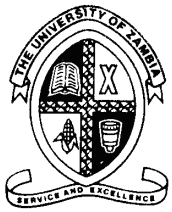

THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF MEDICINE

Incidence and Determinants of Change of Initial HAART Regimen among Outpatient HIV Infected Adults at the University Teaching Hospital in Lusaka, Zambia

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A dissertation submitted to the University of Zambia in partial fulfillment of the requirements for the degree of Master of Science in HIV Medicine

The University of Zambia

Lusaka

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DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University.

Signed……..
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CERTIFICATE OF APPROVAL

This dissertation of Dr. Rusumba Habimana has been approved as fulfilling the requirements for the award of Master of Science in HIV Medicine by the University Of Zambia

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ABSTRACT

Introduction

Durability of the first highly active antiretroviral therapy (HAART) regimen is a major key to long term access, scalability and sustainability of an HIV treatment program. It is important to know the incidence rate of initial HAART regimen change, the reasons and factors associated with change of the initial HAART regimen in Zambia. This study was designed to determine the incidence rate and factors associated with change of initial HAART regimen at the University Teaching Hospital (UTH) from 1st January 2008 to 31st December 2011.

Methodology

This research was a hospital based retrospective cohort study of adult HIV/AIDS patients who were initiated on HAART from 1st January 2008 to 31st December 2011 at UTH adult outpatients ART clinic. Medical charts were reviewed for demographic information, change or no change of initial HAART regimen, type of initial HAART regimen, date of initiation, date of change, and reasons or factors of change. The incidence rate of change of initial HAART regimen was calculated. We assessed characteristics of patients who changed their initial HAART regimen and reasons for change. Cox proportional hazard models were performed to analyze factors associated with change of initial HAART regimen.

Results

Incidence rate of change and factors associated with change of initial HAART regimen was obtained from 341 medical charts. 154/341 (45.2%) of patients had their initial HAART regimen changed. The incidence rate of change was 17.5 per 100 person-years. The proportion of change due to treatment failure was 1.8%. The most common reasons for change of initial HAART regimen were drug unavailability (stocks out and drugs cost) 46.1%, non-adherence 19% and renal toxicity 5.2%. The type of initial HAART regimen was significantly associated with change of initial HAART regimen.

Conclusions

It is important to evaluate reason-specific trends in the incidence of change of initial HAART regimen in order to better understand the determinants of changes. Given the findings that drug unavailability was responsible for nearly half of all changes of initial HAART regimens, better health systems need to be implemented to ensure steady supply of drugs to patients. Also there is a need for research that helps to develop better screening modalities for renal toxicity, considering that tenofovir is part of the recommended first line regimen in Zambia.

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DEDICATION

I dedicate this work to my parents KALINDYE RUSUMBA and M'FUNGULO; I dedicate also this work to my wife KASHINDI ETABO and my children MACINTOSH AKONKWA, DAVID BAHATI AND SOLOMON AMANI. You have been of great support; for sure, God will reward you.

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ABREVIATIONS AND ACRONYMS

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
BREC	Biomedical Research and Ethics Committee
CYP	Cytochrome P
DDI	Didanosine
DILI	Drug-induced liver injury
D4T	Stavudine
EFV	Effavirenz
FTC	Emtricitabine
GI	Gastrointestinal
HAART	Highly active antiretroviral therapy
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IQR	Interquartile range
IRIS	Immune recovery inflammatory syndrome
IV	Intraveinous
LPV/r	Lopinavir/ritonavir
NNRTIs	Non-nucleoside reverses transcriptase inhibitors
NVP	Nevirapine
PIs	Protease inhibitors

PMTCT	Prevention of mother to child transmission
SD	Standard deviation
TDF	Tenofovir
3TC	Lamivudine
TB	Tuberculosis
UGT	Uridine diphosphate glyconyltransferase
UN	United Nations
UNZA	University of Zambia
USA	United States of America
UTH	University Teaching Hospital
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine

CHAPTER 1

1.0 INTRODUCTION

At the end of 2010, 6,650,000 people were receiving highly active antiretroviral therapy (HAART) for treatment of human immunodeficiency virus (HIV) in low-and-middle-income countries, an increase of over 1.4 million people or 27%, from December 2009 (1). The goal of HAART is to produce virologic suppression and immunologic reconstitution. There are several HAART regimens that achieve this goal. However, we know that up to 55% of regimens are changed within the first year (2).

There are many reasons why HAART regimens need to be changed. Some reasons for change of HAART regimens include treatment failure, treatment toxicity, potential drug-drug and/or drug-food interactions and poor adherence (3). Treatment failure is defined as the absence of a sustained favorable response to HAART (4). With successful initial HAART, the HIV viral load is expected to decline by at least ten fold every two to eight weeks, and should be below the limit of detection of most viral load assays within six months of HAART initiation (4). If these goals are not achieved, the HAART regimen may be changed.

Treatment toxicity has been reported with all antiretroviral drugs and is among the most common reasons for switching or discontinuing therapy as well as for medication non-adherence (5). Adverse reactions due to HAART may be mild, moderate or severe. The beginning of therapy is the period during which adverse reactions or undesirable symptoms will likely, to a large extent, contribute to non-adherence to HAART (6).

Potential drug-drug and/or drug-food interactions can be the reason of HAART regimens changes especially when there is a need of redesigning a regimen that minimizes undesirable interactions. All protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized in the liver by cytochrome P (CYP) 450 system, particularly by the CYP3A4 isoenzyme. Co-administration of drugs that are metabolized by these enzymes may result in competition for these enzymes, causing a decrease in metabolism and a high plasma level of the other agents. The list of drugs that

may have significant interactions with PIs or NNRTIs is extensive and is continuously expanding (7).

Poor adherence encompasses much more than patients not taking their medicines as directed (8). Adherence for patients on antiretroviral therapy includes adherence to care (sticking to antiretroviral care) and adherence to treatment (sticking to treatment). 100% adherence is needed in order to achieve these goals. Any drop in adherence to below 95% is associated with higher rates of resistance to therapy (9).

In addition to the many reasons patients change HAART regimens, there are also multiple factors associated with change of HAART regimens that are interdependent and associated with treatment failure, adverse effects of antiretroviral agents, and poor adherence. Because the first regimen is usually the most potent and durable and there are a limited number of antiretroviral drugs available, it is important to try to understand why these regimen changes occur so that we target efforts at preventing regimen change. Thus, this study is undertaken to determine the incidence and determinants of change of the initial HAART regimen at UTH, Lusaka, Zambia during the period of January 2008 to December 2011.

CHAPTER 2

REVIEW OF LITERATURE

2.1 DEFINITIONS

Regimen change may be defined as a treatment switch or modification, treatment cessation or discontinuation, or treatment intensification. HAART switch or modification is a substitution of at least one antiretroviral drug in the regimen. Dosage adjustments to regimens are not considered to be modification (10). HAART discontinuation is a simultaneous stopping of all antiretroviral drugs without initiation of a subsequent regimen for more than two weeks (11). Interruption of treatment is not considered a regimen change and because of limited available data, it is not recommended for use in general clinical practices (12-14). Treatment intensification is an addition of new antiretroviral drugs to an otherwise unchanged regimen (11).

Incidence is a measure of the risk of developing some new condition within a specified period of time. The incidence rate is the number of new cases per population at risk in a given time period. When the denominator is the sum of the person-time of the at risk population, it is also known as the person-time incidence rate (15).

2.2 INCIDENCE OF HAART REGIMENS CHANGE

There are several studies from around the world that highlight incidence of HAART change. A retrospective cohort study was conducted in Mali by Landier J et al (16), to determine the incidence and reasons for switching to second-line HAART (in an HAART programme based on routine standard of care in sub-Saharan Africa). As of March 2008, 865 patients were enrolled in this study. Median follow-up under HAART was 15 months, during which 207 HAART modifications (in 155 patients) were observed corresponding to an incidence rate of 16.2 per 100 person - years. Of the 207 HAART modifications, 40 (26%) were switched to a second line regimen, an incidence rate of 3.3 per 100 person-years (95% CI: 2.4-4.4). The main reasons reported for switching to second line were: treatment failure based on clinical evidence in 18 (45%) patients (confirmed by immunological and/or virological failure), occurrence of severe intolerance in 13 (33%) patients, and error in diagnostic or management of an HIV-2 infection in 4

(10%) patients. In the five remaining patients, the reason for switching was not documented.

In a cross-sectional study by Kiguba R et al conducted among HIV sero-positive adults who were currently on HAART, or who had been initiated on HAART 2 years prior at the Mulago Hospital and the Joint Clinical Research Centre (JCRC) in Kampala, Uganda, 94/686 (13.7%) patients had discontinued therapy at some point, and 175/686 (25.5%) had modified their initial HAART regimen. Among those discontinuing therapy, the decision was made by the patient in 43/94 (45.7%) of the cases; among those modifying therapy, the decision was made by the physician in 167/175 (95.5%) of the cases. The most frequently cited reasons for discontinuation were that drugs were too expensive (43%), to avoid side effects and toxicity (21.1%) and drugs out of stock (10.5%). Modification of drugs was based on the physician's decision in the vast majority of cases (95.5%), and the most common reasons cited were to avoid side effects (71.8%) and high drug cost (23.3%) (17).

In a retrospective cohort study, by Cardoso W et al between January 1996 and December 2006 with follow-up through August 2008, on the incidence of modifying or discontinuing first HAART regimen in Rio de Janeiro, Brazil, the overall HAART modification incidence rate was 28.3 per 100 person-years (95% CI: 26.0-31.0). The reasons for change were toxicity in 186/670 (40%); treatment failure in 91/670 (19.6%) and other reasons in 187/670 (28%) (10). Other reasons and detail about toxicity were not documented.

In a retrospective cohort study done at the University of Alabama at Birmingham by Robinson S et al (2), 1917 Clinic Cohort had evaluated short-term HAART regimen discontinuation (within 12 months of regimen initiation) between January 1995 and August 2004. Multivariable multinomial logistic regression models accounting for dependent observations were fit to assess the relationship between patient factors and type-specific regimen discontinuation. Among 738 study participants, 1026 of 1852 HAART regimens (55%) were discontinued within 12 months of initiation. Discontinuation for gastrointestinal (GI) toxicity (23%) was more common in patients lacking private health insurance and those with a history of intravenous (IV) drug use, whereas non-GI toxicity (22%) was more common in younger patients and females. African-American patients and those with a history of IV drug use were more likely to

stop a regimen due to virologic failure/non-adherence. Loss to follow-up was more common in younger patients, individuals who were not insured, and those with a history of IV drug use. These findings show that particularly vulnerable and marginalized patients are more at risk for treatment discontinuation.

2.3 FACTORS ASSOCIATED WITH CHANGE OF HAART REGIMENS

Factors associated with change of HAART regimens include medication-related factors, patient-related factors, prescriber-related factors, government-related factors, biologic factors and concomitant conditions.

2.3.1 MEDICATION-RELATED FACTORS

Complexity of the regimen is one of the biggest obstacles for patient adherence. Studies find that patients on once daily regimens are much more likely to comply than patients who are required to take their medicine (s) multiple times each day (18). Beyond the complexity of the regimen, concern about medication side effects remains a powerful barrier to patient adherence. In a 2005 survey of 2,507 American adults conducted by Harris Interactive, nearly half of the respondents (45%) reported not taking their medicines due to concerns about side effects (19). In addition, in the Cicconi P et al study, drug intolerance and toxicity was the major cause of HAART discontinuation. The type of regimen used at treatment initiation significantly predicted the rate ratios of subsequent changes (20). Drug classes and treatment availability is another factor for initial HAART regimen change (21). Since late 2007, the Zambian adult first line regimen is based on tenofovir (3). This regimen is known to be stable; however, in patients predisposed to renal failure tenofovir based regimen can be modified or discontinued because of the risk for renal failure.

2.3.2 PATIENT-RELATED FACTORS

Non-adherence of patient is probably one of the most common reasons why patients may fail their initial HAART regimen and need to be changed. A common reason why patients do not take their medicines is simply forgetfulness (22). Another significant barrier is the inability to understand and act on instructions for taking the medication. A study done among American adults found that 60% or more of patients being followed could not correctly report what their physicians told them about medication use 10 to 80 minutes after receiving the information (23).

Lack of treatment preparation and support, socio-economic factors (high cost of ARVs where it is not free of charge, lack of transportation, food insecurity, marital status), active psychiatric disease or substance abuse, difficult in swallowing, alternate beliefs (herbal medicine, faith healing), and travel frequency contribute to poor HAART adherence and are associated with change of HAART regimen (8).

Patient perception and understanding about his or her disease influence the conscious choice not to take their medicines as prescribed or to discontinue therapy (24). Along with these attitudes and beliefs, the duration of the course of therapy also contributes to whether and how patients take their medicines. Adherence rates have been found to decline over time when patients are treated for chronic conditions (25).

Differences in host genetics that affect drug metabolism, factors affecting drug absorption, drug pharmacokinetics and drug-drug interactions are primarily associated with insufficient drug levels (26). Hepatic enzymes, CYP2B6 and UGT2B7 play a major role in the metabolism of the widely used antiretroviral drugs efavirenz, nevirapine and zidovudine. Many associations have been described between CYP2B6 and UGT2B7 variants, antiretroviral pharmacokinetics and/or therapy outcomes (27). Several cytochrome P450 systems isoforms are known to have multiple alleles with distinct phenotypes and direct effects on drug metabolism. CYP3A4, the isoform principally involved in the metabolism of HIV PIs and NNRTIs has recently been noted to have several polymorphisms. Variable expression of 3A4 will affect antiretroviral metabolism and may explain some of the observed interpatient variability of the PI and NNRTI agents. A recently described nuclear receptor, Pregnane X, appears to influence the extent of P450 system enzyme induction, adding further to multiple factors responsible for differential drug metabolism and perhaps response to HAART (28). In Cardoso W et al (10) study on the incidence of modifying or discontinuing first HAART regimen and its determinants in a cohort of HIV-infected patients, women had a higher hazard for short-term toxicity modification. Additionally, women presented with more severe adverse events than men, including a higher incidence of neuropathy. This may be explained by biological differences between the sexes and genetic factors influencing the pharmacokinetics of specific drugs and thus their plasma levels (29, 30). In old individuals, a higher incidence of toxic effects may reflect altered pharmacokinetics, impaired drug metabolism, and frequent co medication with a potential for drug-drug interactions (31). Vulnerable population including females, younger individuals, African-Americans, patients lacking

health insurance, indigent urban patients, intravenous drugs user were more likely to experience HAART regimen change. In the Elzi L et al study on the treatment modification in Human Immunodeficiency virus-Infected Individuals Starting Combination Antiretroviral Therapy between 2005 and 2008 (32), women and individuals of nonwhite ethnicity were more likely to modify their antiretroviral treatment because of drug toxicity or intolerance.

2.3.3 PRESCRIBER-RELATED FACTORS

Poor communication between the patient and the clinician leads to medication errors and non-adherence. A meta-analysis of 21 studies assessing the quality of physician-patient communication in the USA, found that patient health outcomes are improved with good physician-patient communication (31).

In addition to poor communication, the provider may have little to no experience in treating HIV disease. The clinician may choose a regimen with low potency. Alternatively, the wrong dose may be prescribed or dispensed and even though the patient may be perfectly adherent, this suboptimal dose may be the cause for treatment failure (26).

2.3.4 GOVERNMENT-RELATED FACTORS

Change in policy and guidelines by the government may be a factor for treatment change especially if people who have to implement the policy and guidelines are not well informed regarding the new decisions. In late 2007, the ministry of Health, Zambia decided to phase out progressively the 40 milligrams D4T and replaced it with TDF because of its side effects which include wasting and nerve disorder. The same period co-formulated TDF/FTC was introduced as preferred first line. In 2008, co-formulated TDF/3TC was introduced due to its cheaper cost. The 2010 Zambian adult ART guideline adopted TDF/FTC as preferred first line agent (33).

2.3.5 BIOLOGIC FACTORS

Higher baseline CD4 counts is associated with increased rates of treatment discontinuation, frequently without switching to alternative drugs, suggesting a lower motivation to continue an antiretroviral regimen causing adverse effects in patients with less urgent indication for HAART (31). Discontinuation of nevirapine (NVP) is indicated

in female and male patients with CD4 counts over 250 cells/mm^3 and 400 cells/mm^3 respectively in order to prevent hepatotoxicity (7). High baseline viral loads, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, low hemoglobin is likely to influence the change of HAART regimen.

2.3.6 CONCOMITANT CONDITIONS

Patients who are treated for concomitant co-infections, including opportunistic infections are likely to modify the HAART regimen (4). Occurrence of active tuberculosis and/or hepatitis B virus infection may lead to a change of HAART regimen in order to reduce likelihood of drug-drug interactions that can lead to adverse events (3). Other concomitant conditions that can lead to HAART regimen change include renal failure, pregnancy, and mental disorder.

Hepatotoxicity, drug-induced liver injury (DILI) following HAART is more common in HIV/HCV co infection. The greatest risk of DILI may be observed in co infected persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease). Patients receiving or considering therapy with ribavirin should avoid didanosine (ddi), stavudine (d4T), and zidovudine (ZDV). ARV agents with greatest risk of DILI should be used with caution (7). Patients diagnosed with tuberculosis (TB) while receiving HAART should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins. The patient's regimen may need to be modified to permit use of optimal TB treatment regimens. A rifamycin is a crucial component for the treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate glyconyltransferase (UGT) 1A1 enzymes and are associated with interactions with most ARV agents. Rifampin is a strong enzyme inducer, leading to enhanced drug clearance and greater reduction in ARV drug exposure. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of CYP 450 enzyme system, its metabolism may be affected by the NNRTIs or PIs. After determining the drugs and doses to use, patients should be closely monitored to assure good control of both TB and HIV (7).

CHAPTER 3

STATEMENT OF THE PROBLEM/STUDY JUSTIFICATION (RATIONALE)

Durability of the first HAART regimen is a major key to long term access, scalability and sustainability of HAART program (9). To maximize the positive effect of HAART on clinical outcome, the initial HAART regimen must be potent and durable. In general, the efficacy of a second regimen is inferior to that of a first regimen (34-36). It is important to identify factors that may have contributed to failure of initial HAART regimen and address them before the change is made to avoid premature failure of the next regimen.

There are significant differences in rates and factors associated with change of HAART regimens between countries. The incidence rate and risk factors associated with change of HAART regimens are unknown in Zambia. It is important to identify the types of and risk factors for change in order to inform policy decisions and inform management strategies for optimizing adherence.

HYPOTHESIS

1) Null hypothesis: The incidence rate of change of the initial HAART regimen is greater than 20% among outpatient adults at UTH from January 2008 to December 2011.

2) Alternate hypothesis: The incidence rate of change of initial HAART regimen is less than or equal to 20% among outpatient adults at UTH from January 2008 to December 2011.

OBJECTIVES

General objectives:

To determine the incidence rate (from January 2008 to December 2011) and risk factors associated with change of initial HAART regimen among outpatient adults at UTH.

Specific objectives

1) To determine the incidence rate of change of initial HAART regimen from January 2008 to December 2011

2) To estimate the proportion of modification/discontinuation due to treatment failure versus non-treatment failure

3) To describe risk factors associated with modification/discontinuation due to treatment failure versus non-treatment failure

CHAPTER 4

RESEARCH METHODOLOGY

4.1 STUDY DESIGN

This was a retrospective chart review study.

4.2 SETTING

This descriptive study was conducted at the outpatient adult ART clinic at the University Teaching Hospital (UTH) a tertiary referral center, located in Lusaka. UTH provides health care (secondary and tertiary) to much of the Lusaka population and the patients referred from all the provinces of Zambia. The target population was patients who attended the outpatient adult ART clinic at UTH from January 2008 to December 2011. This clinic was established in 2008 and does not serve any specific catchment area because it is a tertiary referral center for the entire country. On average the clinic sees 1200 new cases per year approximately.

4.3 PATIENTS

The target population was all adult HIV/AIDS infected patients who initiated HAART at the UTH outpatient ART clinic from first January 2008 to thirty first December 2011.

4.3.1 Inclusion criteria

The inclusion criteria were adults (≥ 18 years of age) who initiated HAART regimens at the UTH outpatient ART clinic from January 2008 to December 2011.

4.3.2 Exclusion criteria

1. Women who received ART solely for PMTCT

2. Patients who started HAART at the inpatient or outpatient clinic but did not have at least one follow-up appointment at the outpatient clinic

3. Patients who started HAART prior to 2008 or after December 2011

4. Transferred patients out-side UTH

5. Incomplete files

4.4 SAMPLING METHOD

This study used a simple random sampling. The sampling frame is described in 4.6 below. Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) was used to generate a simple random sampling.

4.5 SAMPLE SIZE ESTIMATION

A sample size of 352 was determined based on the ability to pull nine charts per day over the 40 days allocated to gather information. This number would allow us to measure a HAART change rate of <20% at a precision of +/-4%, with 95% confidence, assuming a finite population of 6100 ART initiators in the clinic.

4.6 STUDY PROCEDURE

After obtaining the approval of University of Zambia (UNZA) Biomedical Research Ethics Committee (BREC) and Medical Superintendent, the data team generated the list of all patients initiated on HAART between January 2008 to December 2011 in adult outpatient ART clinic. A simple random sample was generated from the list. Using the patient's identity number and name, files were pulled from the file room according to the random sampling numbers generated by Microsoft Excel. Data were entered from the files directly onto the data extraction tool (Appendix B). Data collection tool focused on two areas: change, modification or discontinuation of the initial HAART regimen, and risk factors associated with change of the initial HAART regimen.

4.7 STATISTICAL ANALYSIS

Data was entered into Microsoft Access 2007 (Microsoft Corporation, Redmond, WA) and analyzed with STATA software (Version 11; Stata Corporation, College Station, TX). Demographic information such as the age and gender of patients who changed their initial HAART regimens was analysed. The incidence rate per person-years of follow-up was estimated. Kaplan-Meir curve for change of initial HAART regimen was generated. Chi – square test was performed on categorical variables. Cox proportional hazards model was used in the univariable and multivariable analysis to determine factors associated with change of initial HAART regimen. Statistical significance was considered for p value < 0.05.

4.8 ETHICAL CONSIDERATIONS

Confidentiality was the major concern during the study. This concern was addressed in the following manner:

-Ensured no name was used on data collection tool

-Unique identifier/code number was used to make a list of all patients initiated on HAART from January 2008 to December 2011

-This unique identifier code number was used on the data collection tool

-A registry linking patients ID number and name and the unique identifier/code number was kept confidential in a lockable place and was accessible only by the principle investigator

-Extraction of data was done on an isolated desk away from patients

-All analysis was done using de-identified data

-This research was approved by the University of Zambia Biomedical Research Ethics Committee (UNZA BREC).

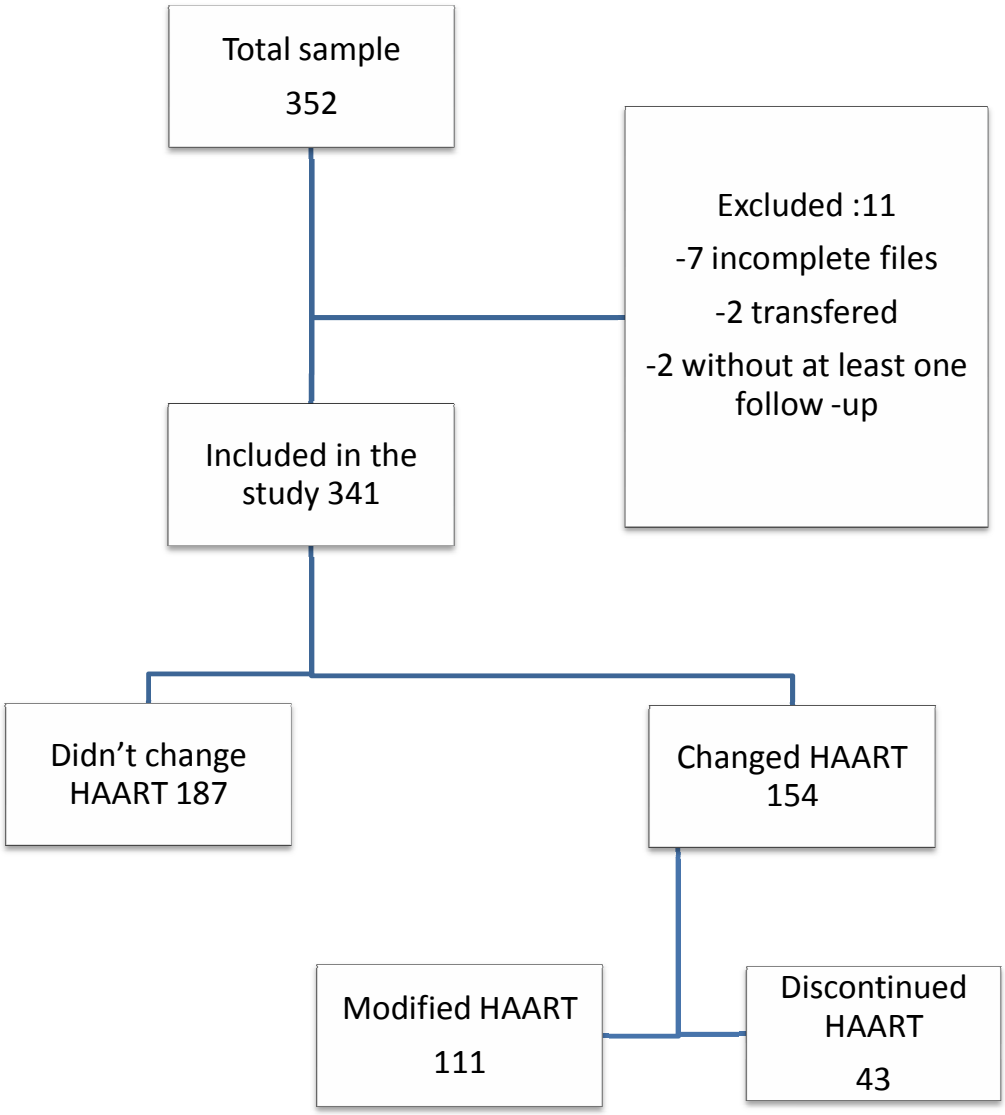
CHAPTER 5

RESULTS

5.1. GENERAL DESCRIPTION OF THE OVERALL COHORT, THE FLOW DIAGRAM AND BASELINE CHARACTERISTICS OF THE TOTAL COHORT

A total of 6100 patients initiated HAART from January 2008 to 31 December 2011. From the sampling frame list, 352 patients were selected. Of these, 11 were excluded from the study for reasons specified in figure 1. The remaining 341 patients met the inclusion criteria and were included in this analysis. Of these, 187 patients did not change the initial HAART regimen, and 154 patients did change the initial HAART regimen. A total of 111 patients modified the initial HAART regimen and a total of 43 patients discontinued the initial HAART regimen.

Figure 1. Schematic showing the study design and subjects who changed and who did not change the initial HAART regimen during the period from 1st January 2008 to 31st December 2011



Baseline characteristics of patients included in the study from first January 2008 to 31 December 2011 are described in table 1. The majority of patients were female 184/341 (54.0%). The mean (± SD) age at the first treatment was 38 years (± 9). The median age 37 years [interquartile range (IQR): 32-44)]. A total of 200/341 (58.6%) patients were married and 80/341 (23.5%) patients were widowed or divorced. Of the 341 patients 26 (37.0%) had access to secondary school and 69/341 (20.2%) had access to tertiary education. The majority of patients 164/341 (48.1%) had an income per month over 500 Kwacha. For the location of residence, 128/341 (37.5%) of patients were located in medium cost area and 108/341 (31.7%) of patients were located in low cost area. TDF/FTC/EFV was the most common initial HAART regimen prescribed with 213/341 (62.5%) followed by TDF/3TC based regimen with 46/341 (13.5%). The majority of patients 178/341 (52.1%) had a CD4 count below 200cells/mm^3, and 85/341 (24.8%) patients had a CD4 Count between 201-350cells/mm^3.

Of 154 patients who changed the initial HAART regimen, 74 (48.1%) were male. A total of 93/154 (60.4%) of patients who changed the initial HAART regimen were married and 34/154 (22.1%) were widowed or divorced. For the education level, 55/154 (35.7%) of those who changed the initial HAART regimen had access to secondary education and 34/154 (22.1%) to tertiary education. Patients who changed the initial HAART regimen with an income per month over 500 Kwacha were 74/154 (48.1%), and 22/154 (14.1%) had an income situated between 201 and 500Kwacha. For the location of residence, 60/154 (39.0%), 53/154 (34.3%), and 40/154 (26.0%) of patients who changed the initial HAART regimen had their residence located in medium, low cost and high cost area respectively. The majority of patients who changed the initial HAART regimen 78/154 (50.6%) had TDF/FTC/EFV as initial HAART regimen, and 38/154 (24.7%) had TDF/3TC based regimen as initial HAART regimen. CD4 count below 200cells/mm^3 was 74/154 (48.1%) in patients who changed the initial HAART regimen.

Table 1. Baseline characteristics of the population (N = 341)

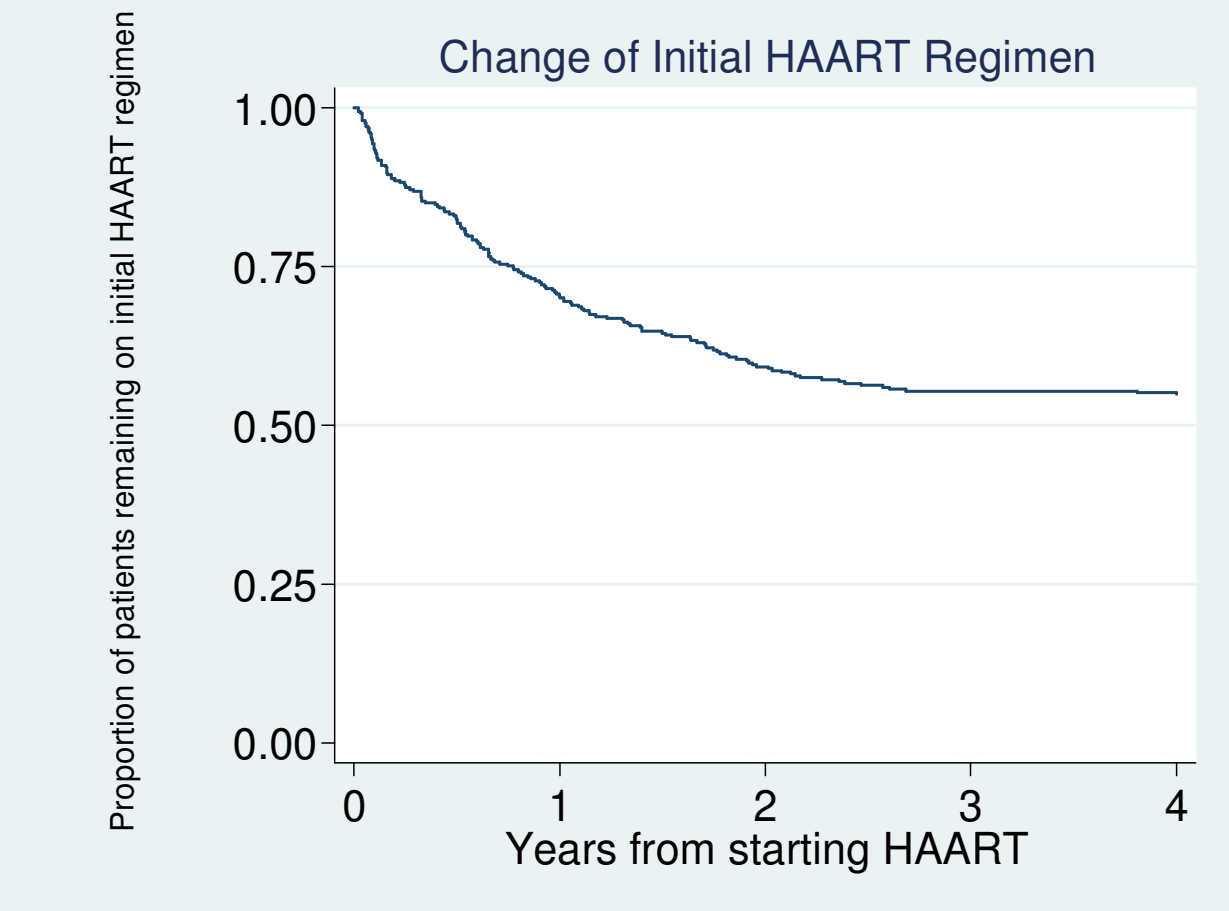
Characteristics	Total (n=341)	Changed (n=154)	Not changed (n=187)	P
Gender				0.50
Male	157 (46.0)	74 (48.1)	83 (44.4)	
Female	184 (54.0)	80 (51.9)	104 (55.6)	
Age				0.51
Mean = 38 (SD:+/- 9)	-	-	-	
Median = 37 (IQR: 32-44)	-	-	-	
Marital status				0.88
Married	200 (58.6)	93 (60.4)	107 (57.2)	
Not married	45 (13.2)	19 (12.3)	26 (13.9)	
Widow/divorced	80 (23.5)	34 (22.1)	46 (24.6)	
Unknown	16 (4.7)	8 (5.2)	8 (4.3)	
Education level				0.56
None	11 (3.2)	4 (2.6)	7 (3.7)	
Primary	44 (12.9)	16 (10.4)	28 (15.0)	
Secondary	126 (37.0)	55 (35.7)	71 (38.0)	
College/University	69 (20.2)	34 (22.1)	35 (18.7)	
Unknown	91 (26.7)	45 (29.2)	46 (24.6)	
Household income per month (in Kwacha)				0.78
<50*	4 (1.2)	1 (0.7)	3 (1.6)	
50 – 100	4 (1.2)	1 (0.7)	3 (1.6)	
101- 200	20 (5.9)	8 (5.2)	12 (6.4)	
201- 500	42 (12.3)	22 (14.1)	20 (10.7)	
>500	164 (48.1)	74 (48.1)	90 (48.1)	
Unknown	107 (31.3)	48 (31.2)	59 (31.6)	
Location of residence				0.27
Low cost area	108 (31.7)	53 (34.3)	55 (29.4)	
Medium cost area	128 (37.5)	60 (39.0)	68 (36.4)	
High cost area	104 (30.5)	40 (26.0)	64 (34.2)	
Unknown	1 (0.3)	1 (0.7)	-	
Initial HAART regimen				0.001
TDF/FTC/EFV	213 (62.5)	78 (50.6)	135 (72.2)	
TDF/FTC/NVP	24 (7.0)	9 (5.8)	15 (8.0)	
LPV/r based regimen	4 (1.2)	3 (1.9)	1 (0.5)	
TDF/3TC based regimen	46 (13.5)	38 (24.7)	8 (4.3)	
ABC/3TC based regimen	21(6.1)	8 (5.2)	13 (7.0)	
D4T/3TC based regimen	17(5.0)	14 (9.1)	3 (1.6)	
AZT/3TC based regimen	16 (4.7)	4 (2.6)	12 (6.4)	
Baseline CD4 count (cells/mm^3) Prior to starting HAART				0.08
<200	178 (52.1)	74 (48.1)	104 (55.6)	
201-350	85 (24.8)	37 (24.0)	48 (25.7)	
>350	12 (4.0)	4 (2.6)	8 (4.3)	
Missing	66 (19.1)	39 (25.3)	27 (14.4)	

*50 Kwacha equals approximately 10 USA dollars

5.2. CHANGE RATE AND DESCRIPTION OF THOSE WHO CHANGED THE INITIAL HAART REGIMEN.

Total follow-up duration was 882 person-years, and median follow-up duration per person was 8 month [interquartile range (IQR), 2.4-16]. A total of 154 patients changed their initial HAART regimen, corresponding to an overall incidence rate of 17.5 per 100 person-years (95% CI: 14.9-20.5) (Fig.1). Change date was incorrectly documented for 1 participant; hence precise date of change was not available. A total of 102 changes (66.7%) occurred within 365 days. An additional 37 changes (24.2%) occurred in the second year on HAART. Only 9.15% of changes (14/153) occurred more than 2 years after initiation of therapy (Fig. 2).

Figure 2. Kaplan-Meier estimate of change of initial HAART regimen



5.3. STATISTICAL COMPARISON OF THOSE WHO CHANGED AND THOSE WHO DIDN'T CHANGE THE INITIAL HAART REGIMEN

Among male patients 74/157 (47.1%) changed, and 83/157 (52.9%) didn't change their initial HAART regimen. In female patients 80/184 (43.5%) changed, and 104/184 (56.5%) didn't change their initial HAART regimen. Among patients with household income between 201 and 500Kwacha 22/42 (52.4%) changed their initial HAART regimen, and 20/42 (47.6%) didn't change the initial HAART regimen. For LPV/r based regimen, 3/4 (75.0%) of patients changed the initial HAART regimen, and 1/4 (25.0%) didn't change. A total of 38/46 (82.6%) patients on TDF/3TC based regimen changed the initial HAART, and 8/46 (17.4%) didn't change. And among patients on D4T/3TC based regimen, 14/17 (82.4%) changed the initial HAART regimen, and 3/17 (17.6%) didn't change (Table 2). There was no statistically significant difference in gender ($p= 0.50$), age ($p = 0.51$), marital status ($p = 0.88$), education level ($p = 0.56$), household income per month ($p = 0.78$), location area ($p = 0.27$) and baseline CD4 count between patients who changed and who didn't change the initial HAART regimen. The difference between change and no change was statistically significant for the initial HAART regimen ($p = 0.001$).

Table 2. Comparative analysis between those who changed and those who didn't change

Characteristics	Total (n=341)	Changed (n=154)	Not changed (n=187)	P
Gender				0.50
Male	157 (46.0)	74 (47.1)	83 (52.9)	
Female	184 (54.0)	80 (43.5)	104 (56.5)	
Age				0.51
Mean = 38 (SD:+/- 9)	-	-	-	
Median = 37 (IQR: 32-44)	-	-	-	
Marital status				0.88
Married	200 (58.6)	93 (46.5)	107 (53.5)	
Not married	45 (13.2)	19 (42.2)	26 (57.8)	
Widow/divorced	80 (23.5)	34 (42.5)	46 (57.5)	
Unknown	16 (4.7)	8 (50.0)	8 (50.0)	
Education level				0.56
None	11 (3.2)	4 (36.4)	7 (63.6)	
Primary	44 (12.9)	16 (36.4)	28 (63.6)	
Secondary	126 (37.0)	55 (43.7)	71 (56.3)	
College/University	69 (20.2)	34 (49.3)	35 (50.7)	
Unknown	91 (26.7)	45 (49.5)	46 (50.5)	
Household income per month (in Kwacha)				0.78
<50*	4 (1.2)	1 (25.0)	3(75.0)	
50 – 100	4 (1.2)	1 (25.0)	3 (75.0)	
101- 200	20 (5.9)	8 (40.0)	12 (60.0)	
201- 500	42 (12.3)	22 (52.4)	20 (47.6)	
>500	164 (48.1)	74 (45.1)	90 (54.9)	
Unknown	107 (31.3)	48 (44.9)	59 (55.1)	
Location of residence				0.27
Low cost area	108 (31.7)	53 (49.1)	55 (50.9)	
Medium cost area	128 (37.5)	60 (46.9)	68 (53.1)	
High cost area	104 (30.5)	40 (38.5)	64 (61.5)	
Unknown	1 (0.3)	1 (100)	-	
Initial HAART regimen				0.001
TDF/FTC/EFV	213 (62.5)	78 (36.6)	135 (63.4)	
TDF/FTC/NVP	24 (7.0)	9 (37.5)	15 (62.5)	
LPV/r based regimen	4 (1.2)	3 (75.0)	1 (25.0)	
TDF/3TC based regimen	46 (13.5)	38 (82.6)	8 (17.4)	
ABC/3TC based regimen	21 (6.1)	8 (38.1)	13 (61.9)	
D4T/3TC based regimen	17 (5.0)	14 (82.4)	3 (17.6)	
AZT/3TC based regimen	16 (4.7)	4 (25.0)	12 (75.0)	
Baseline CD4 count (cells/mm^3) Prior to starting HAART				0.08
<200	178 (52.1)	74 (41.6)	104 (58.4)	
201-350	85 (24.8)	37 (43.5)	48 (56.5)	
>350	12 (4.0)	4 (33.3)	8 (66.7)	
Missing	66 (19.1)	39 (59.1)	27 (40.9)	

5.4. REASONS FOR CHANGE OF THE INITIAL HAART REGIMEN

Drug unavailability was the most common reason for initial HAART regimen change 71/154 (46.1%) followed by non-adherence to the antiretroviral treatment 29/154 (18.8%) and antiretroviral drugs sides effect 26/154 (16.9%). The most common side effect was renal toxicity as defined in appendix B with 8/154 (5.2%). Pregnancy was also one of the reasons of changing the initial HAART regimen with 6/154 (4.0%). Among the 111 patients who had modifications of their initial HAART regimen 4 (3.6%) were due to treatment failure and among the 43 patients who had their initial HAART discontinued 2 (4.7%) were due to treatment failure (Table 4).

Table 3. Reasons for change of initial HAART regimen

Reasons	**Modification N (%)**	**Discontinuation N (%)**
Treatment failure	4 (3.6)	2 (4.7)
Antiretroviral drugs side effect	21 (18.9)	5 (11.6)
Concomitant conditions	14 (12.6)	3 (7.0)
Non-adherence	-	29 (67.4)
Other reasons -Desire of pregnancy -Prescriber error -Death -Drug unavailability	 - 1 (0.9) - 71 (64.0)	 1 (2.3) - 3 (7.0) -

Table 4. Detailed reasons for change of initial HAART regimen

Reasons	Modification (n=111)	Discontinuation (n=43)	Total (n=154)
Antiretroviral drugs side's effect, n (%)			
-renal toxicity	6 (5.4%)	2 (5.0%)	8 (5.2%)
-peripheral neuropathy	2 (1.8%)	-	2 (1.3%)
-gynecomastia	5 (4.5%)	-	5 (3.2%)
-insomnia	1 (0.9%)	-	1 (0.6%)
-confusional state	1 (0.9%)	-	1 (0.6%)
-extensive macular rash	2 (1.8%)	1 (2.3%)	3 (2.0%)
-lipoatrophy	1 (0.9%)	-	1 (0.6%)
-abacavir hypersensitivity	1 (0.9%)	-	1 (0.6%)
-risk of hepatotoxicity (CD4>250 cells/ml)	1 (0.9%)	-	1 (0.6%)
-liver toxicity	-	1 (2.3%)	1 (0.6%)
-severe gastrointestinal intolerance	1 (0.9%)	1 (2.3%)	2 (1.3%)
Treatment failure, n (%)			
-immunologic failure	1 (0.9%)	2 (5.0%)	3 (2.0%)
-virologic failure	3 (2.7%)	-	3 (2.0%)
Concomitant conditions, n (%)			
-tuberculosis	3 (2.7%)	-	3 (2.0%)
-amenorrhoea	3 (2.7%)	-	3 (2.0%)
-pregnancy	3 (2.7%)	3 (7.0%)	6 (4.0%)
-kaposi sarcoma	1 (0.9%)	-	1 (0.6%)
-resolution of preexistence HBV	1 (0.9%)	-	1 (0.6%)
-preexistence renal dysfunction	3 (2.7%)	-	3 (2.0%)
Non-adherence, n (%)			
-Defaulter	-	10 (6.5%)	10 (6.5%)
-Missing clinic appointment	-	19 (12.3%)	19 (12.3%)
Other reasons, n (%)			
-desire of pregnancy	-	1 (2.3%)	1 (0.6%)
-prescriber error	1 (0.9%)	-	1 (0.6%)
-death	-	3 (6.0%)	3 (2.0%)
-drug unavailability	71 (63%)	-	71 (46.1%)

Cox proportional hazards model were applied to determine the independent association of sociodemographic risk factors and initial HAART regimen on the change of the initial HAART regimen (Table 5.). The adjusted hazards ratio of change of initial HAART regimen were in patients who used TDF/3TC, LPV/r and D4T/3TC as part of their regimen 3.90 (95% CI: 2.61-5.84), 3.55 (95% CI: 1.06-11.89), and 2.60 (95% CI: 1.46-4.62) respectively (Table 5.).

Table 5. Association with change of initial HAART regimen

(5a) Association of sociodemographic risk factors

Variable	**Incidence of change (per 100 person-years)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Gender			
Male	18.7	1	1
Female	16.5	0.92 (0.67-1.26)	0.93 (0.65-1.33)
Age			
19-29	19.6	1	1
30-40	18.1	0.90 (0.59-1.38)	0.86 (0.53-1.40)
41-51	17.2	0.88 (0.55-1.39)	0.87 (0.51-1.47)
>52	11.5	0.65 (0.31-1.36)	0.69 (0.31-1.55)

(5b) Association of initial HAART regimen

Initial HAART regimen	**Incidence of change (per 100 person-years)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
TDF/FTC/EFV	12.6	1	1
TDF/FTC/NVP	14.4	1.20 (0.60-2.39)	1.36 (0.67-2.78)
LPV/r based regimen	56.3	3.58 (1.13-11.36)	3.55 (1.06-11.89)
TDF/3TC based regimen	67.1	3.78 (2.54-5.62)	3.90 (2.61-5.84)
ABC/3TC based regimen	14.3	1.15 (0.56-2.39)	1.24 (0.59-2.59)
D4T/3TC based regimen	42.9	2.68 (1.52-4.74)	2.60 (1.46-4.62)

The most common reasons for change of TDF/FTC/EFV to TDF/3TC/EFV were TDF/FTC stocks out and TDF/3TC cheaper cost 32/88 (36.4%). The most common reasons of change of TDF/3TC/EFV to TDF/FTC/EFV were TDF/3TC stocks out, and TDF/FTC reduced cost 29/88 (33.0%). Pregnancy was the reason of change of TDF/FTC/EFV to TDF/FTC/NVP 5/88 (6.0%) and to AZT/3TC/NVP 2/88 (2.3%). Renal toxicity or preexistence renal dysfunction was the reason of change of TDF/FTC/EFV and TDF/3TC/EFV to ABC/3TC/EFV. Pre-existing renal dysfunction was defined based on identification of previous unrecognized abnormal creatinine and/or creatinine clearance below 50ml/min. LPV/r based regimen was changed because of severe gastrointestinal intolerance to TDF/FTC/EFV and because of its component of TDF/FTC and TDF/3TC to TDF/3TC/LPV/r and TDF/FTC/LPV/r respectively. D4T/3TC combination regimen was changed mostly because of peripheral neuropathy 2/88 (2.3%), and government decision to phase out D4T 2/88 (2.3%) (Table 6).

Table 6. Reasons for change of TDF/FTC, TDF/3TC, LPV/r and D4T/3TC based regimens (N=88)

Variable	Reason for change	Second regimen	N (%)
TDF/FTC based regimen	1) -TDF/FTC stocks out, -FTC/3TC in stock, largely replaces TDF/FTC after introduction of a co-formulated TDF/3TC in 2008 by the Ministry of Health due to its cheaper cost	TDF/3TC based regimen	32 (36.4%)
	2) Antiretroviral drugs side effect: renal toxicity	ABC/3TC/EFV	4 (4.6%)
	3)Concomitant conditions -Preexistence renal dysfunction -Pregnancy	 ABC/3TC/EFV TDF/FTC/NVP AZT/3TC/NVP	 3 (3.4%) 5 (5.7%) 2 (2.3%)
TDF/3TC based regimen	1) 2010 ART Guidelines adopt TDF/FTC as first line ART regimen (cost difference between TDF/FTC and TDF/3TC became negligible in that period) -TDF/3TC stocks out -Non new of TDF/3TC stocks bought by the Ministry of Health	TDF/FTC based regimen	29 (33.0%)
	2)Renal toxicity	ABC/3TC/EFV	2 (2.3%)
LPV/r based regimen	1)Severe gastrointestinal intolerance	TDF/FTC/EFV	1 (1.1%)
	2)Because of its TDF/3TC component	TDF/FTC/LPV/r	1 (1.1%)
	3)Because of its TDF/FTC component	TDF/3TC/LPV/r	1 (1.1%)
D4T/3TC based regimen	1)Antiretroviral drugs side effect: -Renal toxicity -Peripheral neuropathy -Lipoatrophy	 ABC/3TC/EFV TDF/FTC based regimen AZT/3TC based regimen ABC/3TC/NVP	 1 (1.1%) 1 (1.1%) 1 (1.1%) 1 (1.1%)
	2)Treatment failure	TDF/FTC/LPV/r	1 (1.1%)
	3)Concomitant condition (Tuberculosis)	D4T/3TC/EFV	1 (1.1%)
	4)Phasing out D4T	TDF/FTC based regimen	2 (2.3%)

CHAPTER 6

DISCUSSION

We carried out a retrospective cohort study on the incidence and determinants of change of initial HAART regimen of adults enrolled at UTH's outpatient adult ART clinic from 1 January 2008 to 31 December 2011. 154 patients of 341 patients who were included in this study changed their initial HAART regimen, representing an incidence rate of 17.5 per 100 person-years (95% CI: 14.9-20.5). Drug unavailability (stocks out and cost), was the most common reason for change of initial HAART regimen. The initial HAART regimen was the only factor associated with change (p=0.001). Patients on TDF/3TC, LPV/r and D4T/3TC based regimen had high hazards ratio of change of initial HAART regimen.

The incidence rate of change of initial HAART regimen of adults enrolled at UTH's outpatient adult ART clinic is relatively low compared to incidence changes in Western cohorts and some developed countries. In the literature, the incidence of change of initial HAART regimen varies greatly. It is generally high in Western Cohorts reaching up to 55% (2) but less in developed countries. In the Swiss HIV Cohort study (32) the total rate of modification of the initial HAART regimen was 41.5 per 100 person-years (95% CI: 37.6-45.8). A study done in Rio de Janeiro, Brazil had found an incidence rate of change of initial HAART regimen of 28.3 per 100 person-years (95% CI: 26.0-31.0) (10). In the treat Asia HIV Observational Database (TAHOD), the overall rate of antiretroviral therapy change was 29 per 100 person-years (21). Within TAHOD, higher income countries had a greater rate of antiretroviral treatment change than low-income countries. In our setting the low rate of antiretroviral treatment change could be explained by a simplified and stable regimen introduced in 2008. A simplified and stable regimen is a main factor for adherence of patients to antiretroviral therapy. Complexity of the regimen is one of the biggest obstacles for patient adherence (18). An adherence of 100% is needed to prevent the occurrence of resistance, treatment failure and change of antiretroviral therapy. Unfortunately viral load and resistance testing were not and still not being routinely performed in our setting to confirm the success of initial treatment and virological control in the patient. In Western countries where viral load and resistance testing are routinely performed, switches may have been triggered much earlier because of a known increase in viral load. Also drug unavailability impacts the strategies used by clinicians in our setting

to change antiretroviral regimen. A limited number of alternative first line and second line drugs contribute to low change of initial HAART regimen. The incidence rate of change of initial HAART regimen observed in our cohort (17.5 per 100 person-years) is comparable to that found in other cohort studies in Africa. A study done by Landier J et al in Mali (16) had found results in accordance with ours. In Mali the incidence rate of change of initial HAART regimen were found to be 16.2 per 100 person-years. Though rates of initial HAART regimen change may be lower in Africa, the goal should always be to strive for a zero percent change rate.

Drug unavailability (stocks out and cost) was the most common reason of the initial HAART regimen change, 71/154 (46.1%) in our study. TDF/FTC/EFV is the most widely used combination in our setting. In 2008, TDF/FTC became part of the first line regimen; however, for cost reasons as well as an endorsement by WHO stating that 3TC and FTC were interchangeable, the Ministry of Health, also introduced co-formulated TDF/3TC. TDF/3TC largely replaced TDF/FTC from the beginning of 2009 to the end of 2010. During this time, many patients were switched back and forth between the two regimens due to stock outs of TDF/FTC and/or TDF/3TC (33). Zambia exhausted the stock of TDF/3TC in 2010 and didn't re-order it since the cost difference between TDF/FTC and TDF/3TC become negligible. In this study, of a total of 17/341(5.0%) patients who were initiated on D4T based regimen, 12/341(4%) were initiated in 2008 and 5/341(1%) were in 2009. The Ministry of Health decided to withdraw D4T from HAART therapy in 2009 because of its irreversible side effects (numbness and burning pain in the hands and feet, and loss of body fat). From that time D4T has been phased out progressively, and Zambia 2010 adult and adolescent antiretroviral therapy protocols recommended that D4T-containing regimens should not be used unless there are no other alternatives (3). No reasons were documented for the choice of these regimens in 2009, but probably apart for the guidelines recommendations (3) it could be explained by the progressive implementation of the guidelines or people who were supposed to implement the policy and guidelines were not well informed. The most common reasons for change of D4T based regimen in our study were peripheral neuropathy 2/88 (2.3%) and D4T phasing out 2/88 (2.3%). LPV/r based regimen was changed because of its TDF/FTC or TDF/3TC backbone component, and severe gastrointestinal intolerance. The study done by Srasuebkul P et al in the TREAT Asia HIV Observational Database (TAHOD) (21) has similar findings to ours . Srasuebkul P et al found significant association between drug

classes, drugs availability and the rate of antiretroviral treatment change (21). The same study found a strong association between the type of regimen used at treatment initiation and the subsequent change. In our study, patients on TDF/3TC, LPV/r and D4T/3TC combination therapy had a higher rate of change of initial HAART regimen. In the study conducted in Kampala, Uganda by Kiguba R et al (17), the most frequently cited reasons for discontinuation and modification of the initial HAART regimen were drugs cost and drugs out of stock. This study shows that despite the efforts by the Ministry of Health, Zambia to provide HAART without charge to people living with HIV and AIDS, the cost of the drugs was a barrier to ensuring continuity of initial HAART regimen.

Non-adherence to initial HAART accounted for 18.8% of the reason for change of initial HAART regimen and was the leading reason for discontinuation of initial HAART regimen in our study. Non-adherence was characterised by irregularity in taking the prescribed regimen, default or non respect of clinic appointments. Cicconi P et al (20) found poor adherence as second cause of discontinuation of initial HAART regimen after intolerance/toxicity.

HAART adverse events accounted for 26/154 (17.0%) cases of change in our study and was the third reason of change of the initial HAART regimen after drugs unavailability and non-adherence. Renal toxicity was the most common antiretroviral side effect leading to change of initial HAART regimen followed by gynecomastia. These side effects are consequence of the tenofovir and efavirenz based – regimens used in our setting. In three studies (11, 20, 21) antiretroviral side events were the most common reasons for change of initial combination therapy, however in these other studies the types of side effects were not specified.

The proportion of modification and discontinuation of initial HAART regimen were 111/341 (32.6%) and 43/341 (12.6%) respectively. In a study done in Kampala, Uganda by Kiguba R, the proportion of modification and discontinuation of the initial HAART regimen were 175/686 (25.5%) and 94/686 (13.7%) respectively (17). The proportion of modification of initial HAART regimen was high in our study.

The proportion of HAART regimen change due to treatment failure versus non-treatment failure was 1.8% and 43.4%. The low proportion of treatment failure observed in our study can be explained by the fact that we do not do the viral load in every patient in our setting. In the Cesar C et al study (12) done in 7 sites throughout the Caribbean and Latin

America, treatment failure (1.8%) was the third cause of initial HAART regimen change. The first and second causes were adverse events (14%) and death (5.7%) respectively.

In our study the incidence of change of initial HAART regimen was high in younger age groups (19-29 and 30-40 years), but chance could not be ruled out. Robinson S et al (2) and Cicconi P et al (20) had found also a high rate of discontinuation in patient's younger than 30 years compared with those aged 30-45 years. At that age there is a high tendency to discontinuation because of poor adherence. In our setting there is no study dedicated specifically to the incidence rate of change of the initial HAART regimen.

STUDY LIMITATIONS

Medical chart review based study such as this one is unlikely to reflect change of initial HAART regimen in the entire population, as not all the required information was documented in the medical chart; many patients were transferred out-side UTH medical facility after initiation of HAART; and a part of the population was receiving HAART treatment from the private clinics.

CHAPTER 7

CONCLUSION

It is important to evaluate reason-specific trends in the incidence of change of initial HAART regimen in order to better understand the determinants of changes. The study found that the incidence rate of change of initial HAART regimen was 17.5 per 100 person-years. The proportion of change due to treatment failure was estimated to be 1.8%. The proportion of change due to non-treatment failure was estimated to be 43.4%. Drug unavailability (stocks out and cost) was the most common reason for change of initial HAART regimen. The risk factor associated with change of the initial HAART regimen was the type of regimen at the initiation of treatment.

RECOMMENDATIONS

We carried out the study on the incidence rate and factors associated with change of the initial HAART regimen at the University Teaching Hospital and in view of our findings, we recommend the following:

1. Complete assessment of the reasons for change of initial HAART regimen including complete documentation of the all information by the clinician

2. Complete documentation of demographics data by the clinician

3. A thorough assessment of the patient ‘s past medical history and the actual kidney function to minimize the change of HAART due to preexistence kidney dysfunction

4. To the Ministry of Health, Zambia to enhance policies allowing continuous supply of antiretroviral drugs

5. Recommend similar study when routine viral load testing is implemented.

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APPENDICES

A) DEFINITION OF VARIABLES

1) Dependent (outcome) variable

Change of initial HAART regimen: modification or discontinuation of initial HAART regimen

2) Independent (exposure) variables

Risk factors associated with change of initial HAART regimen

1. Demographic factors: age (in years), gender (male, female)

2. Factors: marital status (married, not married, widow/divorced**),** educational level achieved (none, primary**,** secondary, College/University), income per month (below 50,000 kwacha; K51, 000-100,000; K101, 000-200,000; K201, 000-500,000; > K500, 000), location of residence (low cost area, medium cost area, high cost area)

3. Treatment failure comprise: 1. virologic failure (one measure of the VL>1000 copies/ml or two measures of the VL 50-1000 copies/ml at least 3 months apart) after six months of therapy; 2. immunologic failure (fall of absolute CD4 to below baseline or persistent absolute CD4 count levels below 100 cells/mm^3 or 50% fall of absolute CD4 count from on treatment peak values) after six month of therapy and 3. Clinical failure (WHO stage 3 or 4 condition) after six months of therapy

4. ARVs adverse effects defined with a reference of a normal baseline function at time of ART initiation: renal toxicity (rise in creatinine over the upper limit of the normal reference values for serum creatinine or creatinine clearance below 50 ml/min); liver toxicity (AST/ALT>5-fold the upper limits of normal range, 37/36U/L); anemia (Hb<6.5g/dl)-severe gastrointestinal adverse effect; peripheral neuropathy, toxic neuropathy secondary to d-drugs; others

5. Concomitant conditions: tuberculosis, mental disorder, hepatitis B, Hepatitis C, pregnancy

B) DATA COLLECTION TOOL

INCIDENCE AND DETERMINANTS OF CHANGE OF INITIAL HAART REGIMEN AMONG OUTPATIENT HIV INFECTED ADULTS AT THE UNIVERSITY TEACHING HOSPITAL IN LUSAKA, ZAMBIA.

1. CODE NUMBER…
2. AGE (YYYY)…
3. GENDER: 1. M

   2. F

4. MARITAL STATUS:

   1. MARRIED

   2. NOT MARRIED

   3. WIDOW/DIVORCED

   4. UNKNOWN

5. EDUCATION LEVEL:

   1. NONE

   2. PRIMARY

   3. SECONDAR

   4. COLLEGE/UNIVERSITY

   5. UNKNOWN

6. ESTIMATED HOUSEHOLD INCOME PER MONTH

   1. BELOW 50 KWACHA

   2. 50– 100 KWACHA

   3. 101– 200 KWACHA

4. 201– 500 KWACHA

5. OVER 500 KWACHA

6. UKNOWN

7. LOCATION OF RESIDENCE:

1. LOW COST AREA

2. MEDIUM COST AREA

3. HIGH COST AREA

4. UNKNOWN

8. CHANGE OF HAART:

1. YES MODIFICATION DISCONTINUATION

2. NO

9. INITIAL HAART REGIMEN…

10. DD/MM/YYYY OF CHANGE…

11. REGIMEN TWO…

12. FACTORS ASSOCIATED WITH CHANGE OF INITIAL HAART

12.1TREATMENT FAILURE

1. VIROLOGIC FAILURE: YES

VL VALUE (S):1……., (dd/month/year)…

2……., (dd/month/year)…

NO

2. IMMUNOLOGIC FAILURE:

YES CD4 VALUE…

NO

3. CLINICAL FAILURE: YES

CLINIC CONDITION/WHO STAGE…

NO

12.2. ARVs ADVERSE EFFECTS

1. RENAL TOXICITY: YES

CREATININE VALUE……

PROTEINURIA VALUE….

NO

2. LIVER TOXICITY: YES

ALT/AST VALUE……..

NO

3. SEVERE GI INTOLERANCE:

YES

TYPE……

NO

4. ANAEMIA: YES

Hb level…….

NO

5. NEUROPATHY : YES

CNS PERIPHERAL

NO

6. OTHER: YES

TYPE…….

NO

12.3. CONCOMITTANT CONDITIONS

1. TUBERCULOSIS : YES

NO

2. MENTAL DISORDER: YES

NO

3. HEPATITIS B: YES

NO

4. HEPATITIS C: YES

NO

5. PREGNANCY: YES

NO

6. OTHERS: YES

TYPE……

NO