IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 7 Ver.VI (July. 2016), PP 108-121
www.iosrjournals.org

Factors Associated with Virologic Failure Amongst Adults on Antiretroviral Therapy in Nyanza Region, Kenya.

R.K.A. Sang[1], F. O. Miruka[2]

Abstract
Background: *Access to Antiretroviral Therapy (ART) to patients living with HIV (PLHIV) has markedly improved especially in Sub-Saharan Africa. The goal of ART is to ensure viral suppression and prevention of treatment failure which may be clinical, immunological or virologic. Viral suppression is important to better outcomes of treatment. This study aimed at determining the factors associated with virologic failure amongst patients with clinical and/or immunologic failure.*
Methodology: *This was a cross sectional study based on a retrospective review of viral load test electronic data of patients with immunologic and/or clinical treatment failure. A total of 320 randomly selected records of patients tested for viral load were included in the analysis. Statistical Package for Social Sciences (SPSS) was used to analyze the data. Descriptive statistics such as frequency and median was used to describe demographic and clinical characteristics of patients. Univariate, bivariate and multivariate analysis was done to determine the factors associated with virologic failure. Odd ratio was calculated.*
Results: *Among patients with suspected ART treatment failure and viral load test requested to confirm failure, the median age was 39 years; 186 (58.1%) were female; 173 (54.1%) were aged ≤ 40; only 6 (1.9%) had missed ARVs for a period of more than 2 weeks; 31 (9.7%) had missed ARVs due to missing clinic visits; majority (30.6%) of the patients had been on ARVs for more than 4 years; (96.9%) of the patients were on first line ART regimen; 208 (65.2%) had baseline CD4 less than 100 cells/mm^3; baseline median CD4 of 152 cells/mm^3, peak median was 336 cells/mm^3 and median CD4 at the time of viral load request was 170 cells/mm^3. Age younger than 40 years was associated with virologic failure (AOR 2.33, p value 0.0011). Other patient characteristics were not associated with virologic failure.*
Conclusion: *Key factor associated with virologic failure amongst patients with suspected treatment failure is age lower than 40 years.*
Recommendation:*Focus on patients younger than 40 years should be prioritized and comprehensive and focused services friendly to the young need to be strengthened at the health facility level.*

Abbreviations and Acronyms

ART	Antiretroviral Therapy
ARVs	Antiretrovirals
CD4	Cluster Designated 4
D4T	Stavudine
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV/AIDS	Human Immunodeficiency Virus/ Acquire Immunodeficiency Disease Syndrome
HIV-RNA	Human Immunodeficiency Virus-Ribonucleic Acid
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OIs	Opportunistic Infections
OR	Operational Research
PLHIV	People Living with Human Immunodeficiency Virus
PMTCT	Prevention of Mother to Child Transmission
TB	Tuberculosis
TDF	Tenofovir
USA	United States of America
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudin

[1]Egerton University (Faculty of Health Sciences)
[2] Nyanza Provincial General Hospital

CHAPTER 1: Background Information

1.1 Introduction

Human Immunodeficiency Virus/ Acquired Immunodeficiency Disease (HIV/AIDS) remains a heavy burden globally hence continues to be a major global health priority (UNAIDS and WHO 2009). HIV/AIDS pandemic has also continued to be a public health weakness and more so in Sub-Saharan Africa. In 2011 an estimated 34 million people were living with HIV/AIDS worldwide and approximately 1.7 million people died of Human Immunodeficiency Virus (HIV) related illnesses (UNAIDS 2012). Sub-Saharan Africa disproportionately contributes to an estimated 69% (23.5 million) to the global burden. It also accounted for 71% of global new adult HIV infections among adults. Additionally, 70% of all deaths in the world occurred in Sub-Saharan Africa (UNAIDS 2012).

In Kenya, the HIV prevalence rate was 7.1% and 1.4 million were living with HIV in 2007 (National AIDS and STI Control Program and Kenya Ministry of Health 2009) compared to a lower national prevalence of 5.6% and 1.2 million living with HIV (National AIDS and STI Control Program and Kenya Ministry of Health 2013). Nyanza region which has the highest HIV prevalence showed a slight increase from 14.9% in 2007 to 15.1% in 2012 (National AIDS and STI Control Program and Kenya Ministry of Health 2009, National AIDS and STI Control Program and Kenya Ministry of Health 2013).

Since the introduction of ART in 1996, there have been gains including substantial reduction in mortality and morbidity (Montaner, Reiss et al. 1998) with a notable 20 fold increase in access to ART since 2003 (UNAIDS 2012). In countries with adequate resources, Antiretroviral Therapy (ART) has greatly improved the outcomes of treatment for patients with HIV/AIDS (Egger, May et al. 2002, Schneider, Gange et al. 2005,Walensky, Paltiel et al. 2006). Access to ART also expanded greatly due to joint efforts such as the 2003 "3 by 5" initiative with an aim of improving access to ART to 3 million people by the year 2005, political commitment and support by multiple partners (UNAIDS and WHO 2009). This has led to improved overall coverage to 58% amongst adults, 28% amongst paediatrics globally and an overall 56% in Sub-Saharan Africa (UNAIDS 2012). Mortality attributable to HIV/AIDS as evidenced in sub-Saharan Africa has also declined sharply by 32% in a span of 7 years from 2005 to 2011 (UNAIDS 2012).

The primary goal of ART is to achieve long term durable suppression of HIV replication, which confers immunologic and clinical benefits, and in turn leads to a reduction in morbidity and mortality, and improved quality of life. Failure to suppress HIV viral replication results in treatment failure and development of antiretroviral (ARV) drug resistance, which has implications to the individual patient, ART programs, and potential serious public health implications. Despite maintaining patients on ART, studies have shown that a proportion of them fail treatment (Mocroft, Ledergerber et al. 2004).

Recognizing treatment failure early and changing the regimen to alternative effective ARV drugs is paramount in avoiding development of resistance. Treatment failure can be measured in three ways: clinically, by disease progression and World Health Organization (WHO) staging; immunologically, by assessing Cluster Designated 4 (CD4) trends; and by measuring plasma HIV RNA (Human Immunodeficiency Virus Ribonucleic Acid) levels. [Viral loads (VL)] measurement is the most accurate way of assessing treatment failure, and is used in developed countries as standard of care to routinely monitor patients on ART. However, in resource limited settings, viral load measurements are not routinely available, and their use is restricted due to cost and accessibility. WHO and Kenyan National ART guidelines (WHO 2006, Ministry of Medical Services 2011, WHO 2013) therefore recommend use of targeted viral load testing to support confirmation of treatment failure and prevent premature changes to second-line regimens.

1.2 Statement of the problem

ART has demonstrated remarkable benefits in both developing and resource limited settings. However, it presents many challenges, including the need for long term commitment to continuous treatment and monitoring. The primary goal of ART is to achieve long term durable suppression of HIV viral replication, failure to which can result in treatment failure and development of ARV drug resistance, which in turn has implications to the individual patient, ART programs, and potential serious public health implications. Despite maintaining patients on ART, studies have shown that a proportion of them fail treatment (Mocroft, Ledergerber et al. 2004). Several factors have been identified as predictors of treatment failure, including poor drug adherence (Parienti, Massari et al. 2004, Robbins, Daniels et al. 2007), use of sub-optimal drug combinations (Robbins, Daniels et al. 2007), previous ARV exposure (Bahia, Pedroso et al. 2004) and alcohol or drug abuse (Chander, Lau et al. 2006).

In Nyanza region, there is limited information available on the factors associated with treatment failure hence the need to conduct this study which will determine the factors associated with treatment failure amongst adults.

1.3Justification

This study aimed at identifying factors associated with virologic failure amongst patients on ART and with immunologic and/or clinical failure. These findings were of importance to future management of PLHIV with immunologic and/or clinical failure. In addition, the findings would be used to guide interventions that would avert possible virologic failure hence prolong the time that the patient stays on the same regimen without switching to second line ART and as a result reduce the overall cost of treatment and better patient outcomes.

1.4 Objectives of the study

1.4.1 Broad objective

To determine the factors associated with virologic failure amongst adults on antiretroviral therapy with suspected clinical and immunological treatment failure in Nyanza Region.

1.4.2 Specific Objectives

1. To describe the demographic and clinical characteristics of adults on antiretroviral therapy with clinical and/or immunological treatment failure.
2. To determine the proportion of patients with al failure amongst adults on antiretroviral therapy with clinical and/or immunological treatment failure
3. To determine the factors associated with al failure amongst adults on antiretroviral therapy with clinical and/or immunological treatment failure.

1.5 Research questions

a. What are the demographic and clinical characteristics of adults on antiretroviral therapy with clinical and/or immunological treatment failure?
b. What proportion of patients on antiretroviral therapy end up with treatment failure despite being on treatment?
c. What are the factors associated with virologic treatment failure?

1.6 Hypothesis

Virologic treatment failure is associated with age less than 40 years; male gender; baseline CD4 cell count below 100 and prolonged use of ART.

1.7 Literature review

Treatment failure is defined as clinical, immunological and virologic. The World Health Organization (WHO) defines clinical failure amongst adults and adolescents as new or recurrent clinical conditions indicating severe immunodeficiency (WHO clinical stage 4 conditions) after 6 months of effective treatment. Immunological failure as CD4 count falls to the baseline (or below); or persistent CD4 levels below 100 cells/mm^3. Virologic failure as plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support (WHO 2013).

The Kenya Ministry of Health in the guidelines for antiretroviral therapy in Kenya has additional criteria. Amongst adults, clinical failure amongst adults and adolescents as new onset of significant opportunistic infections (OIs) or malignancy, usually WHO stage 3 or 4 condition; recurrence of previously treated OI after at least 6 months of ARVs, downgrading of WHO classification in the course of follow up; unintentional weight loss in a patient who was doing well on ARVs without any overt signs and/or symptom. Immunological failure is defined as CD4 fall to or below pre-ART level or fall by 30% from on treatment peak value or CD4 levels persistently below 100 cells after treatment for at least 12 months of effective ART. Virologic failure is defined as viral load > 1000 copies/ml (Ministry of Medical Services 2011).

Treatment failure may occur due to various risk factors including previous treatment failure, drug resistance, poor adherence to treatment, poor absorption of ARVs, co-morbidities, poor health prior to initiation of ART, drug toxicity and drug interactions and substance abuse leading to poor adherence (US Department of Health and Human Services 2013). Non-adherence to ART is however noted as a key risk factor and a contributor to treatment failure (Ministry of Medical Services 2011). There are however other factors including age, gender, advanced HIV disease, low baseline CD4, ARV regimens and long periods on ART that are associated with treatment failure as indicated by several studies.

Age of the patient on treatment has been shown to affect virologic outcomes amongst patients initiated on ART by several studies though different age categories were considered. A study done in Thailand by Khienprasit and others showed that patients who were on ART and of age less than 40 years were more likely to have virologic failure (Khienprasit, Sirisanthana et al. 2011). In a study comparing the median age between the control group with a median age of 42 years and patients with virologic failure and a median age of 38 years

showed that the difference was statistically significant in favour of the 42 years age group (Parienti, Massari et al. 2004). Anude and others in a study in Nigeria using a viral load cut off of 400 copies/ml and that by Ramirez and others in a study in Mexico using a viral load cut off of 50 copies/ml showed that patients younger than 30 years of age were more likely to have virologic failure (Crabtree-Ramirez, Villasis-Keever et al. 2010, Anude, Eze et al. 2013). In a review of patients on ART enrolled for prevention of mother to child transmission (PMTCT) program and viral load requested to check for effectiveness of ARV regimens they were on and using a viral load cut off of 400 copies/ml, women who were 25 years of age or younger were more likely to have virologic failure (Ng'ang'a, Muttai et al. 2012). Other studies done in Peru and California in the United States of America (USA) also associated younger age with virologic failure (Chao, Tang et al. 2012, Alave, Paz et al. 2013). The only study reviewed that showed no association between age and virologic failure was that done in Brazil (Tuboi, Harrison et al. 2005).

Gender of the patients with immunologic and/or clinical failure has been shown not to be associated with virologic treatment failure. A study done in Massachusetts General Hospital out-patient HIV clinic in the USA; in Clinicas de Porto of Brazil and in Chiang Mai University Hospital in Thailand showed that male gender was not associated with virologic failure (Tuboi, Harrison et al. 2005, Robbins, Daniels et al. 2007, Khienprasit, Sirisanthana et al. 2011). In Africa, a study done in Nigeria by Anude and others and that done in public HIV treatment program in Western Cape, South Africa also showed that male gender was not associated with virologic failure (Datay, Boulle et al. 2010, Anude, Eze et al. 2013). However, a study done in Mexico showed results that female gender was marginally associated with virologic failure (Crabtree-Ramirez, Villasis-Keever et al. 2010).

The level of CD4 cell count at baseline has been associated with treatment failure as shown by several authors. Different CD4 cell count cut offs were applied by different studies in determining virologic failure. In two studies done in Kenya and South Africa respectively using a cut off CD4 cell count of 50, it was found that patients with a CD4 cell count below 50 were more likely to have virologic failure (Datay, Boulle et al. 2010, Kwobah, Mwangi et al. 2012). Similar results were registered in studies done in Peru and Thailand using CD4 cell count of 100 cells as cut off (Khienprasit, Sirisanthana et al. 2011, Alave, Paz et al. 2013) and those done in USA by Robbins and others (Robbins, Daniels et al. 2007) and Ng'ang'a and others amongst PMTCT clients (Ng'ang'a, Muttai et al. 2012). Contrasting results by Crabtzee-Ramirez and others in a study done in Mexico showed no association between baseline CD4 cell count and virologic failure (Crabtree-Ramirez, Villasis-Keever et al. 2010).

Adherence to treatment is vital in ensuring viral suppression amongst patients on ART. Non-adherence therefore results in treatment failure as indicated by several studies. In studies done in Western Cape, South Africa (Datay, Boulle et al. 2010); western part of Kenya (Kwobah, Mwangi et al. 2012); Thailand (Khienprasit, Sirisanthana et al. 2011); Massachusetts USA (Robbins, Daniels et al. 2007); two hospitals in Paris (Parienti, Massari et al. 2004); Brazil (Tuboi, Harrison et al. 2005); and Nigeria (Anude, Eze et al. 2013).

In treatment of HIV, the use of triple ARVs is highly recommended to achieve the goal of treatment. Outcomes of treatment using different regimens may vary as indicated by Kwobah and others who registered no difference on treatment outcomes when comparing Stavudine to Zidovudine and Nevirapine to Efavirenz(Kwobah, Mwangi et al. 2012). Use of Nucleoside Reverse Transcriptase Inhibitors (NRTI) and NNRTI regimens were remotely associated with virologic failure in a Massachusetts study (Kwobah, Mwangi et al. 2012) though contrasting results by Robbins and others showed no significant difference to Ritonavir boosted regimens (Robbins, Daniels et al. 2007) and Crabtree and others who actually found use of NNRTI to be protective to virologic failure. In comparing Protease Inhibitors (PI) based regimen to NRTI only regimen, Chao and others recorded that use of NRTI only regimen were associated with virologic failure (Chao, Tang et al. 2012). In a Nigerian study, the outcomes of patients on Zidovudine (ZDV) based regimen were compared to those of Stavudine (D4T) and Tenofovir (TDF) based regimen where no difference was recorded (Anude, Eze et al. 2013).

Other factors associated with virologic failure include advanced HIV disease (WHO clinical stage 4) (Huong, Bannister et al. 2011); hazardous drinking of alcohol which affect adherence to ARVs (Chander, Lau et al. 2006); previous exposure to ARVs before initiation of ART, change of ARVs due to toxicity, opportunistic infections during ART (Alave, Paz et al. 2013); and baseline haemoglobin level less than 10g/dl (Anude, Eze et al. 2013). In contrast, other studies indicated that marital status and employment status (Datay, Boulle et al. 2010, Anude, Eze et al. 2013); sexual orientation of the patient (comparing heterosexual and non-heterosexual); patient's residence (whether urban or rural), pre-ART opportunistic infections, co-infection with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), (Khienprasit, Sirisanthana et al. 2011). Others include co-morbidities (Chao, Tang et al. 2012); disclosure of HIV status, history of Tuberculosis (TB), socioeconomic status/class, history of smoking at time of viral load testing, herbal medicine use at the time of viral load testing (Anude, Eze et al. 2013) and patients on ART for a period more than 1 year as shown in the study reviewing pregnant women who have been on ART for a period more than 6 months.

CHAPTER 2: Methodology

2.1 Study area

The study area is Nyanza region formerly known as Nyanza Province and is located in southwest part of Kenya. It has a total population of 5.4 million people (KNBS 2010) distributed across six counties namely Kisumu, Kisii, Nyamira, Siaya, Homabay and Migori. Nyanza region has a size of 12,477.1 KM^2 and a population density of 440/Km^2. The predominant tribe is Luo; others are Kuria, Kisii and Luhya. According to the Kenya AIDS Indicator Survey preliminary report of 2012, Nyanza has the highest HIV prevalence of 15.1 compared to the national which is estimated to be 5.6 (National AIDS and STI Control Program and Kenya Ministry of Health 2013) which translates to about 500,000 people living with HIV.

2.2 Study design

Cross sectional study based on a retrospective review of viral load test data in electronic database of patients with clinical and/or immunological failure with viral load test done from January to December 2012. The study design was selected based on its strengths that include ability to determine cause of the problem - which in this study is virologic failure amongst patients who have immunological and/or clinical failure; affordable; ability to estimate risk of an event which in this study is al failure and allows for accurate measurement of exposure variables.

2.3 Study population

In this study, data of adult patients on ART for ≥ 6 months with immunological and/or clinical treatment failure with viral load test done between January to December 2012 and data available in electronic database was reviewed to determine the factors associated with virologic failure was reviewed.

2.4 Sampling technique

Probability random sampling technique was used to select patients who were included in the sample. The records that were finally included in the analysis were selected randomly using a Microsoft Excel randomizer. The records which in Excel sheet were assigned serial numbers which guided selection of records once random numbers are generated. The selected records were assessed for completeness. If a record was incomplete and missing information cannot be corrected, it was replaced with the next randomly selected record until the desired sample size was achieved. Once the intended sample size was achieved, the records were put in a separate database for further cleaning and subsequent data analysis.

2.5 Sample size determination

Data used for this study was derived from electronic patient records from the viral load testing electronic database. A total of 1,919 patient records for viral load tests done in 2012 were reviewed. To determine the study population, patients with repeat viral load tests, patient from other provinces and paediatric data were first be excluded followed by any incomplete records that cannot be reconciled. A total of 9,284 records were finally included as indicated in figure 1 below:

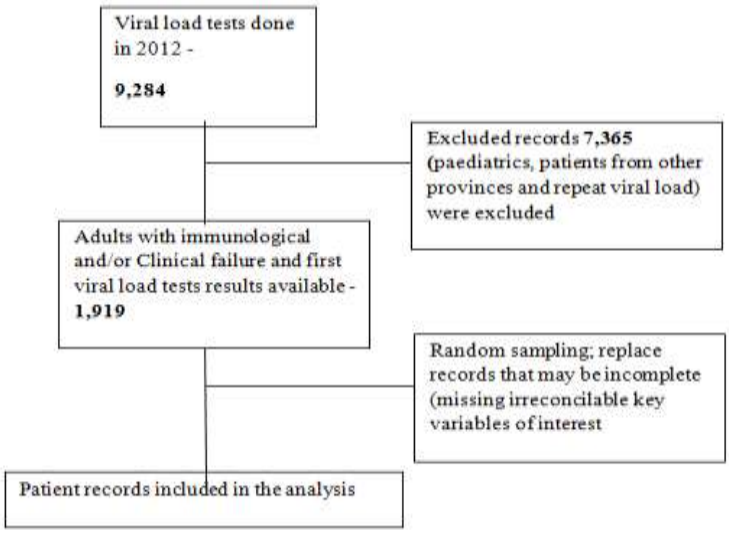

Figure 1: Flow chart showing the records included in the sampling frame

Sample size calculation

To determine the sample size, Mugenda and Mugenda (1999) sample estimation formula was applied. An error of 5 % and 95% confidence level was preferred. The desired sample size (n) was arrived at as indicated in the formula below:

$$n = \frac{(Z^2\ \sigma^2)}{e^2}$$

n= proper sampling size; Z=standard normal deviation; σ= population standard deviation; e= maximum allowable error

The study assumed a confidence level of 95% thus the Z= 1.96 e= 0.05 σ= 0.5

$$n = \frac{1.96^2 x 0.5^2}{0.05^2} = 384$$

Because the estimated total population is less than 10,000 the following formula was applied to determine actual sample size required.

$$nf = \frac{n}{1+\frac{n}{N}}$$

Where nf = is the desired sample size

N= the estimated total population less than 10,000

n= estimated sample when the estimated total population (N) is greater than or equal to 10,000

$$nf = \frac{384}{1+\frac{384}{1919}} = 320$$

The final sample size that was included in the analysis was 320 records.

2.6 Data collection

Data for this study was collected as part of routine patient care and treatment by health care providers who as part of clinical care completed standardized viral load request forms designed using Teleform® version 10.0 Software. The viral load request and result forms are used to collect relevant demographic, clinical and laboratory information. These forms once filled were then scanned into a password protected computer, verified, cleaned and finally stored into access based database. The data sheet shown in appendix I show the variables of interest abstracted from the electronic medical database to create dataset for analyses. This data will then be checked for any inconsistencies and the final variables picked for analysis.

2.7 Quality control

Inclusion and exclusion criteria

Inclusion criteria: - To be included in this study, patients must have had a viral load test between 1st January 2012 and 31st December 2012; only first viral load test done in 2012 was considered; been older than 14 years of age at time of viral load test request and have complete records.

Exclusion criteria: - Viral load test done as repeats (≤ 3 months from the initial); patient below 14 years and with incomplete results were excluded.

Validity and Reliability

Automation of data entry through scanning of forms eliminated the need for manual data entry and as a result minimizing errors. Information bias was minimized by using a designed standard data tool for data extraction to ensure that similar information was extracted from the database for all records included in the analysis. I additionally relied on accurate data in the electronic database. Integrity of data was ensured through data cleaning by checking for outliers and errors, eliminating duplicates and identifying and filling in missing data that were extracted using a data tool to ensure standardization of required information from each patient record.

Selection bias was minimized through random selection of records hence providing an equal opportunity to all patients whose records were in the electronic database. Lastly, confounding was minimized by ensuring that possible confounding factors such as age and sex are included in the multivariate analysis to deal with interaction of one variable on another that may otherwise result in a wrong conclusion on the effect of the variable on the outcome variable, virologic failure.

2.8 Ethical considerations

Human Subjects: The main study SSC No. 1532 from which data for this study was extracted had been approved by the Kenya Medical Research (KEMRI) Ethical Review Committee (ERC) and US Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB). This study proposal was submitted for ethical clearance by Egerton University.

Study Procedures & Risks: Data used for this study is routinely collected as part of clinical services to patients. Chances of inadvertent release of patient information were very remote because identifiers such as patient names were not included in the database used for analysis. Additionally, analysis database was stripped of patient personal identifiers.

Benefits: No direct benefit was gained by the patients but the results will help improve care and treatment for future PLHIVs.

Informed Consent: Informed consent was not sought from the patients to review the data that had already been collected for the following reasons: Patients were not put at risk by this study because data had already been collected and entered into a database. The data analysis process required no contact with the patients and patients continued to receive care and treatment services in accordance with the standards of care in Kenya regardless of this study or its outcomes; rights of patients was not adversely affected; the information being analysed during this study had already been collected and seeking patient's informed consent before reviewing the data will not be done because some patients included in the database may have already defaulted and not be traceable.

Confidentiality: Access to the database used in this study was limited to authorized persons; the database remained in a secured location and in a password protected computer and no individual patient(s) was identified when the results of this study are presented. All results were reported in an aggregate form.

2.9 Data processing and analysis

Data was reviewed for any inconsistencies, missing information and outliers which were then fixed. Data analysis was done using Statistical Package for Social Sciences (SPSS) version 12.0 for Windows (IBM, 2013). Additionally, Microsoft office Excel 2007 was used in creating graphs. A patient was considered to have virologic failure if the viral load is ≥1000copies/ml.

To describe the baseline demographic and clinical characteristics of patients, frequencies of patient characteristics such as age, gender, baseline, peak and current (at time of viral load test request) CD4 cell count by categories and type of regimen (1^{st} or 2^{nd} line ART) was done. Median was also computed for continuous variables like age, CD4 and period on ART because median is not much affected when variables are not normally distributed.

Univariate analysis was done to determine the rates of virologic failure. To determine factors associated with virologic failure, odds ratio (OR) was calculated in bivariate analysis. Factors presumed to be associated with failure and with p values of <0.25 from the bivariate analysis were then be included in the multivariate analysis (adjusting for age and gender). The cut off p value of <0.25 was chosen based on the works of Bendel and Afifi(Bendel and Afifi 1977) and Mickey and Greenland (Mickey and Greenland 1989) which showed that this cut off point allows for the inclusion of all important variables even though it also has the disadvantage of including variables with questionable importance (Hosmer and Lemeshow 2000).

Risk factors analyzed included age, gender, baseline CD4 cell counts dichotomized into two groups (less than or equals 200 mm^3 and above 200 mm^3), clinical and/or immunological indicators and other indicators for viral load request, period on ART.

2.10 Study constraints and limitations of the study

This study had several limitations. First, some patient demographic and clinical information such as marital status, occupation, disclosure of HIV status, employment status, economic status, clinical status (WHO stage) and distance of residence from the health facility were not included because they were not readily accessible; Secondly, baseline viral load test was not routinely done due to resource limitation and only recommended in patients suspected to have failed treatment hence was not included in the analysis. Thirdly, incomplete data may also be a limitation.

CHAPTER 3: Results, Discussion, Conclusion and Recommendations

3.0 Results

3.0.1 Demographic and clinical characteristics of patients

Amongst the patients with suspected ART treatment failure and viral load test requested to confirm failure, the median age was 39 years; 186 (58.1%) were female; 173 (54.1%) and 147 (45.9%) were aged ≤ 40 and > 40 years respectively; only 6 (1.9%) had missed ARVs for a period of more than 2 weeks; 31 (9.7%) had missed ARVs due to missing clinic visits; majority (30.6%) of the patients had been on ARVs for more than 4 years at the time of viral load request; 206 (64.4%) of patients had immunological failure as a reason for requesting for viral load test; majority (96.9%) of the patients were on first line ART regimen; 208 (65.2%) had baseline CD4 less than 100 cells/mm^3;baseline median CD4 at start of ART was 152 cells/mm^3, peak median was 336 cells/mm^3 and median CD4 at the time of viral load request was 170 cells/mm^3 as detailed in table 1 and figures 2-7 below.

Table 1: Demographic and clinical characteristics of patients with viral load requested in 2012, Nyanza Region

Patient Characteristic	Frequency(N=320)	%
Gender		
Male	134	41.9
Female	186	58.1
Median age in years (IQR)	39 (32-48)	
Age group		
≤ 40 years	173	54.1
> 40 years	147	45.9
Missed ARVs for 2 weeks prior to Viral Load request		
Yes	6	1.9
No	314	98.1
Missed ARVs due to missing clinic attendance		
Yes	31	9.7
No	288	90.3
Period on ART		
6 months-1 year	23	7.2
>1 year – 2 years	77	24.1
>2 years – 3 years	72	22.5
>3 years – 4 years	50	15.6
>4 years	98	30.6
Indications for Viral Load testing		
Clinical only	26	8.1
Immunological only	206	64.4
Clinical and immunological	23	7.2
Toxicity and Clinical	16	5.0
Toxicity and Immunological	49	15.3
ARVs regimen		
First line	310	96.9
Second line	10	3.1
CD4 in cells/mm^3		
Baseline ≤ 100	111	34.8
Baseline > 100	208	65.2
Median baseline CD4 (IQR)	152 (75-270)	
Median peak CD4 (IQR)	336 (200-488)	
Median current CD4 at time of VL request (IQR)	170 (96-277)	

Distribution of patients by gender

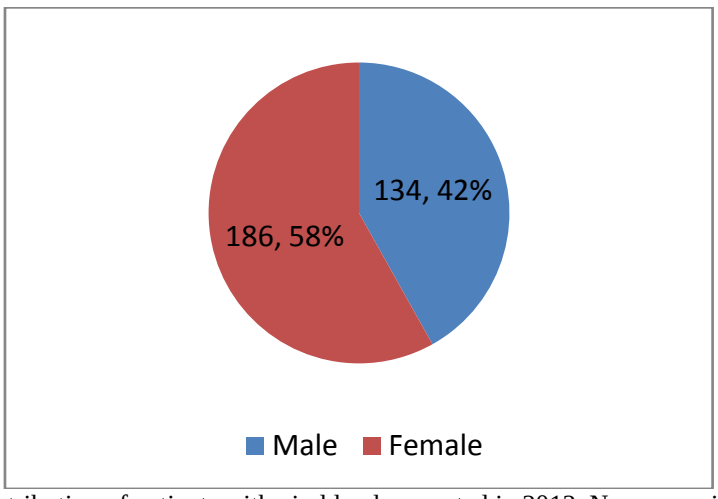

Figure 2: Distribution of patients with viral load requested in 2012, Nyanza region by gender

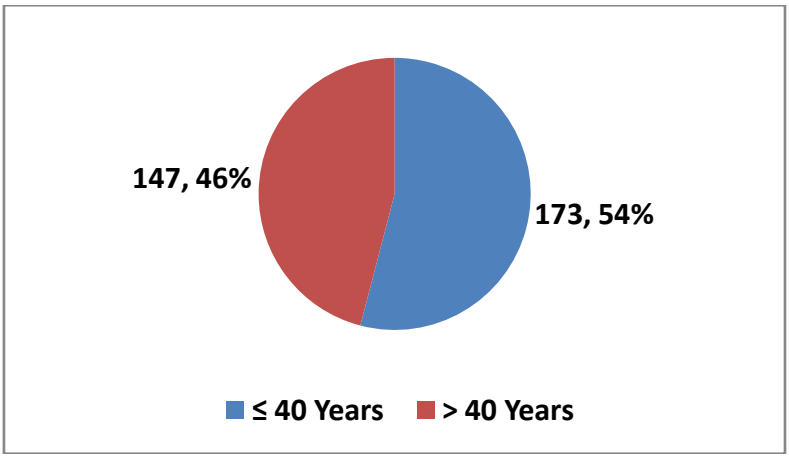

Figure 3: Distribution of patients with viral load requested in 2012, Nyanza region by age groups

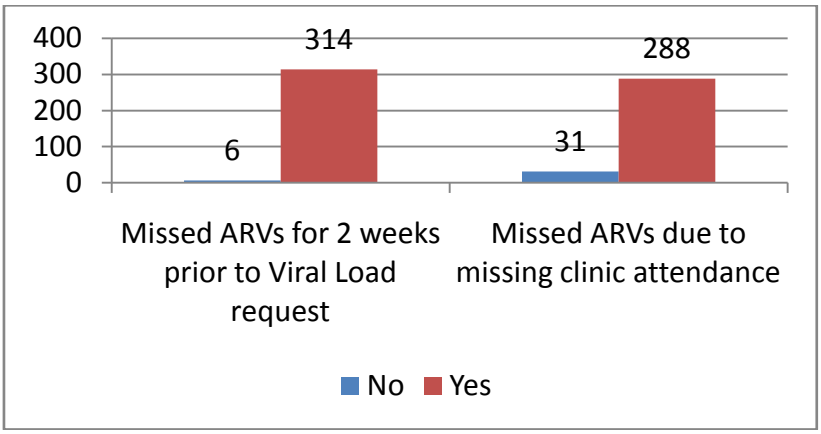

Figure 4: Distribution of patients with viral load requested in 2012, Nyanza region by missing ARVs for 2 weeks prior to viral load request and by missing ARVs due to missed clinic attendance

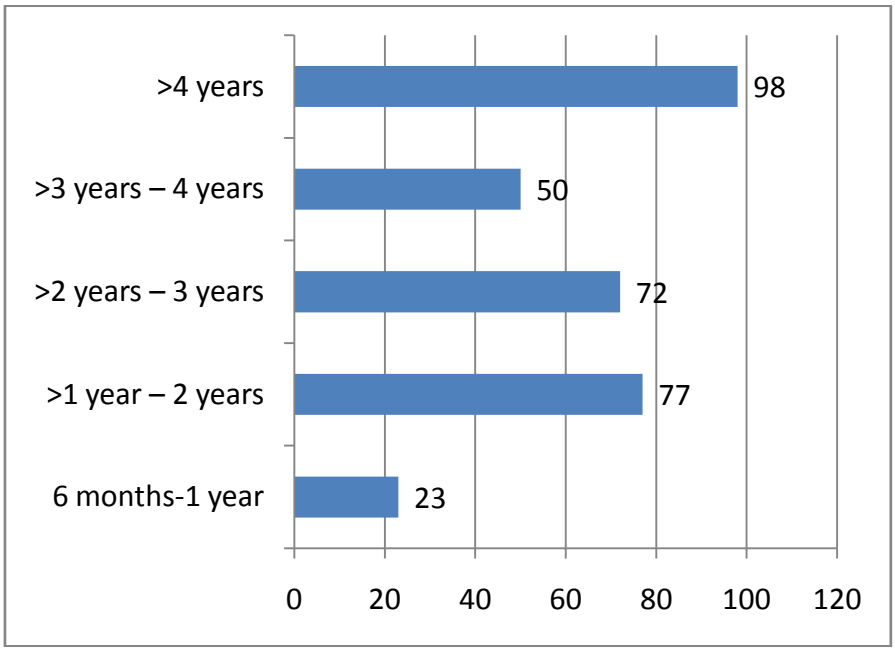

Figure 5: Distribution of patients with viral load requested in 2012, Nyanza region by period of being on ART

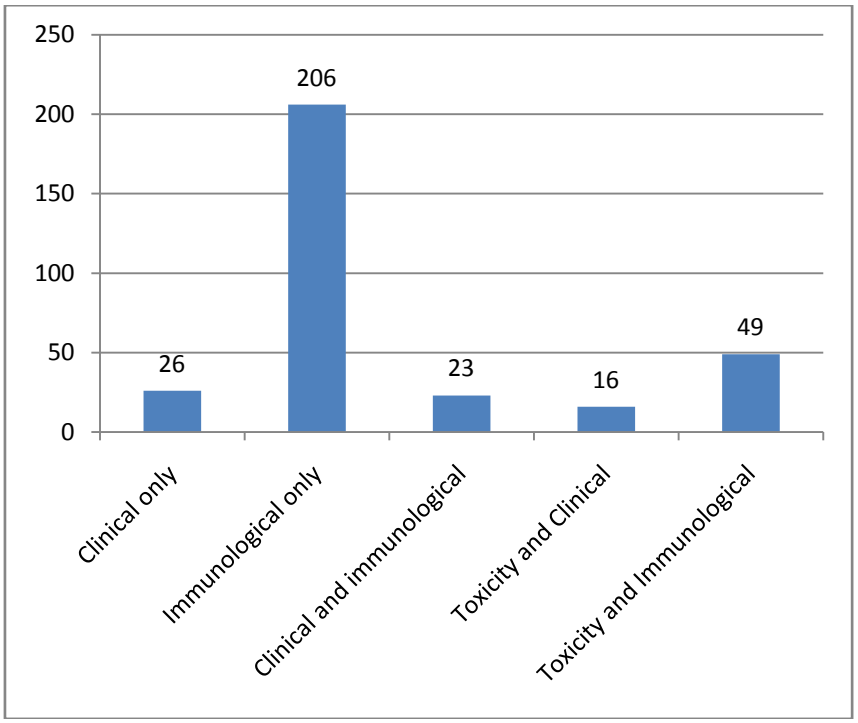

Figure 6: Distribution of patients with viral load requested in 2012, Nyanza region by indication/ reason for viral load request(N=320)

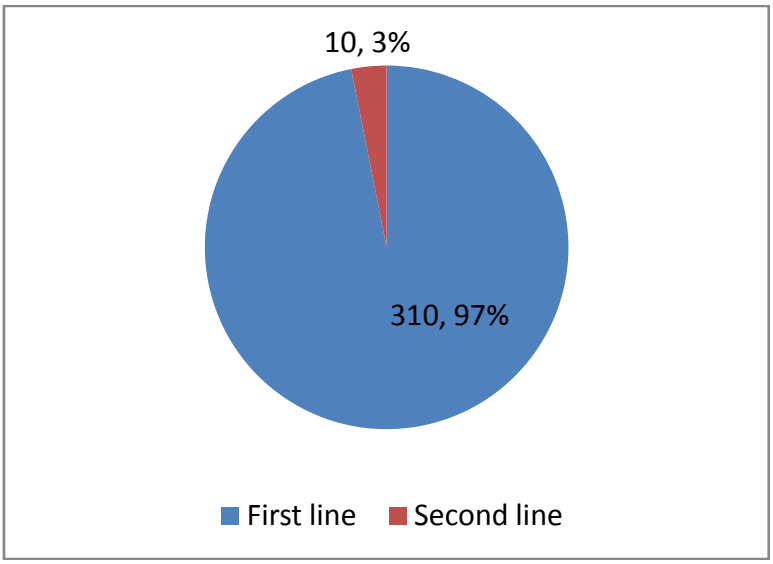

Figure 7: Distribution of patients with viral load requested in 2012, Nyanza region by ARVs regimen

3.0.2 Risk of virologic failure amongst patients suspected to have failed ART

Table 2 below shows the risk of virologic failure per category of patients. In gender, risk of failure amongst males and females was 43.3% and 37.6% respectively. The difference in risk of failure was however no statistically significant. Looking at the different age groups, risk of failure was 48% and 30.6% amongst patients in the ≤ 40 and >40 years age groups; the difference in risk of failure in the different age groups was significant with a p value of 0.0001.

Amongst patients who had missed ARVs in the last two weeks prior to viral load request, 50% had virologic failure compared to 39.8% amongst those who had not missed ARVs and the difference was not of statistical significance. In comparing the risk of virologic failure amongst patients who had missed ARVs due to missed clinic visit (32.3%) to those who had not missed (41%), the difference was not of statistical significance. Looking at the risk of virologic failure by length of time that patients have been on ART, risk of failure was as follows, 47.8% in ≤ 1 year group, 39% in > 1 year to 2 years, 41.7% in > 2 years to 3 years, 38% in > 3 years to

4 years and 38.8% in > 4 years groups. The difference of risks in the different groups was however not of statistical significance.

As for risk of virologic failure by indications or reason for viral load request, 30.8% had clinical indications only, 41.7% had immunological indications only, 56.5% had both clinical and immunological indications, 31.3% had toxicity and clinical indications and finally 16% had toxicity and immunological indications. The difference of risks in the different groups was however not of statistical significance.

The risk of failing based on the regimen the patient was taking, 39.4% of those on first line ART had virologic failure compared to a higher risk of 60% amongst patients on second line. The difference in risk was however not of statistical significances. The difference between patients with CD4 ≤ 100 cells/mm^3(47.7%) and those with CD4 > 100 100 cells/mm^3 (36.1%) was statistically significance with a p value of 0.0001.

Table 2: Risk of virologic failure amongst patients with viral load requested in 2012, Nyanza region

Patient Characteristic	No. of patients(N=320)	No. of patients with VL >=1000 (%)	p-value
Gender			
Male	134	58 (43.3)	0.3088
Female	186	70 (37.6)	
Age group			
≤ 40 Years	173	83 (48)	<0.0001
> 40 Years	147	51 (30.6)	
Missed ARVs for 2 weeks prior to Viral Load request			
Yes	6	3 (50)	0.6137
No	314	125 (39.8)	
Missed ARVs due to missing clinic visit			
Yes	31	10 (32.3)	0.3469
No	288	118 (41)	
Time on ART			
6 months-1 year	23	11 (47.8)	0.9317
>1 year – 2 years	77	30 (39)	
>2 years – 3 years	72	30 (41.7)	
>3 years – 4 years	50	19 (38)	
>4 years	98	38 (38.8)	
Indication for Viral Load request			
Clinical only	26	8 (30.8)	0.2474
Immunological only	206	86 (41.7)	
Clinical and immunological	23	13 (56.5)	
Toxicity and Clinical	16	5 (31.3)	
Toxicity and Immunological	49	32.7 (16)	
Regimen			
First line	310	122 (39.4)	0.1896
Second line	10	6 (60)	
Baseline CD4 (cells/mm^3)			
≤ 100	111	53 (47.7)	0.0001
>100	208	75 (36.1)	

3.0.3 Factors associated with virologic failure

Bivariate analysis – unadjusted odds ratio

In bivariate analysis, the only patient characteristic that had statistical difference was age. The chances of patients in the ≤ 40 years age group failing treatment in comparison to the >40 years one was 2.10 times higher and was of statistical significance (p-value 0.0017).

The differences in other patient characteristics including gender, missing ARVs for two weeks prior to viral load test request, missing ARVs due to missing clinic visit, period of time on ART, indications or reasons for viral load request, ARV regimen and CD4 cell count were not of statistical significance as shown in details in table.3 below.

Multivariate analysis – adjusted odds ratio

In multivariate analysis and adjusting for possible confounders, age was the only patient characteristic that had statistically significant difference upon comparison. Patients who were younger than 40 years had 2.33 (p value 0.0011) chance of failing treatment.

The differences in other patient characteristics including missing ARVs for two weeks prior to viral load test request, missing ARVs due to missing clinic visit, period of time on ART, ARV regimen, CD4 and indication for viral load testing were not of statistical significance as shown in details in table 3.0.3 below.

Table 3: Factors associated with virologic failure amongst patients with viral load requested in 2012, Nyanza region

Patient Characteristic	OR	95% P value	AOR	95% P value
Gender				
Male	1.27	0.3092	1.51	0.1069
Female	**ref**	-	**Ref**	-
Age group				
≤ 40 Years	2.09	0.0017	2.33	0.0011
> 40 Years	**ref**	-	**Ref**	-
Missed ARVs for 2 weeks prior to Viral Load request				
Yes	1.51	0.6161	2.01	0.4346
No	**ref**	-	**Ref**	-
Missed ARVs due to missing clinic visit				
Yes	0.69	0.3492	0.53	0.1433
No	**ref**	-	**Ref**	-
Time on ART				
6 months-1 year	**ref**	-	**Ref**	-
>1 year – 2 years	0.70	0.4784	0.69	0.4560
>2 years – 3 years	0.78	0.4810	1.13	0.8166
>3 years – 4 years	0.67	0.5091	0.82	0.7125
>4 years	0.69	0.4661	0.94	0.8991
Indication for Viral Load request				
Clinical only	**ref**	-	**ref**	-
Immunological only	1.61	0.0727	1.75	0.0698
Clinical and immunological	2.93	0.2861	3.11	0.2310
Toxicity and Clinical	1.02	0.9739	1.00	0.9999
Toxicity and Immunological	1.09	0.8679	1.33	0.6035
Regimen				
First line	0.43	0.2015	0.43	0.3482
Second line	**ref**	-	**ref**	-
Baseline CD4 (cells/mm^3)				
≤ 100	**ref**	-	**ref**	-
>100	0.62	0.0431	0.65	0.0854

3.1 Discussion

3.1.1 Baseline demographic and clinical patient characteristics

In this study, amongst the patients with suspected ART treatment failure and viral load test requested to confirm failure, the median age was found to be 39 years; 186 (58.1%) were female; 173 (54.1%) aged 40 years or younger; only 6 (1.9%) had missed ARVs for a period of more than 2 weeks; 31 (9.7%) had missed ARVs due to missing clinic visits; majority (30.6%) of the patients had been on ARVs for more than 4 years at the time of viral load request; 206 (64.4%) of patients had immunological failure as a reason for requesting for viral load test; majority (96.9%) of the patients were on first line ART regimen; 208 (65.2%) had CD4 cell count more than 100; baseline median CD4 at start of ART was 152 cells/mm^3, peak median was 336 cells/mm^3 and median CD4 at the time of viral load request was 170 cells/mm^3 . There was no study reviewed that had detailed out demographic and clinical characteristics in a similar pattern for comparison.

3.1.2 Factors associated with virologic failure

In this study, gender was found not to be associated (AOR 1.51, p value 0.1069) with virologic failure. This is supported by studies that showed no association of male gender to virologic failure. Studies by Khienprasit*et. al.* in a study USA, Thailand and Brazil (Khienprasit, Sirisanthana et al. 2011) and Anude*et. al*in studies done in Nigeria and South Africa (Anude, Eze et al. 2013). A contrasting study done by Crabtree *et. al.* indicated that female gender was associated with virologic failure (Crabtree-Ramirez, Villasis-Keever et al. 2010).

Age below ≤ 40 years was associated with virologic failure in this study (AOR 2.33, p value 0.0011)and supported by several studies including those done by Khienprasit*et. al.*(Khienprasit, Sirisanthana et al. 2011), Parienti*et. al.*(Parienti, Massari et al. 2004), Anude and others (Anude, Eze et al. 2013), Crabtree-Ramirez and others (Crabtree-Ramirez, Villasis-Keever et al. 2010), Ng'ang'a and others (Ng'ang'a, Muttai et al. 2012), Alave and others (Alave, Paz et al. 2013) and Chao and others (Chao, Tang et al. 2012). However, Tuboi and others in a study in Brazil showed no association between age and virologic failure (Tuboi, Harrison et al. 2005).

Although literature reviewed including those by Data*yet. al*, (Datay, Boulle et al. 2010); Kwobah*et. al*, (Kwobah, Mwangi et al. 2012); Khienprasit*et. al*, (Khienprasit, Sirisanthana et al. 2011); Robbins *et. al*, (Robbins, Daniels et al. 2007); Parienti*et. al*, (Parienti, Massari et al. 2004); Tuboi*et. al*, (Tuboi, Harrison et al. 2005) and Anude*et. al*, (Anude, Eze et al. 2013) showing that non-adherence to ART is associated to treatment

failure, this study demonstrated that there was no association between missing ARVs (AOR 2.01, p value 0.4346) or clinic visits (AOR 0.53, p value 0.1433) with virologic failure. This may have been contributed to by a criterion that required that all patients had to be screened and managed for non-adherence before requesting for a viral load test.

Several studies including those by Datay*et. al*, (Datay, Boulle et al. 2010); Kwobah*et. al*, (Kwobah, Mwangi et al. 2012); Khienprasit*et. al*, (Khienprasit, Sirisanthana et al. 2011); Robbins *et. al*, (Robbins, Daniels et al. 2007); Ng'ang'a*et. al*, (Ng'ang'a, Muttai et al. 2012); and Crabtzee-Ramirez *et. al*, (Crabtree-Ramirez, Villasis-Keever et al. 2010) indicated an association between low baseline CD4 and treatment failure. This study however has demonstrated contradictory finding (AOR 0.65, p value 0.0854) showing no association between low baseline CD4 and treatment failure.

In determining whether the regimen that the patient was given at initiation has any association with treatment failure, there was no association (AOR 0.51, p value 0.3482) recorded. This is supported by results recorded by Robbins and others (Robbins, Daniels et al. 2007) and Crabtree and others (Crabtree-Ramirez, Villasis-Keever et al. 2010). Results in this study were however in contradiction to those recorded by Kwobah and others (Kwobah, Mwangi et al. 2012) who showed that NRTI and NNRTI based are remotely associated with treatment failure and Chao and others (Chao, Tang et al. 2012) who registered results showing that patients on NRTI only based regimen are associated with treatment failure. However, the study did not measure association between NRTI only based regimen and treatment failure.

The study was however unable to evaluate other factors including WHO clinical staging, hazardous alcohol intake, previous exposure to ARVS through e.g. Prevention of Mother to Child Transmission (PMTCT), co-morbidities during ART intake, baseline haemoglobin, marital status, Employment status, sexual orientation, patient residence (urban or rural) and disclosure which have been documented as factors associated with treatment failure.

3.2 Conclusion

Based on the results of this study, the key factor associated with virologic failure amongst patients with suspected treatment failure is age lower than 40 years hence present a problem that need to be addressed.

3.3 Recommendations

Based on the findings of this study, recommendations include:

1. Focus on patients younger than 40 years should be prioritized to ensure better treatment outcomes and avoidance of treatment failure. This is to facilitate identification of possible barriers to treatment and developing possible solutions.
2. Comprehensive and focused services that is friendly to the young need to be strengthened at the health facility level. This is to ensure that services that are responsive to the need of the young patients on treatment are implemented.

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