based				
NVP based	601(39.20)	455(29.68)	1	1
EFV based	130(8.48)	347(22.63)	0.736(0.605-0.895)*	0.573(0.465 -0.707)**
NRTIs regimen based				
D4T based	600(39.14)	342(22.31)	1	1
Non-D4T based	131(8.54)	460(30.00)	0.507(0.418-0.615)**	0.397(O.323-0.487)**

*- *statically significant at p<0.05 and ** -significant at p<0.001*

EFV-based regimen had lower hazard [HR, 0.573(95% CI; 0.465 - 0.707); p< 0.001] for MOD than NVP-based regimen. In the case of NRTIs, lower risk for MOD was observed in non-D4T containing regimens [HR, 0.397(95% CI: 0.323 – 0.487); p<0.001]. From all initial regimens, TDF-3TC-EFV combination had lower hazard in comparison with D4T-3TC-NVP combinations at HR, 0.300(95% CI: 0.221 -0.408); P < 0.001. As shown in table 7, increasing order of hazard for MOD was: TDF-3TC-EFV < TDF-3TC-NVP < AZT-3TC-NVP < AZT-3TC-EFV < D4T-3TC-EFV when compared with D4T-3TC-NVP with hazard ratio of 0.300, 0.386, 0.493, 0.502, and 0.994 respectively.

7. Discussion

This cohort study was done in Jimma University Specialized hospital, southwest Ethiopia. It has provided an important insight into the rate, reasons and risk factors associated with modification or discontinuation (MOD) and toxicities of HAART regimens among 1533 patients who started HAART as part of routine clinical care. This work adds to the previous cross-sectional studies done in Ethiopia at Hawassa and Dassie referral hospitals (20, 29) where risk factors for MOD and toxicities were not assessed. The median follow-up of patients is 54 months of which previous studies at the two sites were not longer than 6 months. This cohort only included treatment naïve patients, but the previous two studies included experienced and naïve patients.

The clinical and CD4 cells of the study population demonstrate late HAART initiation. At HAART initiation more patients were in advanced stage of immunodeficiency. This has been observed in studies from both developed and developing countries.(26-27, 37) This was also in agreement with both observational studies done in Ethiopia at Dassie and Hawassa referral hospitals.(20, 29) These might be due to less enrolment of the patient's into pre-ART care and less awareness about HIV/AIDS testing and counselling that lead to presentation with advanced HIV disease. The promotion of early HIV diagnosis and early assessment of ART eligibility is recommended.

A total of 1102(71.8) patients were started ART with CD4 cell count of ≤ 200 cells/mm^3. This was in line with study on ART in 12 resource limited countries from 2005-2006 in sub-Saharan Africa reported to be 77%.(10) Although we did not assess the current data (after January 2010) as it is similar trend as a previous or not, our data showed major challenge to implement new treatment guideline recommendations (initiate treatment at CD4 ≤ 350 cells/mm^3 (21, 38)) This is in agreement with previous guideline recommendations in resource limited countries to initiate HAART at CD4 count less than 200 cells/mm^3(10, 26) and 2005 and 2007 Ethiopian ART guidelines.(39-40) There was slight increase of median CD4 counts from 111 to 144 cells/mm3 in our settings when compared with study done on ART in sub-Saharan Africans from 1996-2006.(10) Higher baseline CD4 count was observed in developed countries.(22)

Several studies (21, 37, 41-42) have shown that peoples starting treatment at low CD4 cell count could have poor treatment outcome. However, this study did not show a similar trend as more than two thirds of the patients started HAART at CD4 cell count of ≤200 cells/mm^3, only 24 patients reported to have treatment failure by clinicians. Study from Brazil showed 19.6% MOD due to treatment failure from 58.6% of less than 200 CD4 cell counts. However, we assessed 169(11.02%) patients to have treatment failure from subsequent CD4 counts and death reports. In our setting the availability of treatment options and viral load are limited. Therefore, it might be a reason for low report of treatment failure by clinicians. Other reason might be because of we did not assess treatment failure after first modification or discontinuation. Any apparent reason for good prognosis inside of patients was not determined.

Two third of prescribed first line regimens contained D4T in our cohort patients. This is in agreement with WHO public heath approach recommendation of D4T as first line ART drug in resource limited countries previously. This is due to its wide availability, long viral suppress and low cost when prescribed as fixed dose combination.(9) However, developed countries guidelines moved D4T from preferred to alternative ART due to its toxicities.(43) Unlike the sub-Saharan countries, only 15% of overall patients used D4T containing regimen in Latin America countries.(10-11, 27) The high utilization of D4T in sub-Saharan countries might be due to its high availability and less need for initial laboratory equipment to determine baseline haematology.(9)

Two third of patients started HAART before September 2008 were on NVP-based regimen. This result was comparable with the study done on ART in resource limited settings from 1996-2006 in sub-Saharan and WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings countries at 2006.(9-10) and 2007 antiretroviral therapy guideline of Ethiopia.(39) No patient started protease inhibitors (PI)-based regimen as his/her first line regimen in our settings. However, studies from developing countries like Uganda and Brazil reported 5-25% of patients started PI-based regimen.(15-16, 30) Overall higher prevalence of NNRTIs based initial regimens in developing countries than developed countries were observed. This might be due to their high availability, convenience, tolerability and low cost of drugs.(9-10, 41, 44)

Overall prevalence of MOD was 47.7% corresponds with 10.59 per 100 PY incidence rate. This finding is comparable to that found in other cohort studies from developing countries.(16, 30) However, cohort studies from developed countries like London (UK), Italy and Brazil showed higher incidence rate of MOD from 28.3-41.5 per 100 PY.(15, 18, 36) This study also observed high prevalence of MOD after treatment initiation at 16.8% and 34.2% within the first three and 12 months respectively. These rates are comparable to those reported in other cohorts.(18-19, 22, 36) The median time to MOD in our study was 24.37 months which is higher than median time to MOD found in resource-rich settings. This is also lower than that reported from clinical trials.(44-45) These low rates and long median time to MOD in our cohort study were expected as viral load monitoring, regular CD4 count monitoring and availability of subsequent antiretroviral treatment options are limited when compared with resource rich settings. (10)

ART drugs toxicities were the predominant and the main reason for HAART modification, even within the first 3 months of therapy. This is consistent with other cohort studies. (18-19, 31, 36, 44) Anemia, CNS toxicities and rash were the most common toxicities occurring within the first year. Unlike our cohort study: nausea, vomiting and diarrhea were also other early toxicities reported as a reason for HAART modification in other cohort studies.(22, 33) These GI discomforts are managed symptomatically and less considered as treatment limiting toxicities in our setting. Availability of protease inhibitors was limited as they are expected to be the main cause of GI symptoms.(24, 46) Patients in advanced immune suppression were also expected to have these GI symptoms and HAART initiation can lead to improvements in these GI symptoms.(33, 47) All these might be a reason for no report of GI symptoms.

Like Ugandans and other studies, (15, 28, 30) our cohort determine fat changes (lipodystrophy and lipoatropphy) and peripheral neuropathy were the most frequent toxicities. They were also the frequent long term toxicities, after 2 years. These toxicities profile may be expected considering the high frequency of regimens containing D4T in our cohort. Unlike our setting and other sub-Saharan countries, studies from Latin American countries and others showed haematological toxicities as most common toxicities reported.(10-11, 26-27) This difference was not unexpected as

ZDV was the most commonly prescribed among NRTI in Latin Americans and less likely to be associated with fat changes (11, 27-28). There was no report of discontinuation due to toxicities in ART follow-up record of our setting. Studies conducted in India and Uganda (16, 30) showed that cost was one of the most common reasons for discontinuation of HAART, but in this study it may not be an important reason as drug reach to the patient with fee-free.

Our result showed that patients in advanced immunosuppressant and past opportunistic infection at HAART initiation had lower risk of toxicities. Unlike our result, other studies showed advanced immunosuppressant were associated with high risk of toxicities.(15, 48) We did not find any apparent reason for less risk of toxicities observed among these cohorts. Our cohort did not show statically significant association between CD4 counts and risk of toxicities.

Patients' positive for TB screen before HAART start had higher risk for toxicities. This is similar with study done in rural Uganda.(28) This might be due to additional toxicities of isoniazide when administered with D4T especially in the case of peripheral neuropathy, despite pyridoxine use.(28, 49) Additional toxicities of anti-TB drug may increase the risk of ART toxicities. (50-51)

Patients greater than 35 years of age had high hazard of toxicities. Comparable with this result, other studies showed that fat changes and symmetrical peripheral neuropathy associated with older age.(28, 48) Elderly people are more frequent to show reduced hepatic and kidney reserve. Treatment may accelerate mitochondrial dysfunction, nucleoside reverse transcriptase inhibitors may contribute to muscle wasting.(52) Age was also shown to increase the risk of renal tubular disease in association with TDF.(53-54) The fact that ART prolongs life of patients and also less commonly studied on older individuals may complicate the future management of ART therapy and prophylaxis. Therefore, attention should be given to age as risk factors for toxicities.

Patients above primary education level had higher risk of toxicities than others. Although we did not assess their knowledge, this might be expected to be due to better awareness of ART associated toxicities among these groups.

Stavudine was the ARV with most reported toxicities in our study patients. ART regimens containing D4T were also had higher hazard of toxicities than non-D4T containing. This corresponds to finding in other studies (27, 34) that NRTI are mitochondrial DNA toxic, resulting in several adverse effects. Mitochondrial toxicity of D4T is expressed by peripheral neuropathy, lipodystrophy, lipoatrophy and dyslipidemia.(34) The result from our cohort study was in line with these findings, which is evidence of the close association between D4T and fat changes. Therefore, D4T will no longer recommend in clinical practices and WHO national guidelines, including our setting.(26) TDF had least reported toxicities that might show it is safe drug. Other study also showed safety and efficacy of TDF.(55) Due to new coming of the drug and less routine monitoring of renal and liver function test it is challenge to conclude its safety in our cohort patients. Therefore, less toxic non-D4T containing ART drugs like TDF and Abacavir (ABC) use is recommended in our current clinical practices.

New TB treatment was also a major reason for modification with a short median follow up of 4 months, especially for NVP-based regimens. This was due to interaction of NVP with anti-TB drug such as rifampin.(50, 56) In order to avoid this drug interaction clinicians replace the NVP with EFV.(39, 46) Poor TB screen might be reason for early MOD of NVP-based regimens. Also being in high stage of immunodeficiency on presentation to care may expose the patients to develop TB early.(47, 50) In other hand, short median time to modification of ART due to new TB treatment may raise a question on proper implementation of WHO guideline which recommends intensive TB case finding in patients co-infected with HIV.

Treatment failure were expected and reported (15, 17) late after HAART initiation. In agreement with these expectation and reports, this study shows low rate of treatment failure with long period of follow up (23.7months) compared to other reasons. This late occurrences may be a primary reason for low rate. Comparable with other cohorts (15-

16, 18, 31, 57) from developed and developing countries, we observed low probability of modification due to TF with late occurrences. These might be due to limited access to viral load and regular immunological monitoring. This implies that virologic failures were probably greatly underestimated. In addition to these two parameters, availability of subsequent treatment options might be a constraint for timely report of treatment failure in our setting. From subsequent CD4 counts we analysed greater than two fold increase of treatment failure than reported one. This explains immunological failure also may be underestimated in our setting.

In our setting, prevalence of early MOD of HAART after initiation was lower than (12.45%) results of previous studies.(14-15, 24) Result from one single treatment centre reported that 26% of patients modified their HAART regimen within six months of starting HAART of which drug toxicities accounted greater than half. In agreement with these studies, we found more than half of early regimen modification was due to drug toxicities. Other studies showed that 21–25% of HAART initiators discontinued due to drug toxicities.(18,32) Unlike these studies, no documented reports of toxicities as reason for HAART discontinuations. This low prevalence of early modification in our settings might be due to different reason: 1. due to limited subsequent treatment options; 2. there was no report of gastrointestinal toxicities which were mostly reported in other studies (15, 17) as early reason for modification; 3. although early toxicities were the main cause for early modifications, they had lower prevalence than longer term toxicities. This was due to high prevalence of ART drugs (D4T) causing long term toxicities.

This cohort identified high hazard of treatment failure for early modification or discontinuation. This may primarily explained as the process of regimen modification may delay appropriate viral suppression and/or immune reconstruction. Consistent with this study, one study(17) found that early modification of the HAART regimen delay CD4 cell recovery and viral suppression at 6–12 months after the start of HAART in advanced HIV patients. In our study virological response and month of immunological delay was not determined. Other explanation might be, patients who modify or discontinue regimen due to adverse events or other reasons apart from treatment failure , like our cohort study, were more frequently experienced virological failure.(58)

Although our data source (ART follow-up record) did not identify, proactively early MOD of regimens to more convenient or less toxic in order to minimize side effects or long term toxicities may be important for adherence and long-term viral suppression.(56,57) Their finding may support the new clinical practice of modifying D4T to other tolerable ART drugs.

Another reason for treatment failure might be due to non-adherence. This is due to experiencing of intolerable toxicity early in the course of HAART may reduce patients' adherence to antiretroviral drugs. One study demonstrated that patients reporting a high number of symptoms soon after initiation of HAART were at higher risk of future non-adherence.(27) In agreement with this clinical trial one study suggested that a modification of regimen might itself be associated with poorer adherence, irrespective of drug toxicity.(12) Our study did not evaluate therapeutic adherence.

In this cohort study, patients who started HAART after September 2008 of calendar year showed 1.5 times hazard for MOD than before September 2008. However, studies from developed countries and Brazilians showed high hazard of MOD of treatment for those starting HAART when HIV/AIDS treatment started.(18, 57, 59) This was probably related to the late occurrences of modification for patients initiating HAART before 2008 due to lack of subsequent treatment regimen options. The new coming of TDF after calendar year of 2008 might be primarily probable reason. Ambulatory and bedridden patients had higher risk for MOD than working patients. This might be due to lack of physical activity and increased probability of developing co-morbidities in this cohort group. One study in Spain showed Physical activity is a protective factor for the development of fat redistribution syndromes (60). Other supportive study showed concurrent treatments of co-morbidities with HAART increase risk of toxicity(47).

Unlike other studies, (11, 15) this cohort did not identify past opportunistic infection before HAART initiation as independent predictor for MOD. However, patients' positive for TB screening had higher hazard for MOD than those negative for TB screen. Studies show that co-morbidities in patients with advanced disease and concurrent treatments for opportunistic diseases may affect antiretroviral tolerance and thereby increase risk of toxicities(47). In addition, there might be poor initial HAART

regimen selection mechanism in our setting as near to half of patients (49.8%) reported to be positive for TB started NVP containing regimen. WHO guideline recommends to start EFV based regimens for those positive for TB (26, 46). Therefore, lack of proper follow of WHO guidelines might be a cause for early MOD. This implies a need to investigate a drug therapy problem on ART patients with TB as co-morbidities and its risk factors.

Efavirenz-based regimens had lower hazard for MOD than NVP-based. This is similar with other studies.(11, 14-15, 22, 57) This high hazard of NVP-based regimens may be explaining by the use of fixed dose combinations containing D4T and NVP which had high prevalence of modification. Another justification may be due to high prevalence of modification of NVP due to new TB treatment in our cohort patients. This is due to drug interaction between NVP and anti-TB drugs, specifically with rifampin (50, 56).

D4T containing regimens had higher hazard for modification or discontinuation than patients on ZDV or TDF, unlike studies from Latin Americans and SHCS cohort studies.(11, 22) These may be described due to high prevalence of D4T containing regimen in our cohort patients and increasing rate of mitochondrial toxicities of this drug.(24, 27, 55) The possible reason for difference between two countries is due to less prevalence of D4T containing regimen in Latin American and SHCS cohort studies.(11, 22)

Like a multi cohort study from Latin America and Caribbean's (11) our study did not observe consistent associations between gender, religion or age and risk of antiretroviral MOD, although other studies have found that younger age and female gender predict MOD.(19, 22, 61) Also unlike Ugandan observational study (16) this study did not find association between marital status and MOD. After the first MOD, most patients remained on first line regimens. This is comparable with resource limiting setting countries.(10-11, 26)

Our study had several limitations. One of the major limitations of this study was the high number of unspecified toxicities and reason for MOD. In addition to these, only treatment limiting toxicities were reported rather than overall toxicities. Out of a total of

431 reported toxicities, 297 were not specified and simply indicated as toxicity. We did not identify why they couldn't fill the form as the numerical codes were given for both reason for modification and common specific toxicities. Toxicities, treatment failures or other reasons were reported only if they were prompt to regimen MOD. Therefore, their frequency cannot be used to estimate their actual occurrence. Lack of viral load measuring and regularly monitoring of CD4 count was also the other measure limitation that lead to underestimation of treatment failure.

Our cohort study didn't consider treatment modifications or discontinuation shorter than 30 days because this was the minimum time that patients collect their drug and also have consultation with their physician. Due to limited treatment options in our setting, early (within one month of HAART start) toxicities and other reasons did not prompt to regimen MOD. It is known that shorter treatment MOD or interruptions have potential impact on treatment outcomes, particularly using NNRTI based regimens; (16) such interruptions occur frequently in real life but generally have not been considered in other cohort studies.(30-31)

This cohort didn't assess the outcome of second and above MOD. Outcome of second regimens was also not assessed as it was beyond the scope of this study. Although they have different definition, modification and discontinuation were considered as one event.

8. Conclusion

High prevalence of modification was due to drug toxicity, even within the first six months. New TB drug treatment, being pregnant and treatment failure were common reasons for modification of first HAART regimens. Patients' positive for TB screen at HAART initiation and initiated D4T and NVP containing first regimens had high risk for both MOD and toxicities. Older age (>35), WHO clinical stage I & II and achieving greater than primary level education had high hazard of toxicities. Early modification or discontinuation is associated with hazard of treatment failure. Close monitoring and management of toxicities are crucial for durability of highly active antiretroviral therapy.

9. Recommendation

- D4T and NVP were the ARVs mainly associated with toxicities and modification or discontinuation; therefore patients on these drugs should be closely monitored.
- Need for intensified TB case finding as TB cases were main reason for modification of HAART early.
- Clinician should closely follow older patients with HIV and on HAART as they risk factors for HAART toxicities.
- Federal HIV/AIDS Prevention and Control Office should:
    - Regularly update the antiretroviral therapy guidelines as new and less toxic ARV become available (TDF and ABC).
    - Carry out a national study to determine the rate and reason for MOD of antiretroviral therapy and associated risk factors.
- Further investigations should be carried out on the suitability of the patient record forms currently in use and the training provided for clinicians and data clerk workers in toxicities recording and reporting.
- Prospective study should be done to have detail information of the patients in our setting and also nationally.

References

1. UNAIDS, unicef, WHO. GLOBAL AIDS RESPONSE PROGRESS REPORTING: 2013 Construction of Core Indicators for monitoring the 2011 UN Political Declaration on HIV / AIDS Geneva, Switzerland 2013.
2. WHO UNAIDS, Unicef. GLOBAL HIV/AIDS RESPONSE: epidemic update and health sector progress towards universal access report. Geneva, Swizerland 2011.
3. HAPCO. Country Progress Report on HIV / AIDS. Federal Democratic Republic of Ethiopia. Addis Ababa, Ethiopia2012.
4. WHO UNAIDS. epidemiological fact sheet on HIV/AIDS and sexually transmitted infections 2011.
5. Central statics agency. Ethiopia Demographic and Health Survey. Addis Ababa, Ethiopia march, 2012.
6. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet. 1998 Nov 28;352(9142):1725-30.
7. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002 Jul 13;360(9327):119-29.
8. Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet. 1998 Feb 21;351(9102):543-9.
9. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet. 2006 Aug 5;368(9534):505-10.
10. Keiser O, Anastos K, Schechter M, Balestre E, Myer L, Boulle A, et al. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. Trop Med Int Health. 2008 Jul;13(7):870-9.
11. Cesar C, Shepherd BE, Krolewiecki AJ, Fink VI, Schechter M, Tuboi SH, et al. 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. 2010;5(6):e10490.

12. Miller LG, Golin CE, Hays RD, Liu H, Beck CK, Kaplan AH, et al. Impact of antiretroviral regimen switches on adherence. HIV Clin Trials. 2002 Sep-Oct;3(5):355-60.

13. Nevin CR, Ye J, Aban I, Mugavero MJ, Jackson D, Lin HY, et al. The role of toxicity-related regimen changes in the development of antiretroviral resistance. AIDS Res Hum Retroviruses. 2011 Sep;27(9):957-63.

14. Mocroft A, Youle M, Moore A, Sabin CA, Madge S, Lepri AC, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. AIDS. 2001 Jan 26;15(2):185-94.

15. Cardoso SW, Grinsztejn B, Velasque L, Veloso VG, Luz PM, Friedman RK, et al. Incidence of modifying or discontinuing first HAART regimen and its determinants in a cohort of HIV-infected patients from Rio de Janeiro, Brazil. AIDS Res Hum Retroviruses. 2010 Aug;26(8):865-74.

16. Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, Balakrishnan P, Saghayam S, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. J Acquir Immune Defic Syndr. 2006 Jan 1;41(1):53-8.

17. Park WB, Choe PG, Kim SH, Jo JH, Bang JH, Kim HB, et al. Early modification of initial HAART regimen associated with poor clinical outcome in HIV patients. AIDS Res Hum Retroviruses. 2007 Jun;23(6):794-800.

18. Hart E, Curtis H, Wilkins E, Johnson M. National review of first treatment change after starting highly active antiretroviral therapy in antiretroviral-naive patients. HIV Med. 2007 Apr;8(3):186-91.

19. Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi EM, Antinori A, Gatti F, et al. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naive patients. HIV Med. 2010 Feb;11(2):104-13.

20. Woldemedhin B, Wabe NT. The Reason for Regimen Change Among HIV/AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Southern Ethiopia. N Am J Med Sci. 2012 Jan;4(1):19-23.

21. Jordi Navarro-Mercadé MC, Vicenç Falcó, Eva Van Den Eynde, Adrian Curran, Joaquín Burgos, Sara Villar Del Saz, Estrella Caballero, Imma Ocaña, Mercè Perez-

Bernal, Esteban Ribera and Albert Pahissa. Long-Term Effectiveness of First-Line Antiretroviral Theraphy in a Cohort of HIV-1 Infected Patients. J Antivir Antiretrovir 2012;4(2).

22. Elzi L, Marzolini C, Furrer H, Ledergerber B, Cavassini M, Hirschel B, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. Arch Intern Med. 2010 Jan 11;170(1):57-65.

23. Pogany K, van Valkengoed IG, Prins JM, Nieuwkerk PT, van der Ende I, Kauffmann RH, et al. Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm3: 48-week Treatment Interruption in Early Starters Netherlands Study (TRIESTAN). J Acquir Immune Defic Syndr. 2007 Apr 1;44(4):395-400.

24. Barron Y, Cole SR, Greenblatt RM, Cohen MH, Anastos K, DeHovitz JA, et al. Effect of discontinuing antiretroviral therapy on survival of women initiated on highly active antiretroviral therapy. AIDS. 2004 Jul 23;18(11):1579-84.

25. Ahdieh Grant L, Silverberg MJ, Palacio H, Minkoff H, Anastos K, Young MA, et al. Discontinuation of potent antiretroviral therapy: predictive value of and impact on CD4 cell counts and HIV RNA levels. AIDS. 2001 Nov 9;15(16):2101-8.

26. Walensky RP, Wood R, Ciaranello AL, Paltiel AD, Lorenzana SB, Anglaret X, et al. Scaling up the 2010 World Health Organization HIV Treatment Guidelines in resource-limited settings: a model-based analysis. PLoS Med. 2010;7(12):e1000382.

27. Murphy RA, Sunpath H, Kuritzkes DR, Venter F, Gandhi RT. Antiretroviral therapy-associated toxicities in the resource-poor world: the challenge of a limited formulary. J Infect Dis. 2007 Dec 1;196 Suppl 3:S449-56.

28. Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermin J, et al. Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. J Acquir Immune Defic Syndr. 2007 Apr 1;44(4):456-62.

29. Mulugeta A, Chanie T. Cause of antiretroviral drug changes among patients on antiretroviral therapy at the art center in dessei regional referral hospital, ethiopia. IJPSR. 2012;3(1):120-5.

30. Kiguba R, Byakika-Tusiime J, Karamagi C, Ssali F, Mugyenyi P, Katabira E. Discontinuation and modification of highly active antiretroviral therapy in HIV-infected

Ugandans: prevalence and associated factors. J Acquir Immune Defic Syndr. 2007 Jun 1;45(2):218-23.

31. O'Brien ME, Clark RA, Besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. J Acquir Immune Defic Syndr. 2003 Dec 1;34(4):407-14.

32. Manosuthi W, Thongyen S, Chumpathat N, Muangchana K, Sungkanuparph S. Incidence and risk factors of rash associated with efavirenz in HIV-infected patients with preceding nevirapine-associated rash. HIV Med. 2006 Sep;7(6):378-82.

33. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. AIDS Rev. 2009 Jan-Mar;11(1):30-8.

34. Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998 Oct 1;12(14):1735-44.

35. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. Clin Infect Dis. 2007 Oct 15;45(8):1093-101.

36. Momory Keita, Cécile Chouquet, Lise Cuzin, Mohamed Cissé, Thierry Lang and Cyrille Delpierre. Incidence and Risk Factors of First-Line HAART Discontinuation: Is it Worth Choosing Competing Risk or Standard Survival Approaches? J AIDS Clinic Res 2012;3(10).

37. Sterling TR, Chaisson RE, Keruly J, Moore RD. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. J Infect Dis. 2003 Dec 1;188(11):1659-65.

38. Adolescents PoAGfAa. Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

39. HAPCO, FMoH. Guidelines for management of opportunistic infections and anti retroviral treatment in adolescents and adults in ethiopia. 2007.

40. HAPCO, FMoH. Guidelines for management of opportunistic infections and anti retroviral treatment in adolescents and adults in ethiopia. 2005.

41. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA. 2006 Aug 16;296(7):782-93.

42. Elisa Zaragoza-Macias DC, Minh Ly Nguyen, Carlos del Rio, and Jeffrey Lennox. Predictors of Success with Highly Active Antiretroviral Therapy in an Antiretroviral-Naive Urban Population. AIDS RESEARCH AND HUMAN RETROVIRUSES
2010;26(2).

43. Department of health and human services. Antiretroviral therapy for hiv infection in adults and adolescents Recommendations for a public health approach 2006 revision 2006.

44. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997 Sep 11;337(11):734-9.

45. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997 Sep 11;337(11):725-33.

46. World health organization, UNAIDS, UNICEF. Antiretroviral therapy for HIV infection in adults and adolescents. Switzerland2010.

47. Gay CL, Napravnik S, Eron JJ, Jr. Advanced immunosuppression at entry to HIV care in the southeastern United States and associated risk factors. AIDS. 2006 Mar 21;20(5):775-8.

48. Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, Holmberg SD. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. Clin Infect Dis. 2005 Jan 1;40(1):148-57.

49. Swaminathan S, Padmapriyadarsini C, Venkatesan P, Narendran G, Ramesh Kumar S, Iliayas S, et al. Efficacy and safety of once-daily nevirapine- or efavirenz-

based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial. Clin Infect Dis. 2011 Oct;53(7):716-24.

50. Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. Int J Tuberc Lung Dis. 2005 Mar;9(3):248-57.

51. Van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K, Farley J. Serious treatment related adverse drug reactions amongst anti-retroviral naive MDR-TB patients. PLoS One. 2013;8(4):e58817.

52. Estrella MM, Fine DM. Screening for chronic kidney disease in HIV-infected patients. Adv Chronic Kidney Dis. 2010 Jan;17(1):26-35.

53. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP, Jr. Older age and the response to and tolerability of antiretroviral therapy. Arch Intern Med. 2007 Apr 9;167(7):684-91.

54. Manfredi R. HIV disease and advanced age: an increasing therapeutic challenge. Drugs Aging. 2002;19(9):647-69.

55. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004 Jul 14;292(2):191-201.

56. Bonora S, Di Perri G. Interactions between antiretroviral agents and those used to treat tuberculosis. Curr Opin HIV AIDS. 2008 May;3(3):306-12.

57. d'Arminio Monforte A, Lepri AC, Rezza G, Pezzotti P, Antinori A, Phillips AN, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. AIDS. 2000 Mar 31;14(5):499-507.

58. Butcher D, Greene J, Duong P, Markson L. Virologic response associated with a change in protease inhibitor therapy. Arch Intern Med. 2000 Feb 14;160(3):394-5.

59. Moore RD, Keruly JC, Gebo KA, Lucas GM. An improvement in virologic response to highly active antiretroviral therapy in clinical practice from 1996 through 2002. J Acquir Immune Defic Syndr. 2005 Jun 1;39(2):195-8.

60. Segatto AF, Freitas Junior IF, Santos VR, Alves KC, Barbosa DA, Portelinha Filho AM, et al. Lipodystrophy in HIV/AIDS patients with different levels of physical activity while on antiretroviral therapy. Rev Soc Bras Med Trop. 2011 Jul-Aug;44(4):420-4.

61. Kempf MC, Pisu M, Dumcheva A, Westfall AO, Kilby JM, Saag MS. Gender differences in discontinuation of antiretroviral treatment regimens. J Acquir Immune Defic Syndr. 2009 Nov 1;52(3):336-41.

Annexes:

Data collection tool

Data collection tool for thesis on reasons for modification or discontinuation of first highly active antiretroviral therapy and risk factors among human immunodeficiency virus infected adult patients at Jimma University Specialized Hospital, South West Ethiopia.

Patient card Number: _____ ART Site: _____

Date of data collection: ____/____/____ (Day/mth/yy).

A. Socio-demographic Information

1. Date of Birth: _____ /_____ /_____

a. Age at HAART initiation: _____.

b. Weight _____.

c. Time of HIV confirmed :_____

d. Year at HAART initiation._____

2. Sex: a. Male ☐ b. Female ☐

3. Marital status a. Married ☐ b. Divorced ☐ c. separated ☐ d. Not married ☐

4. Religion a. Muslim ☐ b. Orthodox ☐ c. Protestant ☐ d. Catholic ☐ e. Other ☐

5. Level of educational a. Illiterate ☐ b. primary ☐ c. secondary ☐ d. tertiary ☐

6. Occupation a. unemployed ☐ b. employed ☐

7. Functional status: a. ambulatory ☐ b. bedridden ☐ c. working ☐

B. Clinical information

8. Eligibility a. clinical ☐ b. CD4 ☐ c. TLC ☐

9. baseline WHO clinical stage a. Stage I ☐ b. stage II ☐ c. stage III ☐ d. stage IV ☐

10. Baselines CD4 count _____.

11. Opportunistic infection a. Yes ☐ b. No ☐

If yes specify: 1._____ 2._____ 3._____ 4._____

12. TB screen (P/N) a. negative ☐ b. positive ☐

Treatment Information

13. First HAART regimen _____.

14. Type of event

i. Alive ☐

ii. Modified ☐

iii. Discontinued ☐

iv. Transfer out ☐

v. Death ☐

vi. Second regimen._____.

vii. Date of event or censoring._____/_____/___.

viii. Reason._____.

C. To be filled after modification or discontinuation

15. Consecutive CD4 counts

CD4						
Time						

16. New opportunistic infections a. Yes ☐ b. No ☐

If yes specify: _____ .

Time of occurrence _____/_____/_____

17. Death a. Yes ☐ b. No ☐

Time of death _____.

Reason _____