ASSESSMENT OF VIROLOGICAL FAILURE AMONG HIV PATIENTS ON FIRST LINE ANTIRETROVIRAL AT KENYATTA NATIONAL HOSPITAL COMPREHENSIVE CARE CENTRE, NAIROBI KENYA

BY

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A ***thesis submitted as a partial fulfilment for a Master of Science degree in Medical Statistics at the University of Nairobi***

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DECLARATION

I declare that this thesis is my original work and has not been presented for a degree award in any other university.

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DEDICATION

This goes to my dad who since I joined this course has been suffering from leukaemia and all along you have been encouraging me despite emotional and financial stress we have been through as a family, to my mum you have been a pillar to me and the rest of the family my the lord increase you and finally to my classmates who always encouraged me to sojourn.

ABSTRACT

Background: Kenya has recorded a high burden of HIV with 1.5 million HIV + persons by 2015. With the adoption of 2016 ART guideline in Kenya all PLHIV now qualify for ART irrespective of WHO clinical stage, cd4 count, age gender, pregnancy status, co-infected status thus increasing the number of patients likely to develop resistance. Once a patient develops resistance to first line, they are put on second line ART regimen which is more expensive and less tolerable. This study seeks to establish the duration of time patients put on first line ART take before developing virological failure and factors influencing it as a step towards guiding the management in adequate planning and budget allocation for management of these patients

Study objective: To assess virological failure among HIV patients on first line ARV at Kenyatta National Referral Hospital Comprehensive Care Centre between the years 2009-2016

Study design and site: This was a retrospective cohort studyconducted at Kenyatta National Referral Hospital Comprehensive Care Centre (KNH-CCC) between 2009 and 2016 with 3 years accrual and 6 years observation periods. The main exposure was poor adherence to first line ART treatment

Study population and sample: HIV infected patients enrolled and initiated into first line ART at the centre between 2009 and 2010. 1470 patients wereselected through simple random sampling from the list of these patients in CCC database with complete follow-up records

Data collection and analysis: A structured data abstraction tool was used for extracting social-demographic, clinical and virological data from medical records data of the selected patients. The data was entered and stored in Microsoft Access 2013. Data cleaning, coding and analysis

wasdone using STATA version 13 SE. The main outcome was the virological failure time. Kaplan Meier estimator was used to estimate the survival function. Log-rank tests was used to compare the survival functions between patients based on adherence to treatment and first line HAART combinations. Log-rank statistic and corresponding p-value will be reported.

Results: Generally patients sampled comprised of age 2 months to 72 years where 75% of the patients were below age 42. 10% of the patients were paediatric while adults composed of 90% having female patient being almost double of the men on follow up. At enrolment clients classified in WHO(3 and 4) were 42.2% and 99% of patients were reported to have been screened for TB, 13% of patients on follow up had NCD were 64% of patients were having EFV based regimen and 35.8% had NVP based regimen. 34.8% were reported to have poor adherence. 75% of patients had CD4 of less than 600 cell/ml with 19.7% of patient reported being obese and 11% were underweight. Kaplan Meier estimated that 50% of patient would fail by 36 months after ART initiation for adult's patients and for paediatric would fail by 42 months after being started on ART. Log rank test conducted showed failure rate differed significantly with relation to age, adherence and regiment type. Adults had 61% risk of virological failure at next time compared to paediatric, patient started on NVP had 18% reduced risk of virological failure compared to ones started on EFV based. Good adherence reduced chance of virological failure by 26% by the next time

Conclusion: patients being started on first line ART at KNH-CCC their failure time depended on age, adherence and type of regimen (EFV or NVP) where in general paediatric had longer period on first line compared to adults patients.

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ACRONYMS AND ABBREVIATIONS

ABC- Abacavir

AIDS- Acquired Immune Deficiency Syndrome

ART- antiretroviral therapy

ARVS – Antiretroviral drugs

AZT- Zidovudine

EFV- Efavirenz

HIV- Human Immunodeficiency Virus

KNH – Kenyatta national hospital

KAIS- Kenya AIDS indicator survey

LPV/r- Boosted lopinavir

r- Retonavir

NASCOP-National AIDS and STI Control Program

NACC – National aids control council

NNRTIs- non-nucleoside reverse transcriptase inhibitors

NRTIs- Nucleoside reverse transcriptase inhibitors

NVP- Nevirapine

PCP- Pneumocystis pneumonia

PMTCT – Prevention of mother-to-child transmission of HIV

RLS- Resource limited settings

STI – Sexually transmitted infections

TB – Tuberculosis

TDF – Tenofovir

UNAIDS- United Nations Program on HIV/AIDS

WHO- World Health Organization

DEFINITION OF TERMS

Undetectable viral load – means virus has been suppressed in the body

0.01 reading of viral load – means undetectable viral load

Adherence form – form filled when client has gone through counselling

Kaposi's sarcoma – form of cancer affecting skin tissues in HIV patients

Follow up time – follow up time of three months was used to monitor failure time

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

HIV is a global pandemic problem with no cure thus HIV+ persons have to be on medication for the rest of their lives. However, without medical care, HIV still leads to AIDS and early death(Scope, 2016).

ART treatment leads to longer and quality life of the HIV patients which at the end results to reduced onward transmission of the virus.The MOH purpose is to scale up HIV care and treatment services as well as promoting prevention services. Many lives have so far been saved with close to 10 million adults and children being put on ART.(Essajee & Kumarasamy, 2014).

WHO advocates for public health approach towards HIV/AIDS care and treatment thus we have rationale of first line, second line and third line /salvage as treatment options for those who are infected. Diagnosis, treatment and offering other health-related support and services to people living with HIV on a daily basis (Europe, 2007). The annual number of new HIV infections has been steadily declining since the late 1990s and there are fewer AIDS-related deaths due to the significant scale up of antiretroviral therapy over the past few years(Getnet, 2014).

Within sub-Saharan region the number of new HIV infection has fallen but the prevalence is extremely high in some countries and most of them rely on donor funds to finance their HIV response.

Kenya is the fourth largest HIV epidemic country in the world where 1.5 million in 2015 were infected and of which 59% adults were on ARV treatment.The Plan defines the implementation framework of the acceleration of HIV care and treatment; thereby contribute to achieving the

90:90:90 targets set for 2019 in Kenya AIDS Strategic Framework2014/15-2018/2019. It will also provide guidance on high impact strategies to achieve set targets based on the county HIV burden and context (National AIDS and STI Control Programme, 2016).

The ultimate goal of HIV treatment programs is for the people living with HIV to be virally suppressed which involves prompt diagnosis, early ARV initiation and ensuring adherence of medication for the people who have been put on medication which if not done leads to viral mutations resulting to treatment failure among the patients.

1.2 Problem statement

The emergence of virological failure to ARV drugs is an unavoidableoutcome of expanding ART and the longer duration of exposure (Meintjes et al., 2015). ART should be potent enough to suppress HIV viremia to undetectable levels, as measured by the most sensitive assay available, and which is durable in its virologic effect (Sik-to, Chin-peng, Chung-ki, & Tak-yin, 2011). Clients who had failed on first-line drug have a higher percentage of more than 46% failing again for second-line drugs, this contributes to the higher number of side effects with greater likelihood of drug resistance and treatment fatigue(Care, 2016). A delay if seeking for treatment failure can also lead to increase in drug toxicity that may lead to the buildup of drug resistance-associated mutations. It may also result in increased morbidity and mortality(Care, 2016).

Many studies indicates that many HIV+ clients who fail the second line ART in resource-limited settings require major PI resistance-associated mutations, this implies that there is failure due to reduced adherence(Meintjes et al., 2015) thus concentrating on first line treatment failure to help knowing the average time patients take on first line ART failure T failure.

1.3 Justification

The main aim of antiretroviral treatment for HIVpersons is to suppress viral load to undetectable levels thus enabling them to live a long and quality life free of opportunist infections. Ideally a patient should have undetectable viral load from six months of starting ART or having been changed from one combination of ART to another in the event of validated virological treatment failure.

With the increasing number of patients being put on treatment at KNH-CCC mainly due to the new WHO/National guideline of test and treat, the number of clients who fail on first line has been increasing proportionally over time and no clear study that has been done to establish how long patients who start on the medication (ART) take before drugs lose their potency to fight the virus given our settings as a developing country or what are the factors contributing to some patients failing earlier than others at the clinic irrespective of standardized HIV care services being offered to all clients being attended at the clinic. With this, there are a number of clients having detectable viral load after short period of initiation of first line ART making them candidate for second line treatment which is more expensive and combinations of single drug have not been availed readily to patients(public hospitals) making their adherence more complex compared to first line ART.

This study sought to find out the time taken for HIV patients to fail i.e. (based on detectable viral load after six months of initiating treatment) on first line with the associated factors contributing to this failure at KNH-CCC. The findings can be used to address challenges arising with treatment failure and help have more specific targeted address to challenges facing clients being started on ART or still on follow up. Additionally findings will form a basis for future research

to be conducted at the clinic or elsewhere and evidence for policy makers in line with HIV patient management.

1.4 Broad objective

To assessvirological failure time and factors associated among HIV patients on first line antiretroviral at KNH-CCC between 2009 and 2016.

1.4.1 Specific objective

1. To determine time taken for patients to develop virological failure for patients enrolling on first line ART at KNH-CCC.
2. To compare time to virological malfunction among HIV patients initiated on different first line ART combinations at KNH CCC.
3. To evaluate factors associated with virological failure among patients on first line ART at KNH CCC.

CHAPTER TWO

LITERATURE REVIEW

2.1 HIV epidemiology

HIV is still a major public health issue globally with 36.7 people living with HIV virus in 2015 which included 1.8 million children and reported 1.1 deaths of HIV related deaths in the same year. The global prevalence of the disease is 0.8% and the majority of this population is living in developing countries. About 2.1 millionnew infections in the whole world were recorded in 2015[1.8 million–2.4 million], this added up to a total of36.7 million HIV+(Pustil, 2016)The world has committed to ending the AIDS epidemic by 2030. How to reach this bold target within the Sustainable Development Goals is the central question facing the United Nations General Assembly High-Level Meeting on Ending AIDS, which was held on 8 to 10 June 2016. The extraordinary accomplishments of the last 15 years have inspired global confidence that this target can be achieved (Pustil, 2016). Since the HIV epidemic was reported, over 78 million people have been infected and out of these 35 million people have died of HIV/AIDS related illness.

In sub-Saharan Africa, an estimated 25.5 million people live with the virus and majority of them are found in East and SouthAfrica.It is still a long term development obstacle in and the prevalence of the disease is still high in some countries despite the effort being put up. Sub-Saharan Africa continues to bear an unwarrantedshare of this problem, even though epidemics across countries in Africa vary considerably: for instance, 22.9 million of these people live in the region and they represent about 68 percent of the total worldwide(Fact, From, World, Indicators, & Africa, 2009).

Kenya is burdened with about 1.5 million HIV infected persons at the end of 2015. Women are more vulnerable to HIV infections compared to men, the national prevalence stands at 7.0 per cent for women and 4.7 per cent for men respectively as per the 2015 HIV estimate report.For instance, in Homa Bay County in Nyanza region; the epidemic is geographically diverse with a range of as high as 26 prevalenceto as low as approximately 0.4 percent in Wajir County in North Eastern region. This high burden accounts for an estimated 29% of annual adult deaths, 20% of maternal mortality, and 15% of deaths of children under the age of five. Thispandemic has also lowered the per-capital output of the country negatively. Many stable and married couples are the most affected as they account for 44% of the new adult infections(Kharsany & Karim, 2016).

2.2 HIV diagnosis and transmission

HIV testing is voluntary and in many cases it is based on informed consent. Many patients who understand the merits and demerits of HIV testing can easily interpret the meaning of the test result. Those who also understand how HIV is transmitted are considered able to provideverbal consent to proceed with HIV testing. For this category of persons, written consent is not considered necessary (Screening & Guide, n.d.).

Diagnosis of HIV is mostly done through blood or saliva for the antibodies of the virus, the diagnosis may take up to twelve weeks because it takes time before the body can produce the antibodies against the virus which are then detected through the antibody test. With advent of new technology one is able to check for the HIV antigen, a protein produced by the virus instantly after infection which when tested can confirm diagnosis quickly after infection. The HIV transmission is only possible if mucusmembrane, damaged tissue or directly injected to

bloodstreamcomes into contact with the body. Some common areas where mucus is found include the mouth opening, rectum virginal and opening of the penis.

2.3 HIV management

HIV management process starts from testing, to linkage to appropriate HIV prevention, treatment and care, and other clinical services. It also consists of coordination with laboratory services in support of quality assurance (QA) and delivery of correct results(WHO), 2016). The main goal of starting ART is to suppress viral replication to reduce patient viral load to undetectable levels. Prolonged viral suppression and the CD4+ lymphocyte count usually increases that is accompanied by a restoration of pathogen-specific immune function(AIDS 2014 Communication Department, 2014). Currently all people who have confirmed infection are ere eligible for ART not putting into account the CD4 level. Waiting for many years before meaningful services can be provided also increases the risk that individuals. It is therefore highly recommended that HIV treatment be initiated earlier. The 2013 WHO guidelines on management of HIV eliminates the challenge of engaging HIV-diagnosed individuals who are not yet eligible for antiretroviral therapy. Before starting, you must ensure that the patient is willing and ready to take ART with good adherence which should be done preferably within two weeks of confirming the infection.

Generally we have several classes of HIV treatment (**Table 1**).

Table 1: Classes of ART treatment

Class	Mechanism of action	Specific action
Nucleoside and nucleotide reverse transcriptase inhibitors	Reverse transcriptase inhibition	Nucleic acid analogues mimic the normal building blocks of DNA, preventing transcription of viral RNA to DNA
Non-nucleoside reverse transcriptase inhibitors	Reverse transcriptase inhibition	Alter the conformation of the catalytic site of reverse transcriptase and directly inhibit its action
Protease inhibitors	Protease inhibitors	Inhibit the final maturation stages of HIV replication, resulting in the formation of non-infective viral particles
Integrase inhibitors (also termed integrase strand transfer inhibitors	Inhibition of viral integration	Prevent the transfer of proviral DNA strands into the host chromosomal DNA
Entry inhibitors	Entry inhibition	Bind to viral gp41 or gp120 or host cell CD4+ or chemokine (CCR5) receptors

(AIDS 2014 Communication Department, 2014)

At any given time a patient should be on a combination of three drugs collectively known as HAART which helps prevent growth of the virus. Further the drug is grouped in different lines for a proper guide on HIV treatment and management, we have: First line, Second line and Third line or salvage.

2.4 HIV treatment failure

Treatment failure is when the viral load is still detectable to above 1000copies after a client being on treatment for more than six months of either starting on a new treatment or being changed to an alternative treatment after failing on a previous one. Despite HIV treatment becoming successful, many patients on second-line ART, mortality and virological failure rates are still high. Virologicalfailure is the growing levels of detectable HIV, RNA which is associated with multiple nucleoside/nucleotide resistancemutations(Ramadhani et al., 2016).

According to WHO guideline, treatment failure can be classified in three groups:

TheWHO 2006 global guidelines define clinical failure when there is a new or recurrent WHO stage 4 condition, Immunological failure when CD4 falls to the pre-therapy baseline (or below) or there is a50% fall from the on-treatment peak value (if known) or CD4 levels are persistently

< 100 cells/mm3 andVirological failure(WHO, 2007).Treatment failure could be associated to a variety reasons like poor treatment adherence, toxicity or drug resistance Change of treatment should be made immediately a virological failure has been confirmed for non-nucleoside reverse transcriptase inhibitors even if resistance testing is not available as a result of low genetic barrier(Ramadhani et al., 2016).

Resistance testing is key in guiding the new regiments to be used and relevance of laboratory technologieshave permitted advances in HIV resistance testing to many clinicians and investigators who are currently using these technologies in the clinical management of HIVtreatment(Development, 2007).Failure is detected and when it is not available, knowledge of common resistance pattern likely to result from the first regiment should be looked into and taken into account. All these two perspectives aid to come up with the three possible combination active drugs to suppress the viral load to undetectable levels.

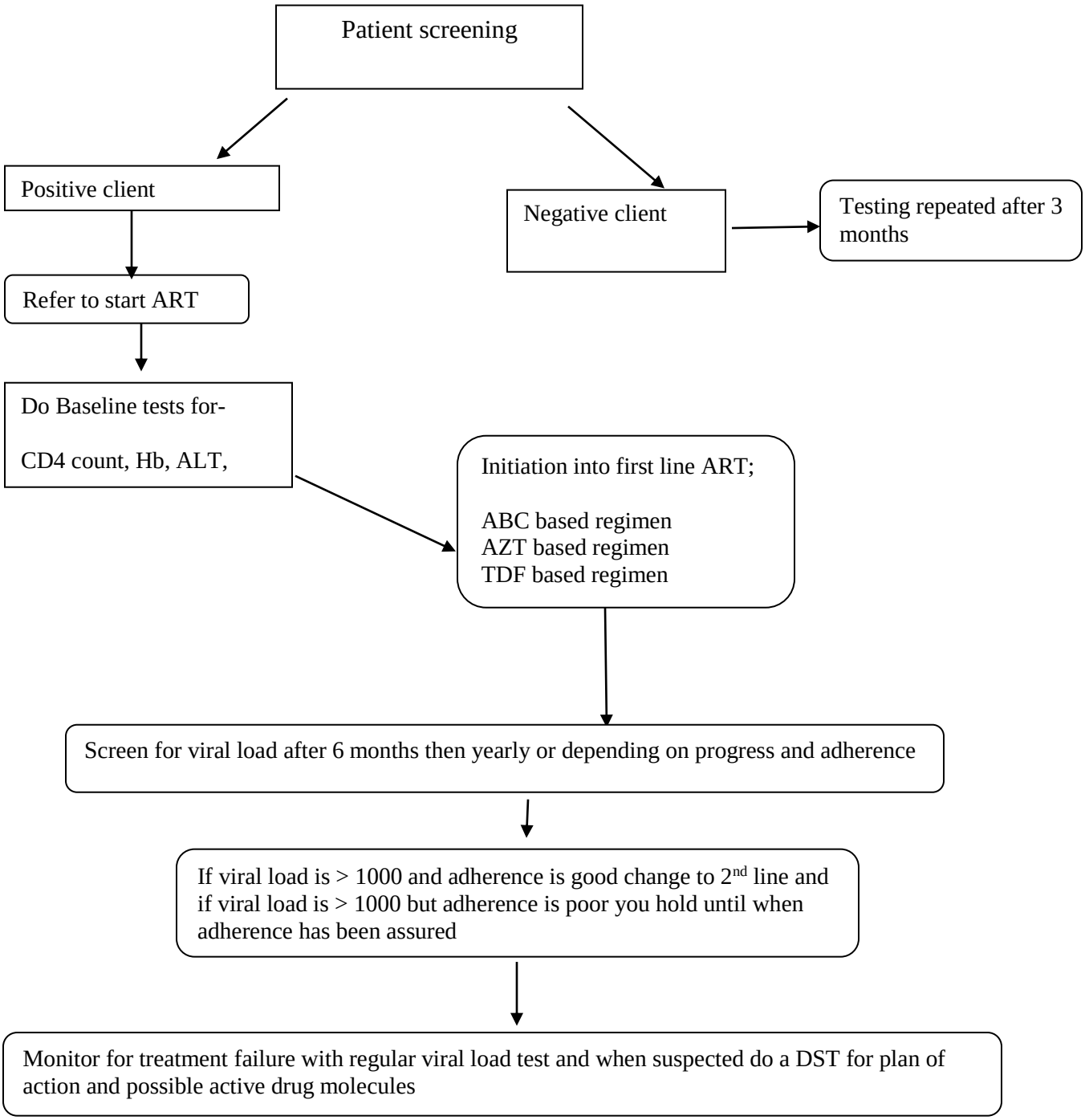
In treatment failure there is a complex drug resistance process of HIV virus learning slowly to run away from the effects of antiretroviral and continue multiplying by achieving genetic mutations that creates knowledgeable mutant virusbecause of its high rate of replication (109 to 1010 variations per person per day) and error-prone polymerase, HIV easily develops mutations that can change susceptibility to antiretroviral drugs. As a result of this, the surfacing of resistance to one or more antiretroviral drugs is the commonest reasons for therapeutic failure. In

addition to this, the emergence of resistance to one antiretroviral drug sometimes confers a decrease in or a loss of susceptibility to drugs of the same class(Development, 2007). In regards to resistance, we have antiretroviral that are not Potent – (ability to prevent HIV from multiplying). Genetic barriers to resistant measures on the number of mutation it takes for the virus to figure out how to escape the effect of the drug. They are of two types namely; Low genetic barriers that only acquires a few mutations to keep multiplying and High genetic barrier that shows that the virus has to acquire many mutations to avoid being suppressed.

2.5 Flow chat on patient follow

The following flow chat shows a sketch diagram from the time a patient is diagnosed to the time he/she is classified to be in a treatment failure where necessary drug changes needs to be instituted.

FIGURE 1: FLOW CHART SHOWING PATIENT MANAGEMENT CYCLE



CHAPTER THREE

METHODOLOGY

3.1 Study design

The purpose of the study was to establish how long a patient takes before developing virological failure where a retrospective cohort study design was adopted to investigate time to virological failure and factors associated among HIV patients enrolled on first line ART at KNH-CCC. The study period will be between 1st January, 2009 and 31st December, 2013 which will serve as the enrolment period with follow up time taking up to December 2016.

3.2 Study site

The study was conducted at Kenyatta National Hospital at the comprehensive care centre clinic in upper hill Nairobi which is an ongoing HIV clinic supported by CDC and working with collaboration of University of Nairobi running from Monday to Friday serving all patients who are able to follow set national guideline for HIV clinic services. At the centre there is registration of patients who have come for the services after which nursing care, clinical care and psychosocial services are given to the clients in addition to nutritional and physiotherapy services given.

3.3 Study population

The study comprised of HIV patients initiated into first line ART betweenJanuary 2009 to December 2011 which served as the recruitment period and were being followed-up at KNH-CCC up to December 2016. Each client was followed up for six years from the time of initiation. The clinic had a total of 9915 active patients on follow up at the end of 2016 with 9063 being classified as adults (≥ 20 years), 362 as adolescents (15-19 years) and 693 as paediatrics (0-14

years). On first line there were 8262 adults, 284 adolescents and 662 children whereas second line comprised of 780 adults, 74 adolescents and 28 children. The few remaining (24 patients) were on third line.

3.4 Sampling method

Due to the heterogeneity of the patient population, two-stage stratification will be done to have a representative sample. The first stratification will be done based on age group. The second stratification in each age group stratum will be based on the six types of first line ART combinations. Simple random sampling with equal allocation will used to select patients in each stratum. Based on annual KNH-CCC reports from 2009 to 2016; approximately 300 HIV patients are enrolled into first line ART. Patients will therefore be recruited for a period of three years starting from 1stJanuary 2009 and followed until the end of the study period (31st December, 2016).

3.4.1 Inclusion criteria

Must be HIV patients enrolled into first line ART at KNH-CCC from 1st January, 2009 to December 2011.

3.4.2 Exclusion criteria

Patients who got enrolled on first line from other centres other than Kenyatta National hospital

3.5 Sample size determination

Based on the main event of interest in the study being virological failure time after starting ART Log rank test was applied to compare the two survival curves therefore sample size was estimated based on this test using the formula below;

$$\boldsymbol{n = n_1 + n_2}$$

$$\boldsymbol{n_1 = AR.n_2}$$

$$\boldsymbol{n_2 = \frac{E}{(AR * P_1) + P_2}}$$

$$\boldsymbol{E = \frac{\left[\frac{(AR+1)^2}{AR}\right] \cdot (Z_{1-\alpha/2} + Z_{1-\beta})^2}{[Log_e(\Delta)]^2}}$$

$$\Delta = \boldsymbol{\frac{Log_e(1 - P_1)}{Log_e(1 - P_2)}}$$

Where:

Δ=hazard ratio (Expected hazard ratio=1.5)

P1= probability for virological failure among HIV patients on first line ART with good adherence (p1=0.24, based on the study by name (Sang et al, 2016)

P2=probability for virological failure among HIV patients on first line ART with poor adherence

AR=Allocation ratio (AR=1)

$\boldsymbol{z_{1-\alpha/2}}$=Standard normal critical value for two side test at **α** type I error (**α=0.05, $z_{1-\alpha/2}$= 1.96)**

$\boldsymbol{z_{1-\beta}}$=Standard normal critical value for **β** type II error (**β=0.20, $z_{1-\beta}$=0.84)**

n1=Sample size in the group of HAART first line patients with good adherence

n2=Sample size in the group of HAART first line patients with poor adherence

Using the formula and defined parameters, minimum sample size require will be n=n1+n2=680

3.6 Data collection

The participants were selected from data retrieved from KNH-CCC electronic medical records (IQ-CARE) which comprised of clinical data, pharmacy data and laboratory investigations which have been captured and stored in the system. The system comprised of all monitoring trail of clients from the time a patient was registered up to the current status comprising of different departments within the clinic. Having special forms for each and every department information retrieving was done through query being run from the IQ-CARE data extraction tool and stored in MS Access database version 2013.

3.7 Data management and analysis

Data will be imported to STATA version 13SE where data cleaning coding and analysis will be done from which exploratory data analysis will be done to summarize the data. Histograms will be plotted to show the distribution of quantitative variables and measures of central tendency (mean/median) and dispersion (standard deviation/inter-quartile range) reported in tables. For categorical variables bar/pie charts will be plotted to show the distribution and frequencies and proportions reported in tables. Kaplan-Meier estimator will be used to estimate survival functions.

Log-rank tests were used to compare the survival functions based on the different first line HAART combinations. Log-rank statistic and corresponding p-value were reported.

Assumption for proportional hazard will be evaluated. Cox proportional hazards model was used to evaluate prognostic factors for virological failure among patients on first line ART and the

assumption was not violated thus frailty model was adopted to estimate the hazard ratios. Hazard ratios and corresponding confidence intervals were reported.

Cox proportional hazards model

$$\boldsymbol{h1(t) = ho(t) * e^{(\beta 1 Xi + \beta 2 Xj \ldots + \beta n Xk)}}$$

Where; $h_1(t)$ = Hazard rate for patient 1 at time t

$h_0(t)$ = Baseline Hazard rate at time t

***xi, xj…xk*=** Prognostic factors

β1,β2,…βn = Coefficients representing the effect of each prognostic factor

3.8Ethical considerations

Ethical approval was sought from the University of Nairobi/Kenyatta National Hospital ethics board where additional permission from the Kenyatta national hospital management health system and head of unit at Kenyatta national hospital comprehensive care center to use the electronic medical records servers was granted.

CHAPTER FOUR

RESULTS

4.1 Profile of the HIV patients at KNH-CCC

Data was collected from a total of 1,472 HIV positive patients who were initiated into antiretroviral therapy between January, 2009 and December 2010 at KNH comprehensive care clinic. The histogram below shows the distribution of the patients' age in years.

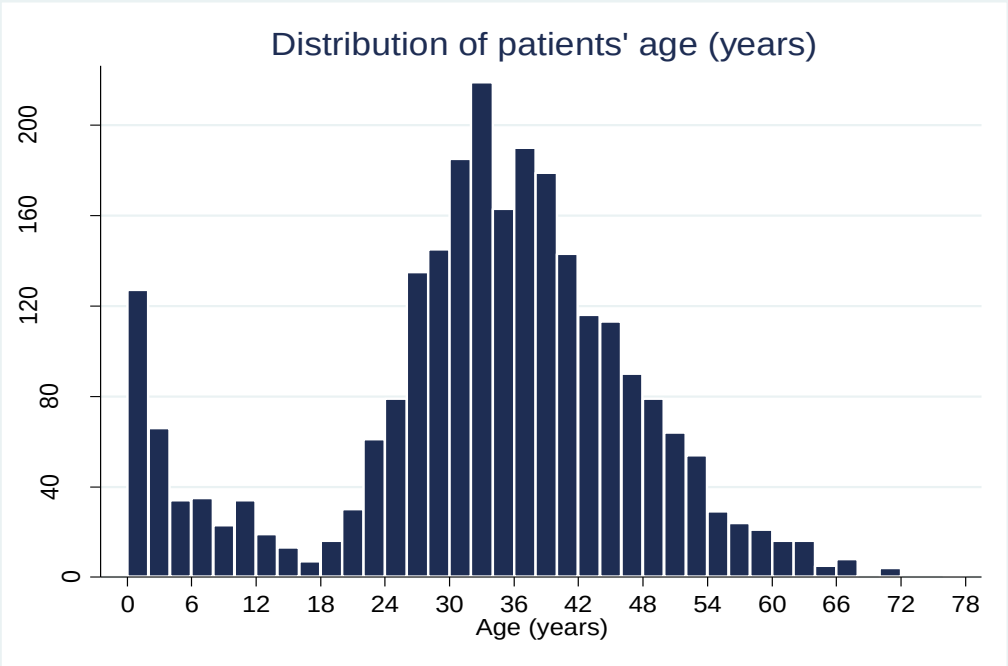


Figure 2: Distribution of the patients' age (years)

The age distribution was bimodal as shown in the graphs; with peaks at 1 year and 33 years. The patients' age ranged from months to 2 months to 72 years. Three quarters of the patients in this study were younger than 41.9 years.

In terms of age groups, adult patients (≥ 15 years were) the most predominant constituting 90% of the population. The rest were pediatric patients (< 15 years of age).

Table 2: Demographic characteristics of the patients

VARIABLE	CATEGORY	FREQUENCY
Gender	Female	892 (60.6)
	Male	580 (39.4)
Age group	< 15 years	141 (9.6)
	≥ 15 years	1331 (90.4)
BMI	Underweight	166 (11.4)
	Normal weight	573 (39.3)
	Overweight	432 (29.6)
	Obese	287 (19.7)

There were more female patients (almost twice the number) than male patients. Only 39.3% of the patients had a normal BMI at the start of ART.

Table 3: Clinical profile of the patients at baseline and treatment history

VARIABLE	CATEGORY	FREQUENCY
WHO stage	Stage 1	398 (33.0)
	Stage 2	299 (24.8)
	Stage 3	384 (31.8)
	Stage 4	125 (10.4)
TB screening results	No signs/symptoms	1398 (99.0)
	On treatment	6 (0.4)
	Suspected TB	8 (0.6)
Any non-communicable disease	No	1268 (86.1)
	Yes	204 (13.9)
Regimen type	EFV	945 (64.2)
	NVP	527 (35.8)
Adherence	Good	959 (65.2)
	Poor	513 (34.8)
CTX Dapsone	Yes	1472 (100)
Missed doses	No	1059 (98.5)
	Yes	16 (1.5)
Delays in taking medication	No	1054 (98.9)
	Yes	12 (1.1)

67.0% of the patients started treatment when the HIV infection had progressed beyond stage 1. Almost all (99%) the patients that had undergone TB screening did not present any signs & symptoms of TB infection. 13.9% of the patients were suffering from at least one non communicable disease e.g. hypertension, diabetes etc.

More than half of the patients (64.2%) were started on EFV based ART regimens. The rest were on NVP based regimens. Using the WHO drug adherence assessment guidelines, 35.8% of the patients were considered as a having poor drug adherence. Almost all the patients did not miss their doses (98.5%) or delay in taking medication (98.9%)

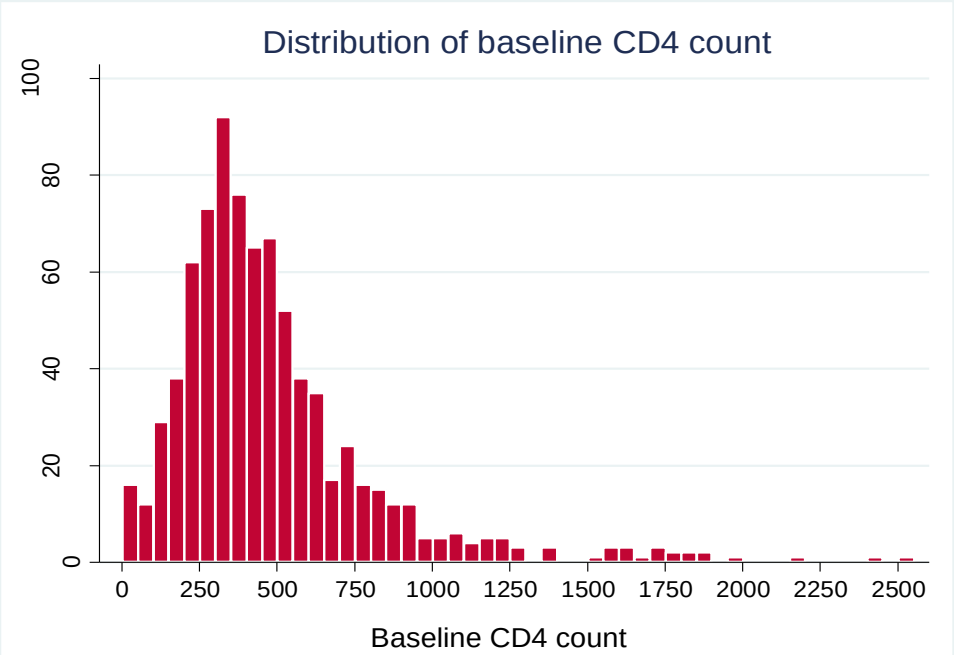


Figure 3: Distribution of the CD4 count in patients at baseline

CD4 count distribution in Figure 2 was right skewed. CD4 count ranged from 2 cells/ml to 2507 cells/ml with three quarters having less than 590 cells/ml

4.2 Estimation of virological failure time

Kaplan Meier method was used to estimate the virological failure function in HIV patients receiving HIV treatment at KNH-CCC. Quarterly time interval was used in the model

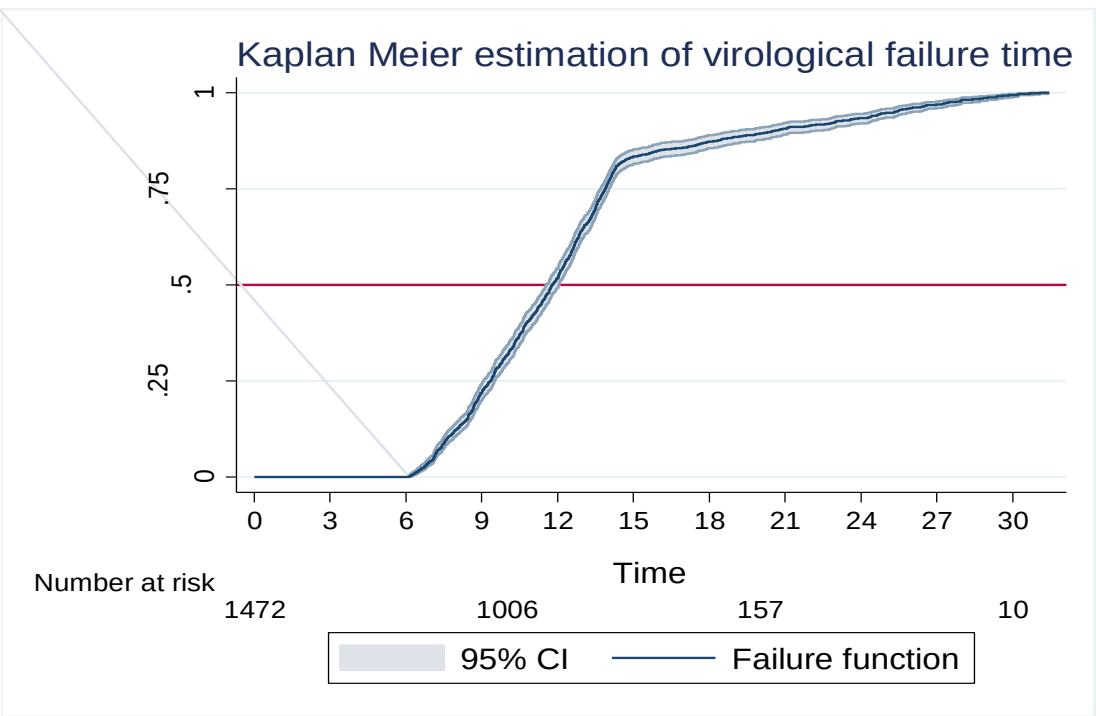


Figure 4: Estimated virological failure time (3 months interval) of patients on ART

Starting with 1472 patients at risk of virological failure, 50% would fail before time 12, which represents 36 months or three years after initiation of ART. For the first 18 months (between time 0 and 6), the probability of virological failure was zero, after which a steady increase in the probability to fail with respect to time was observed until time 15 (45 months later). This was followed by a gradual increase until the end of the study.

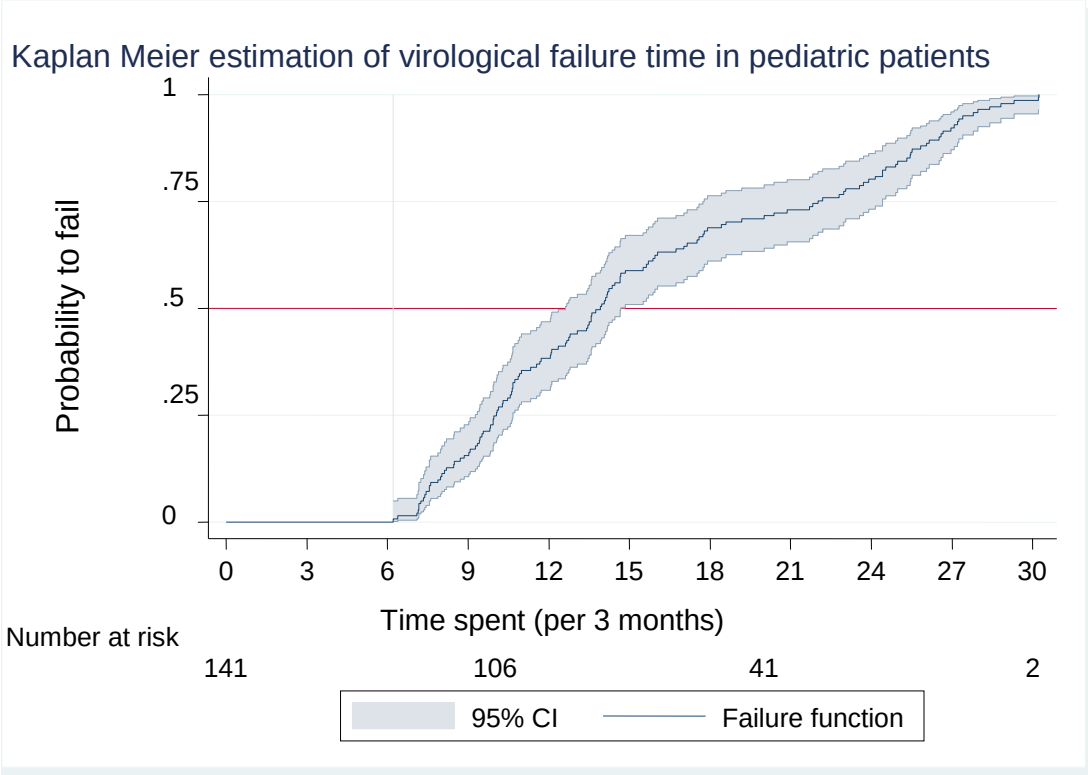


Figure 5: Estimated virological failure time (3 months interval) of pediatric patients

Starting with 141 pediatric patients at risk of virological failure, 50% would die before time 14 (before the 42nd month) from the time of ART initiation

The probability of a pediatric patient to fail virologically was zero for the first 18 months (up to time 6) after which a gradual increase was observed until the end of the study

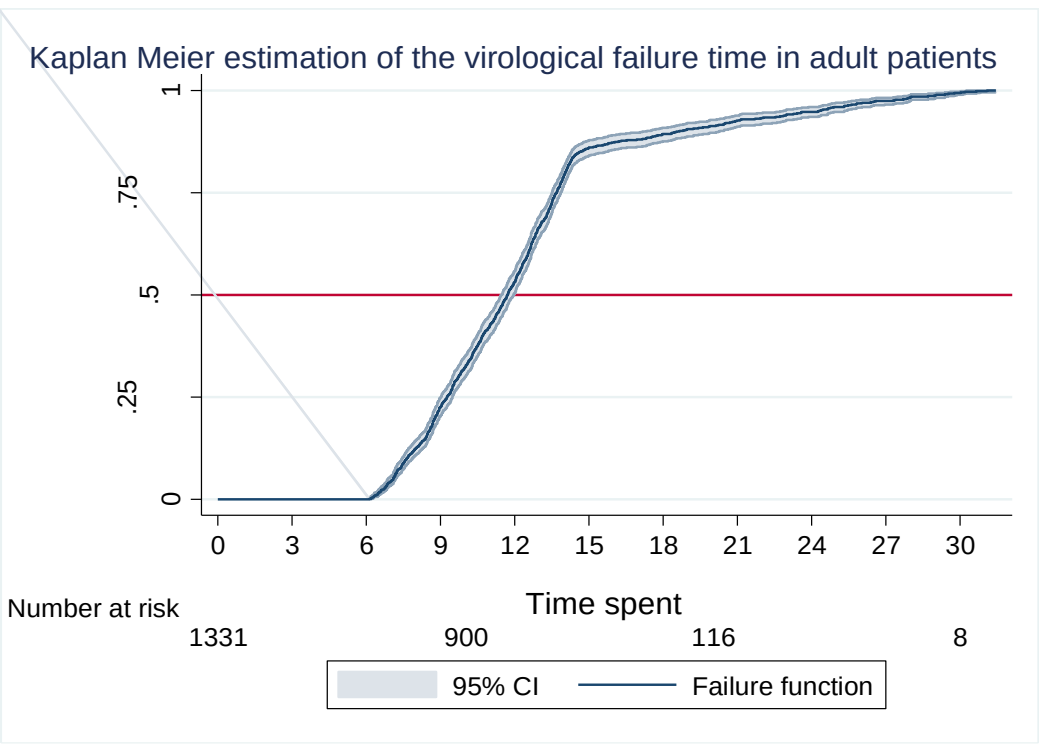


Figure 6: Estimation of virological failure time (3 month interval) of adult patients

Between time 0 and 6, the probability of an adult patient to fail was zero; after time 6 up to time 15, a steady increase in the probability to fail was observed followed by a gradual increase until the end of the study. 50% of the patients on ART would fail virologically before time 12 (by the 3rd year).

4.3 Comparison of failure functions using log rank tests

Log rank tests were done to compare the failure functions by age group, gender, ART regimen type, adherence to treatment and stage of the disease. The test showed that the failure functions differed significantly between adult and pediatric patients ($p<0.001$); between patients on EFV and NVR based regimens ($p=0.024$) as well as between patients with good and poor adherence to ART ($p<0.001$).

Table 4: Comparison of virological failure functions

Variable	Observed events	Log-rank test chi2	P-value
Age group			
Pediatric (<15 years)	141	32.59	<0.001*
Adult (≥ 15 years)	1331		
Gender			
Female	892	1.95	0.163
Male	580		
Regimen type			
EFV	945	5.10	0.024*
NVP	527		
HIV stage			
Stage 1	398	0.99	0.805
Stage 2	299		
Stage 3	384		
Stage 4	125		
Adherence			
Good	959	43.55	<0.001*
Poor	513		

***significant*

A Cox Proportional Hazards regression model was fit to evaluate the adjusted effect of the patient's baseline characteristics on the risk of virological failure at the next time. Only age group, ART regimen type and adherence to ART were found to have a significant effect on the risk of virological failure at the next time.

An adult patient has 61% increased risk of virological failure at the next time (after 36 months of follow up) compared to a pediatric patient, adjusting for the effect of the other covariates in the model. Controlling for the effect of other covariates, patients started on NVP regimens had 18% reduced risk of virological failure at the next time (after 36 months of follow up) compared to patients started on EFV based regimens.

A patient who adheres to treatment has a 26% reduced risk of virological failure at the next time (after 36 months or 45 moths of follow up) than a patient who does not adhere to treatment, adjusting for the effect of the other covariates.

Table 5: Cox proportional hazards regression-determinants of virological failure

Variable	Hazard ratio	95% CI (HR)	P-value
Age group			
Pediatric (<15 years)	**(base)**		
Adult (≥ 15 years)	1.61	[1.19; 2.16]	0.002*
Gender			
Female	**(base)**		
Male	1.04	[0.89; 1.21]	0.609
Regimen type			
EFV	**(base)**		
NVP	0.82	[0.70; 0.96]	0.012*
HIV stage			
Stage 1	**(base)**		
Stage 2	0.94	[0.76; 1.16]	0.560
Stage 3	0.94	[0.77; 1.14]	0.517
Stage 4	0.92	[0.70; 1.22]	0.586
Any non-communicable disease?			
No	**(base)**		
Yes	1.08	[0.87; 1.34]	0.466
Adherence to ART			
No	**(base)**		
Yes	0.74	[0.62; 0.87]	<0.001*
Baseline BMI			
Normal	**(base)**		
Obese	0.95	[0.76; 1.19]	0.671
Overweight	1.05	[0.86; 1.28]	0.628
Underweight	1.09	[0.82; 1.46]	0.540

**significant*

CHAPTER FIVE

DISCUSSION

It is now well known that the use of HIV treatment not only improves the health of people living with HIV, but is also a highly effective strategy to prevent HIV transmission. This is because HIV treatment can reduce the amount of virus (viral load) in the blood and other bodily fluids (such as semen and vaginal and rectal fluids) to undetectable levels. To achieve and maintain undetectable viral load, people living with HIV need to take their HIV treatment as prescribed. In addition to taking HIV medications, regular medical visits are important to monitor viral load (Bayu et al, 2017) to make sure it stays undetectable, and to receive other medical support.

The aim of this study was to find out what factors influence the time a client registered at Kenyatta national hospital comprehensive care center takes to start developing virological failure; a key reason for change of treatment to second line regimen. The study evaluated the effect of the baseline characteristics (age, regimen type, adherence, gender, HIV stage, presence of non-communicable disease (s), and BMI) of the patients on the risk of virological failure using the Cox Proportional Hazards model. The Age of the patient, first line regimen type and adherence to treatment were significantly associate with the time to failure. The median time to failure in the overall population was estimated at 36 months, which is comparable to the median time to failure reported in a study conducted at AMPATH (Kwobah et al, 2012) program in Western Kenya.

Though their criteria for categorizing age was different from this study, studies by Bayu et al. (2017) in North West Ethiopia, Hassan et al, (2014) in Coastal Kenya, and Sang & Miruka (2016) in Nyanza region, Kenya have also reported age of the patient as a significant risk factor for virological failure. In this study adult patients were found to have a significant 61% increased

risk of failing at the next time compared to children. This finding contrasts with the study findings from a study in Swaziland, where children were found to have a 2.6 times higher odd of having detectable viral load compared to adults (Jobanputra et al, 2015). In this study the high risk of virological failure was attributed to the limited available evidence on viral load monitoring in children giving room to poor adherence to treatment an important risk factor for failure. At KNH-CCC, however the monitoring of all patients especially paediatric patients is done actively and reminders sent out to patients missing their clinics as well as counselling to caregivers of HIV infected children. This could perhaps explain why the risk of failure among the children in this study was lower compared to adult patients.

Patients started on Nevirapine regimen had an 18% reduced risk of failure at the next time compared to patients on Efervirenz. The risk estimate in this study was comparable to the odd reported by the AMPATH study (Kwobah et al, 2012) however this association between regimen and failure was not statistically significant as the case in our study. Previous studies have suggested that Nevirapine-based ART is marginally less efficacious compared Efervirenz based regimen but association tests found no significant difference in the risk of virological failure (Manfredi et al, 2004; Wester et al, 2010).

Adherence to antiretroviral therapy (ART) is of critical importance because even minor deviations from the prescribed regimen can result in viral resistance (Chaiyachati, Ogbuoji, & Price, 2014). The study found that those patients who adhere to treatment had 26% reduced risk of virological failure in this clinic. With 34% of patients found to have poor adherence to treatment the clinicians need to prioritize on coming up with strategies to improve adherence to treatment to reduce incidences of drug resistance given the current test and treat policy where an upsurge of patients in care is likely to be experienced.

Clinically 67% of patients started on treatment at the facility, were in WHO stage two and above signifying how rarely people check their HIV status and start treatment. The clinical stage of the HIV infection was not associated with the risk of virological failure in this study. Irrespective

CONCLUSION

The study found age group of patient, type of regimen (Nevirapine/Efervirenz) adherence to treatment to be significantly associated with the time to virological failure. Half of the patients are likely to start failing after 36 months from the start of treatment. Paediatric patients take longer before they start failing compared to adult patients. Health care providers managing the HIV patients should be alerted on the need for ART treatment support that addresses adherence problems especially in adult patients to improve adherence consequently reducing the risk for virological failure due to resistance. There is need to conduct further studies on the association between type of regimen and risk of failure to come up with conclusive report as to whether Nevirapine based regimens are better compared to Efervirenz in sustenance of suppressed viral load.

REFERENCES

Advice, R. (2014). *June 2014*.

AIDS 2014 Communication Department. (2014). Global Fact Sheet : HIV / AIDS. *AIDS 2014 Stepping Up The Pace*, 1–20.

Care, P. (2016). First-line antiretroviral treatment failure and associated factors in HIV patients at the University of Gondar Teaching Hospital , Gondar , Northwest Ethiopia, 141–146.

Chaiyachati, K. H., Ogbuoji, O., & Price, M. (2014). Interventions to improve adherence to antiretroviral therapy : a rapid systematic review, 187–204. https://doi.org/10.1097/QAD.0000000000000252

Development, D. (2007). Guidance for Industry Role of HIV Resistance Testing in Antiretroviral Drug Development Guidance for Industry Role of HIV Resistance Testing in Antiretroviral Drug Development, (October).

Essajee, S., & Kumarasamy, N. (2014). Commentary. *Aids*, *28*(Suppl 2), S147–S149. https://doi.org/10.1097/QAD.0000000000000238

Europe, W. (2007). *HIV/AIDS Treatment and Care : Clinical protocols for the European Region*. Retrieved from papers2://publication/uuid/44A9A50D-F76B-48FB-BA36-1494B6EBB232

Fact, R., From, S., World, T. H. E., Indicators, D., & Africa, S. (2009). Sub-Saharan Africa, 1–9.

Getnet, Y. (2014). Determinants of first line antiretroviral treatment failure in public hospitals of Addis Ababa, Ethiopia: unmatched case control study. *Journal of Biology, Agriculture and Healthcare*, *4*(15), 1–12. Retrieved from http://www.iiste.org/Journals/index.php/JBAH/article/view/14197/14505

Kharsany, A. B. M., & Karim, Q. A. (2016). HIV Infection and AIDS in Sub-Saharan Africa : Current Status , 34–48. https://doi.org/10.2174/1874613601610010034

Manuscript, A. (2013). NIH Public Access, (212). https://doi.org/10.1353/hpu.2013.0014.The

Meintjes, G., Dunn, L., Coetsee, M., Hislop, M., Leisegang, R., Regensberg, L., & Maartens, G. (2015). Third-line antiretroviral therapy in Africa: effectiveness in a Southern African retrospective cohort study. *AIDS Research and Therapy*, *12*(1), 39. https://doi.org/10.1186/s12981-015-0081-8

National AIDS and STI Control Programme. (2016). *Guidelines on Use of Antiretroviral Drugs For Treating and Preventing HIV Infection*.

Pustil, R. (2016). Global AIDS. *Aids*, *17 Suppl 4*, S3-11. https://doi.org/10.1073/pnas.86.15.5781

Ramadhani, H. O., Bartlett, J. A., Thielman, N. M., Pence, B. W., Kimani, S. M., Maro, V. P., … Miller, W. C. (2016). The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected With Human Immunodeficiency Virus in Northern Tanzania. *Open Forum Infectious Diseases*, *3*(1), ofw018. https://doi.org/10.1093/ofid/ofw018

Sang, R. K. A., & Miruka, F. O. (2016). Factors Associated with Virologic Failure Amongst Adults on Antiretroviral Therapy in Nyanza Region , Kenya . People Living with Human Immunodeficiency Virus United States of America, *15*(7), 108–121. https://doi.org/10.9790/0853-15076108121

Scope, T. (2016). Today ’ s HIV / AIDS Epidemic, (August), 2–5.

Screening, H. I. V, & Guide, T. (n.d.). *HUMAN IMMUNODEFICIENCY VIRUS*.

Sik-to, L. A. I., Chin-peng, L. E. E., Chung-ki, L. I., & Tak-yin, T. (2011). *Recommended Principles of Antiretroviral Therapy in HIV Disease*.

WHO. (2007). ART failure and strategies for switching ART regimens in the WHO European Region. Report of the WHO Expert Consultation, (December), 5. Retrieved from file:///C:/Users/NATHANS/Desktop/MSTAT PROP 2014/WHO 2007 switch strategies.pdf

World Health Organization (WHO). (2016). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach - Second edition, 1–480.Bayu B, Tariku A, Bulti AB, Habitu YA, Derso T, Teshome DF. Determinants of virological failure among patients on highly active antiretroviral therapy in University of Gondar Referral Hospital, Northwest Ethiopia: a case–control study. *HIV/AIDS (Auckland, NZ)*. 2017;9:153-159

Hassan AS, Nabwera HM, Mwaringa SM, et al. HIV-1 virologic failure and acquired drug resistance among first-line antiretroviral experienced adults at a rural HIV clinic in coastal Kenya: a cross-sectional study. *AIDS Research and Therapy*. 2014;11:9.

Jobanputra K, Parker LA, Azih C, et al. Factors Associated with Virological Failure and Suppression after Enhanced Adherence Counselling, in Children, Adolescents and Adults on Antiretroviral Therapy for HIV in Swaziland. Paraskevis D, ed. *PLoS ONE*. 2015;10(2)

Kwobah CM, Ann W. Mwangi AW, Koech JK, Simiyu GM, Siika1 AM (2012) Factors Associated with First-Line Antiretroviral Therapy Failure amongst HIV-Infected African Patients: A Case-Control Study. *World Journal of AIDS*, 2012, 2, 271-278

Sang RKA, Miruka FO (2016) Factors Associated with Virologic Failure Amongst Adults on Antiretroviral Therapy in Nyanza Region, Kenya. IOSR Journal of Dental and Medical

Sciences (IOSR-JDMS) e-ISSN: 2279-0853; (15) 108-121

APPENDIX I: DATA COLLECTION TOOL

Social demographics information

1. Study no ----------

2. Age ----------

3. Sex ☐ Male ☐ Female

4. Marital status

Married ☐

Single ☐

Separated ☐

Windowed ☐

5. Education level

College and above ☐

Form level ☐

Class eight level ☐

Below class eight or no education ☐

6. Religion

Christian ☐

Muslim ☐

Others ☐

7. Type of employment

Formal employment ☐

Informal employment ☐

History of treatment

8. Year of starting ARV treatment ----------DD/MM/YYYY

9. Number of years while on ART treatment ----------

10. Year of changing from first line HAART to second line HAART ----------DD/MM/YYYY

11. Number of years while on first line HAART ----------

12. Type of first line HAART

1) AZT/3TC/EFV
2) AZT/3TC/NVP
3) TDF/3TC/EFV
4) TDF/3TC/NVP
5) ABC/3TC/EFV
6) ABC/3TC/NVP

13. History of changing ART drug

☐ Yes ☐ No

14. If yes which drugs was/were changed ----------

15. Reason for changing ----------

16. History of adherence counselling due to defaulting

Yes ☐ No ☐

17. If yes what was the reason ----------

18. WHO stage at enrolment ----------

19. Presence of non-communicable disease at first visit or during the treatment

Lab progress report of patient from enrolment to study current.

20. Initial cd4 report ----------

21. Initial viral load report ----------

22. Viral load report/cd4 at six months of treatment CD4 ---------- VIRAL LOAD ----------

23. Viral load /CD4 at one year of treatment CD4 ---------- VIRAL LOAD ----------
-

24. Trends of cd4/ viral load up to current study period

DATE									
CD4									
DATE									
V.L									

25. Treatment outcome after the follow up period

1) Detectable viral load
2) Undetectable viral load

26. If detectable was the viral load

1) Below 200 copies
2) Between 200 – 1000 copies
3) Above 1000 copies

Psychosocial history

27. Number of adherence sessions done in whole follow up period.

---

28. History of defaulting follow up clinic appointment

Yes ☐ No ☐

29. If client is in school, are they in boarding school or not

Yes ☐ ☐ No

30. If client is married is the partner tested or not

Yes ☐ No ☐

31. Any reported substance abuse

☐ Yes ☐ No

APPENDIX II: ETHICAL APPROVAL

Socio-demographic characteristics of patients

Variable	Category	Frequency	Proportion
Gender	Female Male		
Marital status	Married Cohabiting Single		
Education level	College/University secondary Primary No education		
Religion	Christian Muslim Others		
Employment status	Formal employment Self employed Unemployed Student		
Substance abuse/use	Yes No		

Table 6: Clinical profile of patient at enrollment

Variable	Response	Frequency	Proportion
Malignancy	Yes No		
WHO STAGE at ART initiation	I II III IV		
History of T.B/status	Yes No		
History of N.C.D/status	Yes No		

Pregnancy status	Yes No		
Baseline CD4	< 100 100-250 250-350 350-500		

Table 7: Clinical outcomes of the patients on first line ART

Variable	Category	Frequency	Proportion
ART regimen	ABC/3TC/NVP ABC/3TC/EFV AZT/3TC/NVP AZT/3TC/EFV TDF/3TC/NVP TDF/3TC/EFV		

Table 8: Kaplan Meier survival function

Time (t)	Sample size (N)	Virological failure events (e)	Probability to survive virological failure (S_t)	95% CI of S_t
t_0				
t_1				

Table 9: Factors influencing virological failure (Cox regression model)

Variable	Response	Hazard ratio (Hr)	95% CI (Hr)
Malignancy	No Yes		
WHO STAGE at ART initiation	I II III IV		
History of T.B/status	No Yes		
History of N.C.D/status	No Yes		
Pregnancy status	No Yes		
Baseline CD4	< 100 100-250 250-350 350-500		
ART regimen	AZT/3TC/EFV TDF/3TC/NVP TDF/3TC/EFV ABC/3TC/NVP AZT/3TC/NVP ABC/3TC/EFV		