Factors associated with virological failure among patients on second-line ART at Kenyatta National Hospital.

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

DECLARATION

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

Signature…… **Date …….**

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DEDICATION

This goes to my Family who have stood with me throughout the journey since the beginning of this course. I wish to thank my wife Caroline who made every effort to prepare me each and every day to undertake the course.

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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
KAIS	-	Kenya AIDS indicator survey
LPV/r	-	Boosted lopinavir
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
r	-	Retonavir
RLS	-	Resource limited settings
STI	–	Sexually transmitted infections
TB	–	Tuberculosis
TDF	–	Tenofovir
UNAIDS	-	United Nations Program on HIV/AID

ABSTRACT

Background: The HIV/AIDS scourge posture a serious difficulty to authorities, health operations, including societies throughout the globe. Relevant utilization regarding antiretroviral (ARV's) has enhanced the well-being of several humans with the immunodeficiency virus (HIV). Significant effectiveness regarding HIV medication depends upon the sustenance of immense levels concerning adherence to ARV; notwithstanding, ARV regimens remain often times intricate moreover it can be altered on changing dosing schedules, failing to have decent dietary specifications including subjects exhibiting adverse outcomes. More than half of people in low and middle income nations may not sustain viral suppression on second-line antiretroviral therapy (ART), according to research proffered at the 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018). Entrance toward second-line antiretroviral medication (ART) concerning HIV-positive subjects continues inadequately within South of the Sahara. The World Health Organization advocates a second-line ART for grown-ups of a pair of nucleoside reverse-transcriptase inhibitors + a ritonavir-boosted protease inhibitor. Viral load is recommended on a specific plan of medication as the favored observation procedure for diagnosis and verification of ARV regimen breakdown furthermore if viral load is regularly unavailable

Study Objective: To use multivariate analysis techniques to establish clinical and socio demographic factors related to second-line ART virological failure for patients on follow-up at KNH-CCC.

Methodology: Exploratory analysis was conducted on the categorical variables to provide summaries of the data. Further inferential analysis was done using multivariate and cluster analysis. A multivariable analysis was applied to concurrently examine whether multiple risk factors (referred to as independent variables) are associated with a specific outcome (attributed to as the dependent variable).

Justification: It is important that the patients on second line ART treatment continue staying on this treatment. This study provides important baseline information of factors associated with

failure of second line ART which can be addressed and investigated further to avoid patients being changed to third line ART treatment with its complications and cost implications.

CHAPTER ONE: INTRODUCTION

1.1 Background of the study

Practitioners are still faced with diverse interrelationships among the signs, prognosis including/or additional management and diagnostic classification and of subjects. Consequently, getting every group's inpatient information is critical in numerous regards. Subgroups can be classified into subjects to profit from various interventions. Definite symptom configurations sway a sign for more investigations. Diagnostic groups have advanced over time, by tradition or by gaining pathophysiological perspicacity. Reaction on the sufficiency of the before-mentioned classes frequently transpires on the person's subject level and remains consequently non-systematic. We infrequently discovered systematic studies that favorably utilized multivariate models to data accessible to clinicians. Consequently, it can be of help to model clinicians' choice-making by multivariate approaches, (Hirsch et al., 2011).

The phrase, 'multivariate analysis' and 'multivariable analysis' are utilized frequently in the field of medical and health science. Nevertheless, the multivariate analysis is a multiple outcome analysis whereas multivariable analysis is simply one outcome per interval. Therefore, this study concentrates on multivariable but not multivariate analysis. The multivariable analysis is a statistical mechanism to determine the corresponding contributions of diverse elements to a sole event or result. For instance, some factors are correlated with the formation of the cerebrovascular illness that includes older age, high blood pressure (BP), family history of stroke, diabetes, and elevated cholesterol levels, overweight and smoking of cigarettes. The multivariable analysis enables us to ascertain the independent involvement of various risk determinants (explanatory variables) to the progress of the disease (response variable). In different statements, the chance of

a consequence can be adjusted by other chance variables or synergies, and the effect is evaluated by multivariable analysis, (Reboldi, Angeli, & Verdecchia, 2013).

1.2 HIV Epidemiology

The global AIDS response stands at an uncertain position. An incomplete achievement in protecting lives and preventing fresh HIV infections is opening space toward complacency. At the midway mark toward the 2020 objectives, the speed of growth does not harmonize the world's goal. The amount from AIDS-associated mortality remains meaningful minimum this century, having less than one million persons perishing every year of AIDS-associated diseases, hence gratitude for continued availability of antiretroviral treatment. Given that 3 in every 4 people surviving with HIV presently are aware of their status which has been regarded as the first move to receiving therapy. Moreover presently a record 21.7 million persons remain on medication, a total rise of 2.3 million (M) persons looking back from close of 2016. The levels of increase towards availability of medication should be appraised, though, in the subsequent three years, close to 2.8M persons need to have been cumulated for each year. This is for the reason thatthere happen to be no new devotions to raise resources. There is a severe deficit of health-care operators, moreover there is lingering stigma and discrimination (Sidibe, 2018).

East and Southern Africa continue to be a significant area hardest hit by HIV. This transpires to be base of 6.2% of the globe's inhabitants. However, over half of the cumulative persons suffering from HIV diseases globally (19.4M persons) reside here.

1.3 HIV Diagnosis Care and Treatment

Entirely PLHIV needs to be put on ART medication not considering the level of CD4 amount/percentage, the WHO staging at the time of diagnosis, age, gravidity state, or opportunistic infection involved. ART can be started as early as an individual subject is willing to begin, optionally it can be within 14 days from the point of HIV status ascertainment. Therefore, the very first test regarding PLHIV could include a baseline test concerning the ART introduction to give more centered support in relation to examination at the first assessment, where all PLHIV are supposed to be classified as either an advanced HIV disease or as stable patients. Patients classified as having the advanced diseases will require extra exhaustive evaluation for and management of OIs. Furthermore, once ART is initiated high probability is that they are at a greater danger of developing immune reconstitution inflammatory syndrome. Likewise, through appointments after beginning ART, PLHIV should stay characterized as being either stable or unstable to best satisfy the distinct necessities of the individual patient for medication and follow-up and enhance patient results. This would reduce the difficulty and unnecessary follow-up for those subjects that do not require it, thus decreasing expenses and time associated with clinic visits, (Health, 2016).

Following ART's introduction, patients require to be observed closely concerning the advancement of antagonistic drug effects, recognize and discuss obstacles to adherence including the development of IRIS (especially for those which begin ART amidst high-level HIV infection). An understandable appointment for most patients is usually 14 days and 28 days following ART introduction, later monthly till viral suppression is confirmed. If VL denotes detectable by 6 months, they will require further evaluations and management of the purpose/s concerning detectable viral load having close follow-up till viral suppression is obtained. Clients who have been ascertained to have undetectable viral load can be followed up within a period of 3 months

based on patient choice and caregiver discretion, with extra unplanned appointments if the client develops issues before the due day. Clinical appointments can be apportioned further apart once the patient has continued on ART up to one year or more and satisfies the standards as “stable”. Children and adolescents should be followed up at least every 1-3 months,(NASCOP & 217:pp, 2018).

Problem statement

The greatest number of HIV/AIDS patients put on medication is on a conventional first-line regimen. The first-line regimen includes a blend of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). In case the first-line medication transpires fail, then second-line treatment is executed, using two NRTIs not earlier applied within the first-line medication in addition to one added protease inhibitor (PI). Failure of treatment of the early first-line ART regimen is frequent, although not inevitable(Tsegaye, Wubshet, Awoke, & Addis Alene, 2016). According to various researches, changing patients subsequent to failure of first-line regimens reduces mortality, enhances viral suppression, and promotes immune reconstitution where life expectancy is increased plus reduces drug resistance. Although the figure of changed patients has grown steadily across time, it remains modest as a result of impediments when switching from first-line medicine plus problems of the availability of drugs. Little is understood regarding the challenges of these second-line ART medications mostly in our Kenyan set-up. Several studies have shown that switching patients after failure of first-line regimens lessens mortality, decreases drug resistance, improves immune reconstitution, raises viral suppression and increases life expectancy. Even though some studies

have been carried out in other sub-Saharan countries, there is scanty information available in Kenya about second-line ART failure and the challenges associated with virological failure.

1.4 Justification

A significant increase in the accessibility of antiretroviral treatment (ART), notwithstanding the affordability plus the public quarter's capability to finance, remains one of the 21st Century outstanding public health achievements. Many low and middle-income state programs follow WHO guidelines based on the public health strategy toward ART. This strategy concentrates on maximizing survival at the community level through patterned rules and basic delivery of service, as well as decentralization and shifting of tasks. First-line ART regimens include two nucleoside or nucleotide inhibitors (NRTIs) with one non-nucleoside reverse transcriptase inhibitor (NNRTI); treatment failure demands to switch to second-line ART. WHO summary report of 2004-2005 indicates that even though the cost of ART varied noticeably from one country to the other, the pattern in all these countries indicated that the second-line ART was much more expensive; moreover there have been escalating records of MRD (multidrug-resistant) virus in treatment of experienced patients. This has been a significant contributory originator to first-line antiretroviral treatment (ART) failure which necessitates a physician to change over to the second line, protease inhibitor (PI)-based regimen, with all the factors in mind, as a country we have adopted a test and treat policy meaning more people have been put on treatment, a move that leads to more numbers wanting to be moved to second-line art of treatment. This is a clear understanding of factors that might be associated with failures that must be investigated in order to help those who are already on the second line to continue staying on it for more time hence fewer numbers will need to be changed to the third line which is a more complicated regimen compared to the second line.

The primary objective of his study is to determine factors associated with ART second-line treatment failure which could be multifactorial and not just adherence as it has been initially thought. Furthermore, the results of this study will help identify the dominant concerns that are being linked to the treatment failures and address them in advance, bearing in mind that after a patient is switched to a third-line ART, there are challenges including drug supply inconsistency from the national stores and cost compared to first-line or second-line. This study will provide important baseline information for further investigation.

1.5 Broad objective

To use multivariate analysis techniques to establish clinical and socio demographic factors related to second-line ART virological failure for patients on follow-up at KNH-CCC.

1.6.1 Specific objectives

1. To determine clinical factors related to second-line ART virological failure for patients enrolled, on follow-up at KNH-CCC.

2 To determine the socio-demographic characteristics of patients failing virologically and on second-line ART at KNH-CCC.

3. To establish the median time patients take on second-line ART before they start presenting with virological failure at KNH-CCC.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Globally, a significant figure of HIV-positive subjects obtaining antiretroviral treatment (ART) has duplicated since the year 2010. Moreover, over 17 million individuals were put on ART by 2015. The fatality has decreased and the survival amongst HIV+ subjects has improved. The necessity to change to second-line ART is also expanding along with this advantage to people surviving with HIV (PLHIV) due to more subjects spending a greater duration on ART and failing on first-line ART. By means of added therapy practice on second-line ART, the figure of subjects faulting this medication and needing third-line ART is growing. Contrasting proportions of second-line ART failing treatment have been recorded. Published studies from Asia following two years on second-line ART, failure frequencies fluctuated within 8% & 41%. Studies from Africa informed that the proportion was within 13% and 40%. These researches have similarly explained the varied determinants correlated with second-line ART failures, for instance, the span of first-line ART, delayed discovery regarding first-line ART failure, present and previous ART regimens, age, body mass index and patient observance on ART. The specific mortality incidence was 13% at 5-year follow-up of a second-line ART group in Vietnam and 20% at 5-year follow-up in India. Large mortality in cases who happen to be on second-line ART regimens and the difficulties of controlling this group of subjects under terms regarding observance toward ART drugs, low contact to viral load monitoring and HIV genotype testing, plus the price regarding access to third-line ART are of interest for programs managing PLHIV in countries with access to modest resources, (Kyaw et al., 2017).

WHO endorses viral load testing as a specific favored approach toward monitoring individual clinical response toward ART regarding people surviving with HIV disease (PLHIV). Viral load

monitoring of subjects on ART aids guarantee quick detection and verification of ART failure and also enables clinicians to choose the relevant plan of action on the management subject. While the final intention regarding ART is to decrease HIV-allied morbidity and mortality, the primary intention remains complete and long-lasting viral restraint. Long-term viral suppression demands near-perfect observance to antiretroviral medicines. Further determinants comprise hereditary diversity toward medication metabolism, preceding drug resistance, severe baseline immune suppression, and simultaneous opportunistic infections, (Nsubuga-Nyombi et al., 2018).

By 2016, approximately 790,000 fresh HIV infections representing about 43% of the world's total new infections. South Africa alone carried close to 270,000 of the sub-Saharan's fresh infections in 2016, extra 50% happened in Zambia, Ethiopia, Kenya, Mozambique, Tanzania, Uganda, Zimbabwe, and Malawi. In 2016, merely below 0.5M persons (420,000) perished from AIDS-related diseases in the region, although this figure of mortality has dropped by a big margin wherein 2010 we had close to 760,000 cases. Notwithstanding the progressive cruelty regarding the disease, tremendous paces have been executed towards reaching the UNAIDS 90-90-90 targets. In the year 2016 up to 76 percent of persons suffering from HIV were cognizant regarding their status, 79 percent of them had been put on medication (commensurate to 60% of total persons suffering from HIV in sub-Saharan), plus 83% of persons put on medication had attained viral suppression(AVERT, 2018).

Kenya holds position number four in relation to the HIV epidemic globally (beside Mozambique plus Uganda) having 1.6 M persons suffering from HIV disease by the year 2016. During that same period close to 36,000 patients perished of AIDS-associated diseases. While the aforementioned stands, good news is that in 2010, this has firmly decreased from 64,000. Having the HIV case in Kenya being confirmed in 1984, it remained one of the reasons for sickness in

Kenya by the mid-1990s placing enormous burden towards the healthcare structures plus the economy in general. In 1996, 10.5% of Kenyans had been documented to be suffering from HIV disease, despite the reported prevalence of almost half since then, reaching about 5.9% by the year 2015. This development happened essentially as a result of increased HIV therapy and supervision. In the year 2016, 64% of persons surviving with HIV remained on medication with 51% remaining virally suppressed. Kenya's endemic to HIV is majorly contributed by sexual transmission, suggesting that it touches every segment of the society including kids, youthful people, adults, ladies, and gentlemen. In the year 2015 close to 660,000 kids had been registered as orphaned through HIV disease. Nonetheless, a superfluous amount of fresh infections occurred amongst persons from important populations. It was approximated that 30% of new yearly HIV infections in 2014 occurred amidst these groups. Likewise, the geographic position becomes a determinant with 65% of the total latest infections transpiring in 9 out of the 47 counties in Kenya largely on the West Coast part of the Country. In singular, fresh HIV infections are influential in Nairobi and Mombasa progressed over by 50%, previously, 4,707 cases were recorded in 2013 compared to 7,145 cases in 2015. As a result of that, the occurrence of HIV variance in Wajir is 0.1% while in Homa Bay it stands at 25.4% (Points, 2016).

A multivariable analysis is a statistical method that could be applied to concurrently examine whether multiple risk factors (referred to as independent variables) are associated with a specific outcome (attributed to as the dependent variable). The kind of regression model that is preferred depends principally on the outcome variable plus the purpose of time in the available data, (Wakkee, Hollestein, & Nijsten, 2014). Statistical analysis is a significant segment toward establishing any verdict of either a clinical trial or collection of data. Whilst there exist various kinds of situations in which such an analysis might necessitate to be implemented, pair descriptive

examples are: (1) while clinical trial tests determinations of two or many populations, like healthy versus unhealthy or placebo versus medicine; or (2) when a subject's blood specimen is analyzed and the measured values are equaled upon reference ranges for a healthy person. In both instances, the analysis is usually conducted by linking the representative value of one precise determined number alongside similar precise number of others; furthermore, this estimate is normally performed for specific measured quantity. Nevertheless, such a method will overlook existing associations within various determined quantities. In case the determined quantities comprise a representation of action in a biological system where segments are joined via reactions, regulatory effects or interactions like metabolic or signaling pathways, then traditional univariate strategies will potentially misrepresent the right correct system behavior. Multivariate analysis is likely to tackle this inadequacies and, more precisely to expound the characteristics of a biological network, (Reboldi et al., 2013).

Multivariate statistical analysis pertains to multiple advanced techniques concerning exploring associations amongst multiple variables at the same time. Researchers practice multivariate methods in studies that require more than one dependent variable (likewise identified being the outcome or event of interest), more than one independent variable (additionally understood being the predictor) or both.

Multivariate analyses have been adopted to supplement but not to be a replacement for discerning reasoning within the field of statistical analysis. Great outcomes can purely be generated through these methods if cautious consideration is furnished upon inquests of sample size, variable type, variable distribution, etc. Furthermore, denunciations concerning subjectivity during interpretation can exclusively be won through replication. The computer revolution has presented multiple difficulties for statisticians, not least of which is the smoothness amidst which

experimenters may obtain packages of programs for multivariate analysis, and so circumvent a 'complicated' (for which implies individuals will not do just as he is told), a statistician. There are numerous instances of violations regarding univariate statistical methods. Here, however, the violations are not anticipated to reach such grievously misleading results as in the multivariate case,(Everitt, 1975).

Why this unexpected wave of enthusiasm in multivariate stats? Is it merely another trend? Perhaps it is. There assuredly do prevail in inquiries that can be adequately solved with more uncomplicated statistics, particularly if that data is transpired experimentally and produced under controlled circumstances. Nevertheless, numerous fascinating research problems remain remarkably intricate that they necessitate multivariate models plus multivariate statistics. Furthermore, amidst the exceedingly progressed availability of high-speed computers and multivariate software, these issues can promptly be addressed by various users through multivariate methods earlier accessible exclusively to quite fewer individuals. There is a growing interest lately with observational and quasi-experimental research designs. Some claim that multivariate analyses, such as ANCOVA and multiple regression are possible to apply in implementing the statistical direction of extraneous variables. Given the idea that statistical control is a poor substitute for sound experimental design, in some circumstances chances could be that it is the only working remedy. In some instances, data could be generated even before the research is designed or cases where the experimental or laboratory control don't follow guideline or prohibitively expensive plus sometimes people don't adhere to set code of collecting data from which you still hope to distill some extract of truth,(Carolina, 2014).

A different circumstance could be a case of simple analysis in relation to insufficient aggregates; it happens when specific data on any of the variables remain interrelated or if data has a certain

pattern. Such a circumstance frequently occurs if data was accrued over a period of time. For instance, if the data gathered on a particular subject or a group of subjects following a provided medication, we are unusually involved in understanding the medium answer in the end. Seeing some variations in the states, that is, in seeing some trends is what we are involved in. In multiple circumstances, data is gathered in various components, and each one of them not merely one, but many variables are estimated. For instance, in psychological research, various tests are performed, and every person is subordinated to all experiments. Considering that these are measurements on the similar component (aperson), these variables are interrelatedwhilstshorteningdata on all these variables, this set of connections should form an important part of this review, (Reduction, 1999).

2.2 Key concepts and terms in Multivariate Statistical Methods

To understand multivariate analysis, it remains necessary to understand some of the vocabularies. For instance, a variate is a slanted blending that is concern with variables. The primary objective of the analysis is to determine some fittest mixture of weights. Nonmetric data shows either qualitative or categorical data while, metric data indicates quantitative data.

A) Analysis of variance (ANOVA)

The traditional approach to evaluating the implication of influences by the dissolution of a response's variance into clarified components, linked to differences in those predictors, including a remaining component summarizing experimental error. The impact of a design variable on a response is marked as important if the differences in the response value as a result of variations if the design variables are corresponded with the experimental error. The implication of the impact is yielded as a p-value: typically, the outcome is deemed meaningful if the p-value is lesser than 0.05 (5%).

B) Bias

The methodical variation among predicted plus estimated values and the bias is calculated as the average value of those residuals.

C) Classification

Data analysis techniques put into a task in calculating class membership to be regarded as predictive method in which the reaction is classified as category variable. The primary intention of analysis is to predict the category to which a new sample belongs to. The major approaches involved in implementation of the unscrambled may include SVM classification, SIMCA, LDA plus PLS-discriminant analysis. For example, classification can be used to establish the geographical origin of raw material from various levels of impurities. It can also be used to acknowledge or decline a given product; this depends on its quality.

D) Clustering

This term means a classification technique that does not need any previous information concerning the available samples. The elementary application involves grouping commonly in a "cluster" numerous samples that are suitably near each other.

E) Correlation

Some units comprise of less number of quantity of linear association among two variables. The relationship is estimated as the covariance amid the two variables divided by the square root of the product. It ranges from –1 to +1 in which a positive correlation symbolizes a positive connection amid the two variables, i.e. if one increases, the other tends to increase too. The closer to +1, the more powerful the link is. A negative correlation means a negative connection to link the two

variables, i.e. if one increases, the other tends to decrease. The closer to –1, the more powerful this link

F) Covariance

This is a measure of linear connection among two variables presented on a scale which is a function of the measures of the two variables. Furthermore, it will not denote straightforward interpretation. Consequently, it is ordinarily easier to investigate the correlation alternatively.

G) Cross-validation

This is an approach in which some samples remain held out of this calibration furthermore applied toward forecasting. This is replicated continuously for all samples until kept out once. Validating residual variance are calculated from the prediction residuals. Samples are classified into subgroups or "divisions" in segmented cross-validation with a single segment at a moment kept out of the calibration. This can comprise of various calibration rounds as segments so that predictions are performed on the total trials. Closing calibration is subsequently performed with the total samples and one sample at a time is put out of the calibration per iteration in complete cross-validation.

H) Degrees of freedom

Each number of degrees of freedom on a phenomenon is the number of independent ways in which this occurrence is altered. Degrees of freedom is used to estimate variances and logical variable distributions like, the approximated variance is assumed to signify "corrected for degrees of freedom". If it is calculated, it is the total square of deviations from the mean, divided by the number of sum degrees of freedom.

I) Distribution

This is the pattern of a particular occurrence description of a determined variable or calculated parameter. Practical distributions could remain expressed by a histogram and a number of statistical parameters beget a recognized theoretical distribution that applicable for important testing.

J) F-distribution

Fisher distribution signifies the division of a particular ratio within two variances. In this case, F-distribution presumes that a particular unique measurement follows approximately normal distribution.

K) Linear Discriminant Analysis (LDA)

LDA is the easiest of all classification methods based on Bayes' formula and LDA resolves the best-fit classification parameters of samples by a developed model.

L) Least square criterion

This is the foundation of traditional regression techniques, which consists of reducing the total squares of the residuals. This is comparable to decreasing the usual squared measure amid primary response values plus fitted values.

M) Principal Component Analysis (PCA)

PCA comprises of a bilinear modeling approach that produces an interpretable summary of the central information within a multidimensional data report. Conveyed information by the primary variables is protruded toward a tinier representation of the original ("latent") variables commonly known as principal components. The initial principal component comprises of data variation. The

second principal component comprises of orthogonal and covers essentially enough of the outstanding variation as practicable. During plotting the principal components, one can easily inspect inter-relationshipsamong several variables, furthermore, discover plus read sample patterns, groupings, associations or discrepancies.

2.3 Characterizing and Displaying Multivariate Data

Descriptive statistics give simplistic summaries about (massive volumes of) data. These reports are quantitative (e.g. means, correlations) or presented visually (in charts, scatterplots, etc.). Descriptive statistics can be “univariate” (comprising one variable), “bivariate” (relating pair variables to ascertain whether there are some similarities among them), or “multivariate” (examining whether there are associations among more than two variables). For multivariate accounts, every impact of one factor or variable is detached from others to circumvent distorting results.

In a nutshell, a random variable is a variable whose value relies upon the outcome of a likelihood investigation. Ordinarily, random variables are acknowledged and some kinds of multivariate data simply remain estimates to this principle, such as test scores or a seven-point semantic differential (Likert) scale of dictated answers varying from firmly dissent to accept. Distinctive methods have been extended concerning such data, however, under any circumstances, the common techniques intended for constant data work nearly as well, (Carolina, 2014).

The density function

The population mean

The sample mean

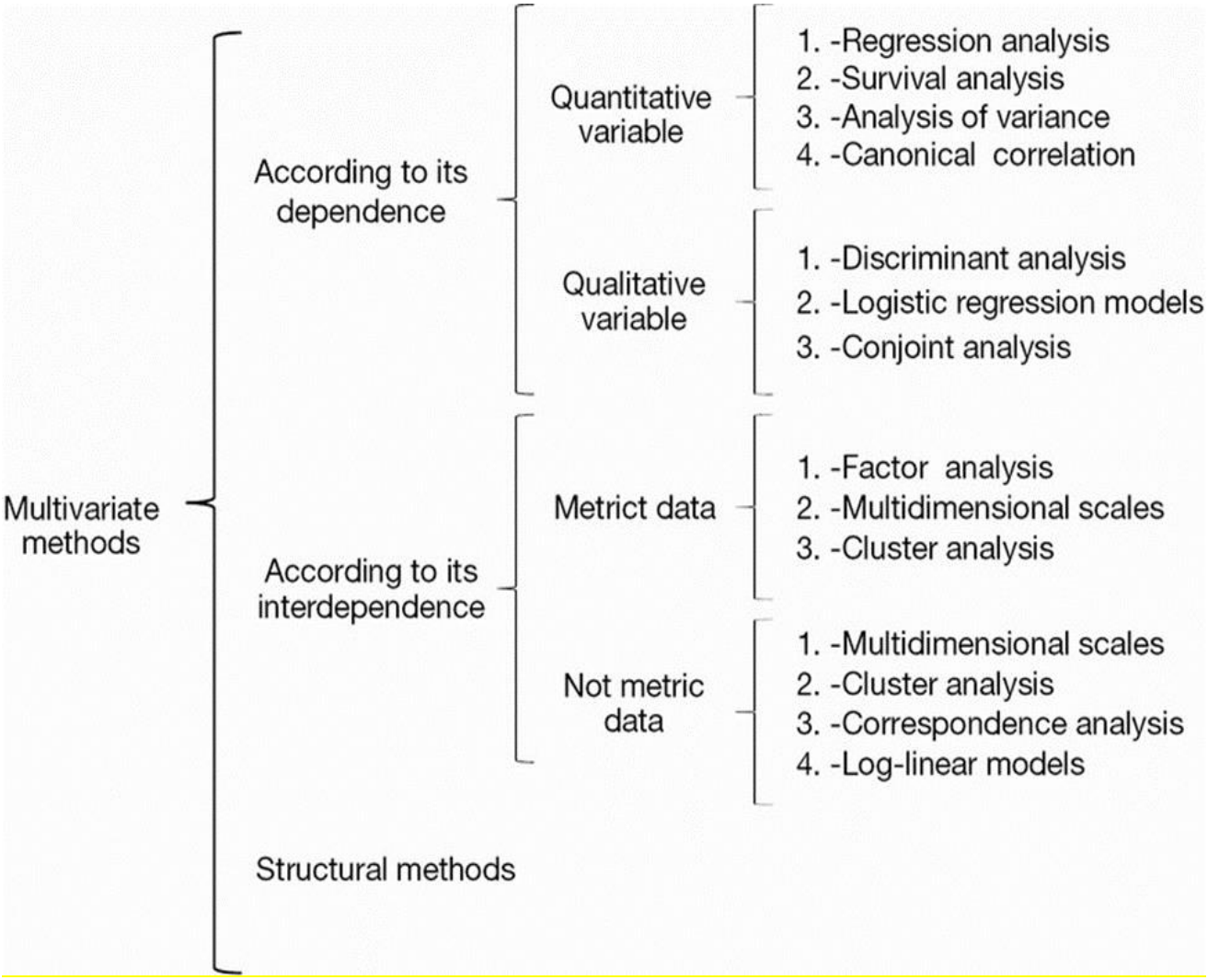
The variance

The standard deviation.

2.4 Types of Multivariate Methods

Formerly, multivariate tests including analysis methods were adopted into statistics to reveal causal associations. Multivariate methods can be subdivided according to distinct aspects. First of all, all stand contrasted according to whether ***the purpose means to find a formation within the combination of data,*** or ***whether specific data is to be reviewed with a particular structure***.

The structure-determining ways incorporate as described in the presentation below,



2.5 Assumptions underlying multivariable models

These are mathematical nations in which we adopt appropriate models for the reason that we understand about data being capable of reflecting the pattern related to the model. If that model seems not matching the data, the perception of the data is at risk of misrepresentation. The underlying presumption of multiple linear regression is that, as these independent variables increase or decrease, the average value of the result increases or decreases in a linear fashion. For instance, a linear combination of age and body mass index in postmenopausal women is the best predictor of bone density. Even though this association among the independent variable and the result must be linear, nonlinear correlations is illustrated by modifying the variables for independent variables to produce a linear correlation to the outcome. Logarithmic and spline conversions are mostly used to model nonlinear correlations, (Katz, 2003).

Logistic regression models; is the likelihood of an outcome plus how such likelihood shifts by a variation in the predictor variables. The fundamental presumption indicates that every one-unit increase in a predictor multiplying the odds of the outcome by a particular factorand the effect of many variables is the multiplicative result of their individual effects. The logistic function generates a probability of outcome encircledby 0 and 1, (Katz, 2003).

Proportional hazards models; indicates that the ratio of the hazard functions for characters with or with noassigned risk factor is equal over the whole study duration. This is identified as being a proportionality assumption. Consider, for instance, research that correlates surgery to watchful waiting in subjects with carotid artery stenosis. In achieving the proportional hazards assumption, the ratio amid the hazard of death with watchful waiting and the risk of death with surgery ought to be consistent across the period of the research. If the hazard of dying is higher with surgery at

the start of the research, then the hazard of death must also be higher to succeed the follow-up period, (Katz, 2003).

The Multiple linear regression, logistic regression, and proportional hazards models arrogates that computations are independent of each other. Separately, some models are not capable of taking into account some outcome occurring more than once in the corresponding character. Although some outcome (such as a tumor) occasionally occurs in one case severally all through the follow-up time, separate concerns may appear frequently to the same subject. For example, an individual might present with relapsing urinary tract diseases in a follow-up period. In such incidents, researchers might apply universal estimating equations correct for the relationship within iterated measurements of similar subjects. General estimating equations are equally used to evaluate outcomes likely to occur in several body parts, (Katz, 2003).

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Introduction

Methodology: Data on patients who failed on second-line ART (viral loads above 1000 despite being on treatment) for the period January 2013 to December 2017 was retrieved from KNH-CCC electronic records, cleaned, coded and stored into MS Access data base. Data analysis was performed using STATA statistical software version 13 SE.

Exploratory analysis was conducted to provide summary of the data. Plotted histograms were generated to show the quantitative variable distribution and measures of central tendency i.e. the mean or median and dispersion (standard deviation/inter-quartile range) in form of tables. Bar or pie charts were plotted for categorical variables to indicate distribution, frequencies and proportions in form of tables.

A multivariable analysis was applied to concurrently examine whether multiple risk factors (referred to as independent variables) were associated with a specific outcome (attributed to as the dependent variable). Results were tabulated and presented in form of tables and charts.

3.2 Study design

The study employed a retrospective cohort study design to determine the multiple factors associated with virological failure of patients who had been started on second-line ART and were on follow up at Kenyatta national hospital.

3.3 Study site

The study site was Kenyatta National Referral Hospital comprehensive care clinic, located at Upper Hill area of Nairobi. This clinic was started in 2001 for purposes of provision of comprehensive HIV care to HIV patients.

3.4 Study population

HIV positive patients on second-line ART regimens whose viral load remained above 1000 despite being on second line ART regimen for the period January 2013 and December 2017

3.4. Inclusion criteria

I. HIV positive patient on second-line ART and suspected to have second-line treatment failure for the period January 2013 and December 2017.
II. The patients who had been continuously followed between January 2013 and December 2017.
III. Patients whose screening records were complete from enrolment to December 2017.

3.5 Exclusion criteria

I. Patients on the second line ART but whose viral load was below 1000
II. Patients who were transferred to KNH CCC whose viral load was above 1000 despite being on second-line ART

3.6 Sampling Method/Sample size

Reports indicated that currently the active patients on follow up in the CCC clinic were approximately 9000. Of these, those currently on second-line ART were up to 2000. Going by the publication that up to 365 of patients were non-adherent to medication, thus all-inclusive patients ever reported to have treatment failure of second-line ART were included into the study so as to have a good number for the power of the study to be sustained.

3.7 Data Collection and Analysis

Data on patients suspected to be failing on second-line ART treatment for the period January 2013 and December 2017 were retrieved from KNH-CCC electronic records, cleaned, coded and stored into MS Access data base. Data analysis was performed using STATA statistical software version 13 SE.

Exploratory analysis was conducted to provide summary of the data. Plotted histograms were done to show the quantitative variable distribution and measures of central tendency i.e. the mean or median and dispersion (standard deviation/inter-quartile range) in form of tables. Bar or pie charts were plotted for categorical variables to indicate distribution, frequencies and proportions in form of tables.

Inferential analysis was done by various multivariate analysis methods including cluster analysis. This was performed on the categorical variables to determine factors contributing to virological failure among patients on second-line medication.

A multivariable analysis was applied to concurrently examine whether multiple risk factors (referred to as independent variables) were associated with a specific outcome (attributed to as the dependent variable). Results are tabulated and presented in form of tables and charts.

3.8 Ethical Considerations

The researcher sought ethical approval from the University of Nairobi/Kenyatta National Hospital Ethics Board. Consequently, further permission was sought from the Kenyatta National Hospital Management Health System and the Head of Unit at Kenyatta National Hospital Comprehensive Care Center to utilize electronic medical records servers. Patient identification details were not included as part of data collection, patients were assigned a unique study identification number.

CHAPTER FOUR: RESULTS.

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE STUDY PATIENTS.

A total of 1120 records on patients who failed on second-line ART for the period January 2013 t o December 2017 were retrieved from KNH-CCC electronic records. Their mean age was 39.56 years with a standard deviation of 14.48. The median age was 41.35 years with IQR of 22.42. T he minimum age was 3.20 and the maximum was 81.2 years old

There were 695 (62.05%) female and 425 (37.95%) male patients.

Majority of the patients 456 (43.02%) were married/cohabiting, 290 (27.36%) were single, 153 (14.43%) were children.

Hundred and forty six (37.44%) of the patients had attained secondary level of education, 132 (33.85%) had primary level education, 98 (25.13%) had post secondary education, 12 (3.08%) had no education and 2 (0.51%) had other level of education (Table 1 below).

Table 1: Socio demographic characteristics of study population

Socio demographic characteristic	Frequency	Percent
Current age		
• Count	1120	
• Mean (SD)	39.56 (14.48)	
• Median (IQR)	41.35 (22.42)	
• Q1, Q3	27.20, 49.62	
• Min, Max	3.20, 81.2	
Gender		
• Female	695 (62.05%)	62.05
• Male	425 (37.95%)	37.95
Marital status		
• Child	153	14.43
• Cohabiting	2	0.19
• Divorced	12	1.13
• Married	456	43.02
• Married monogamous	8	0.78
• Married polygamous	2	0.19
• Other	5	0.47
• Separated	63	5.94
• Single	290	27.36
• Widowed	69	6.51
Level of education		
• None	12	3.08
• Other	2	0.51
• Post-secondary	98	25.13
• Primary	132	33.85
• Secondary	146	37.44

Figure 1: Gender distribution of the study population

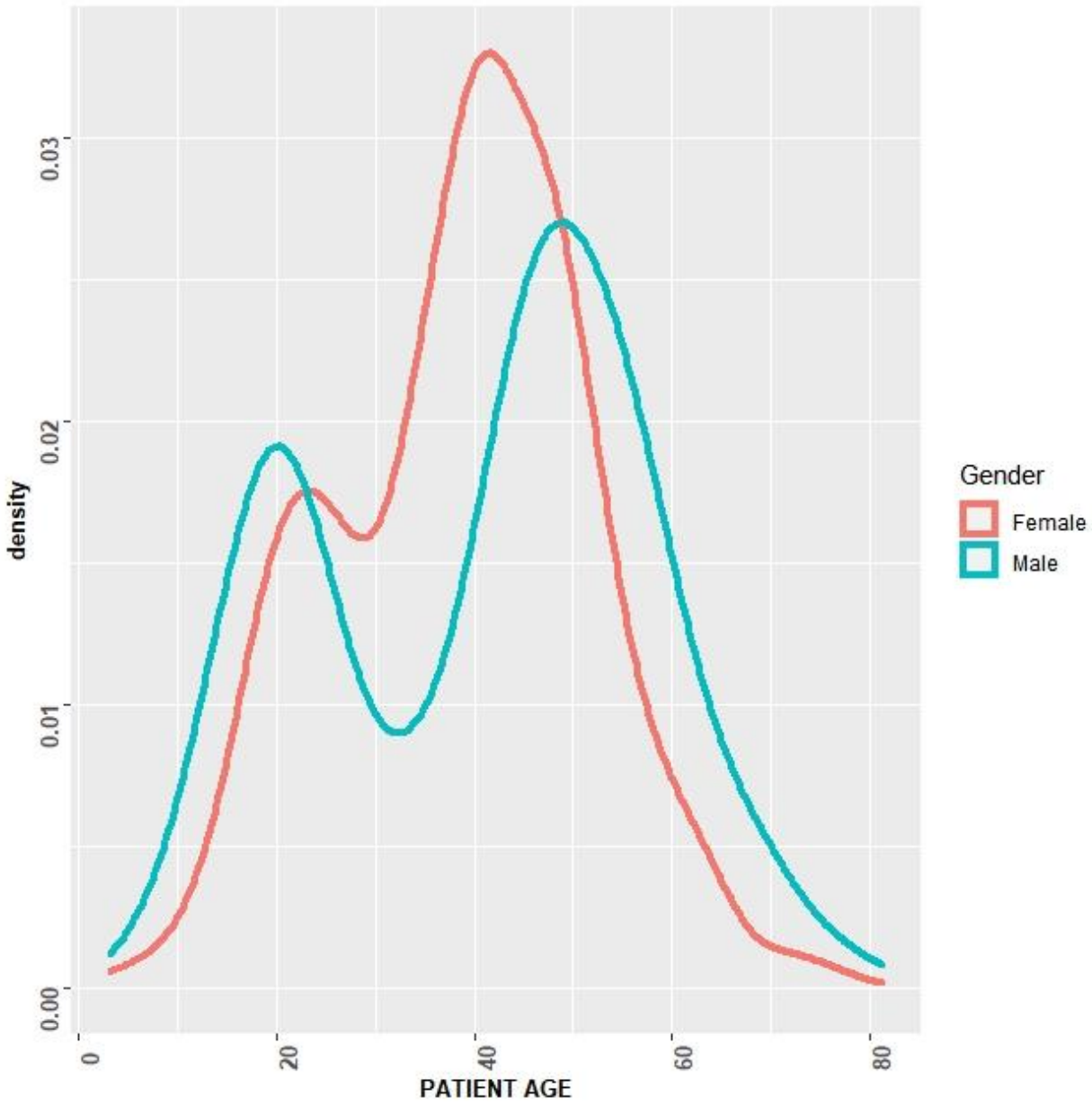


Figure 2: Age and gender distribution

CLINICAL FACTORS OF STUDY PATIENTS.

The most common medication service area was the ART clinic where 1045 (93.30%) got medication service from, 16 (1.43%) had services from maternity and postnatal clinic, 24 (2.14%) from DCC and PrEP while in 34 (3.04%) patients were patients in transit. 1(0.09%) patient had PEP service delivery.

The most common justification for high viral load was routine viral load 234 (75.48%) cases. Ninety eight (50%) of the patients had lost to follow up as the reason for exit while 70 (35.71%) were transferred.

Current status for most patients was active 863 (77.05%), followed by lost to follow up 98 (8.75%). Transfers accounted for 70 (6.25%), while death was 27 (2.41%) of the patients Adherence done after high viral load, patient switch and switching after high level viral load was achieved in 100% of the patients.

Lost to follow up was the most common exit reason 98 (50.0%) of the patients, followed by transfer 70 (35.7%) of the patients.

The mean duration of enrollment was 9.26 months with a SD of 4.35, median was 9.70 months with an IQR of 7.30 (Table 2 below).

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Table 2: Clinical indicators

Clinical	Frequency	Percent
Medication service area • ANC Maternity and Postnatal clinic • ART clinic • DCC and PrEP • Patient in transit • PEP	 16 1045 24 34 1	 1.43 93.30 2.14 3.04 0.09
Viral load result 1 • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max	 1120 167659.19 (642837.37) 19721.50 (103162.50) 1858.00, 105020.5 0.00, 9533744	
Viral load result 2 • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 1067 79023.86 (270628.06) 6503.00 (48401.00) 69.00, 48470 0.00, 3906203 53	
Viral load result 3 • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 1014 60222.88 (357967.93) 1646.50 (30195.75) 20.00, 30215.75 0.00, 1e+07 106	
Viral load result 4 • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 958 41399.83 (220188.58) 236.00 (15447.50) 0.00, 154474 0.00, 4153658 162	
Viral load result 5 • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 877 29967.28 (161287.29) 53.00 (3499.00) 0.00, 3548810 0.00,3548810 243	

High viral load result • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 1120 182641.22 (646871.34) 33485.00 (116625.75) 7149.50,123775.2 1002.00, 9533744 0	
High viral load justification • Baseline viral load • Clinical failure • Confirmation of treatment failure (repeat VL at 3 months) • Immunological failure • Lactating mothers • Pregnant mothers • Routine VL • Single drug substitution	 26 17 18 3 6 6 237 1	 8.28 5.41 5.73 0.96 1.91 1.91 75.48 0.32
Adherence – done after high viral load • Yes	 1028	 100
Switched • Yes	 1027	 100
Switched after high viral load • Yes	 136	 100
Exit reason • Death • Lost • Refused care • Transfer	 27 98 1 70	 13.78 50.0 0.51 35.71
Current status • Active • Death • Lost • Lost – not care-ended • Refused care • Transfer	 863 27 98 61 1 70	 77.05 2.41 8.75 5.45 0.09 6.25
Enrolment duration • Count • Mean (SD) • Median (IQR) • Q1, Q3 • Min, Max • Missing	 1120 9.26 (4.35) 9.70 (7.30) 5.40,12.7 0.10, 24.7 0	

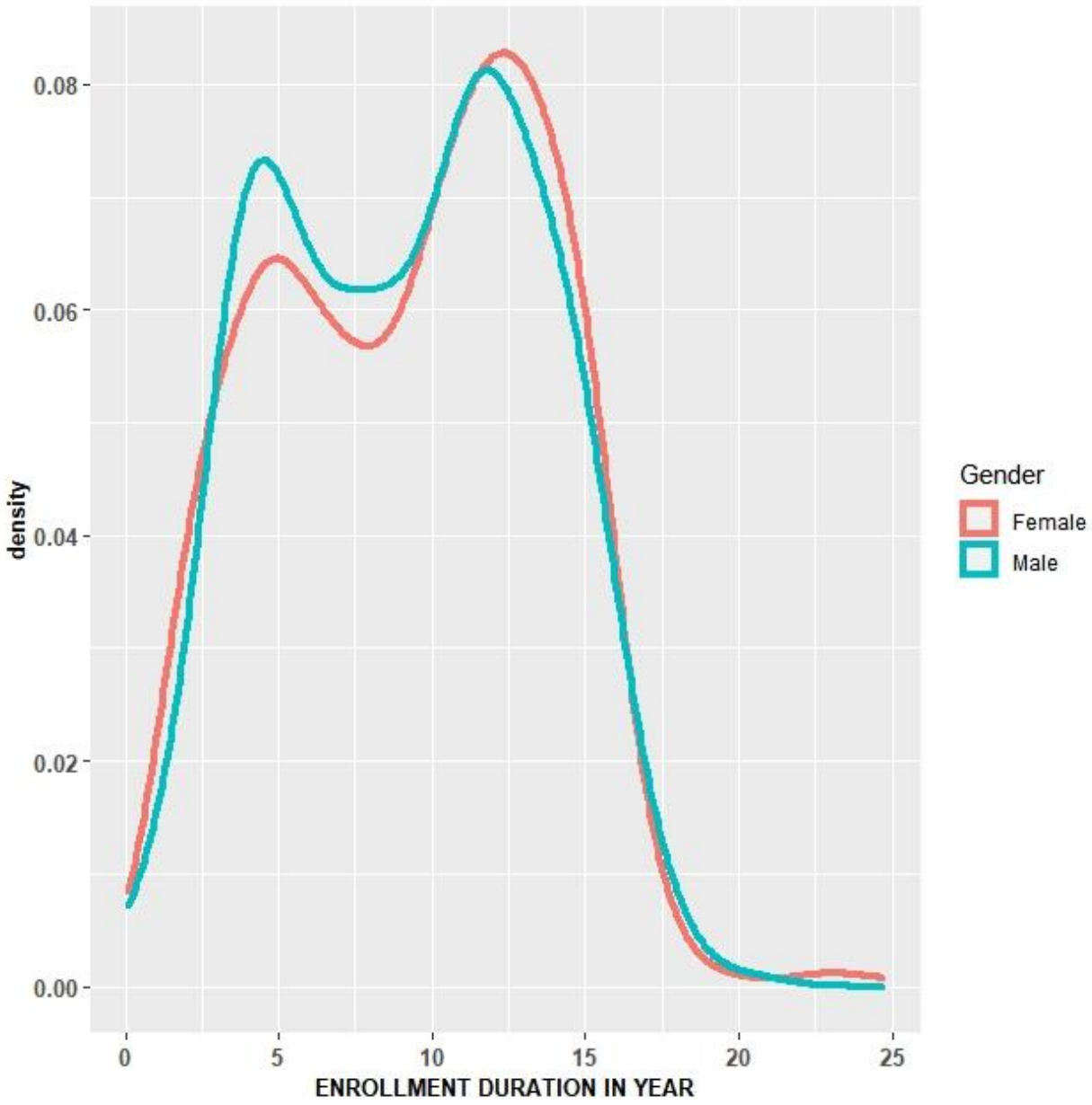


Figure 3: Enrollment duration in years

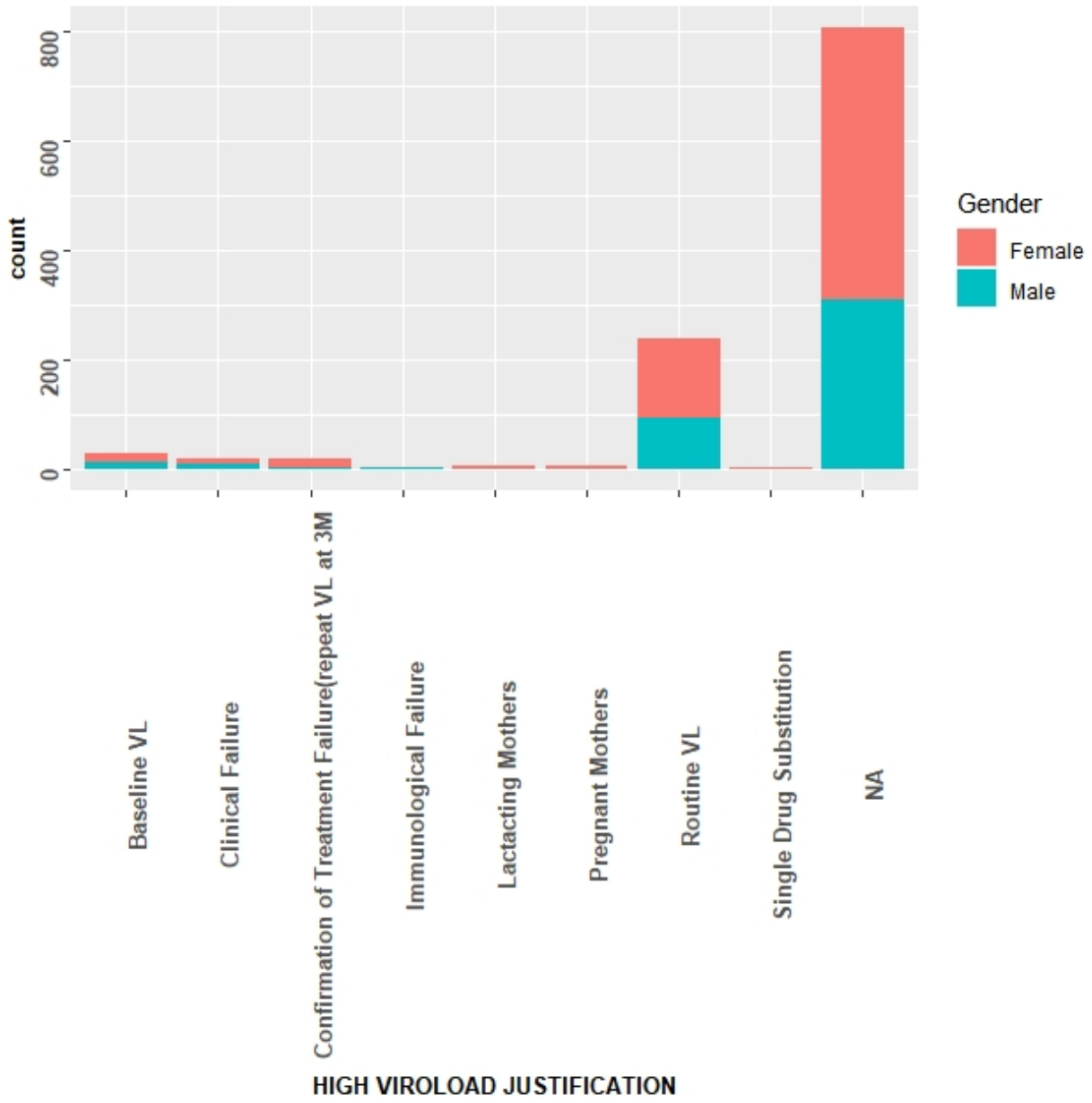
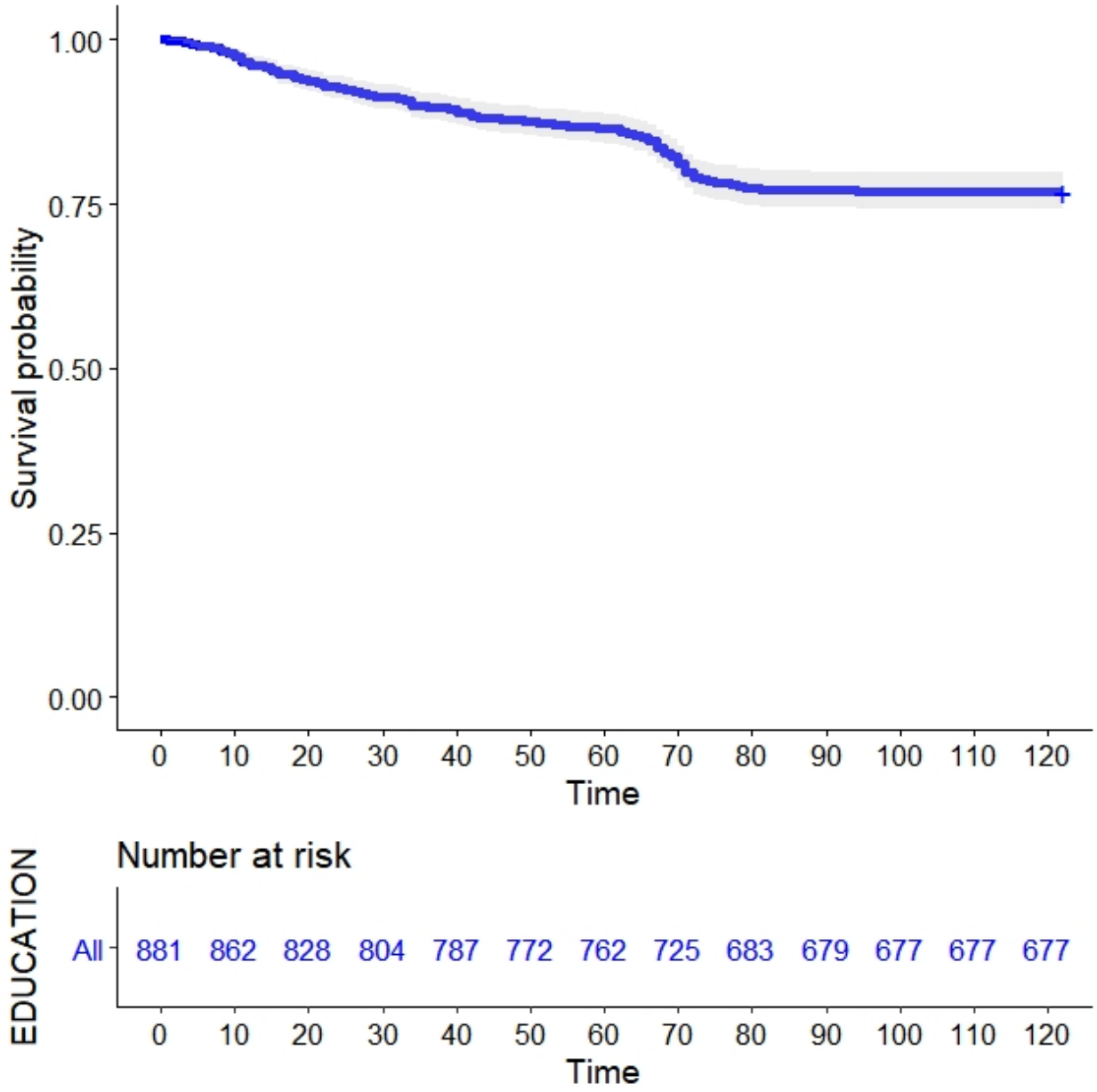


Figure 4: Viral load justification

ANALYSIS

Generally, patients got VL suppression (viral load less than 1000) during the first 80 days after their registration.



Logistic Model:

Only education level and enrollment duration are significantly related to VL suppression. Each d ay spent in the center will increase the chance to get VL suppressed to 14%.

Compare to those without any education level (None), other patients are less likely to have VL s uppressed

	Exp (coef)	P.Value
Regimen AS2	8.416e-01	0.578280
Regimen CS	5.428e-08	0.996045
Regimen Other	1.117e+00	0.753097
Education Level Other	3.972e-08	0.998066
Education Level Post-Secondary	2.140e-01	0.009376
Education Level Primary	3.583e-01	0.062958
Education Level Secondary	2.755e-01	0.018742
Enrolment duration	1.139e+00	0.000159

```
Likelihood ratio test=19.79 on 8 df, p=0.01117
n= 262, number of events= 57
(619 observations deleted due to missingness)
```

Figure 5: Proportional Hazard Ratio model

DISCUSSION

This study aimed at establishing the socio-demographic and clinical factors related to second-line ART virological failure for patients on follow up at KNH-CCC.

Descriptive statistics (univariate analysis) was employed to give summaries on the socio-demographic and clinical data e.g. means SD, median IQR and these were presented in charts and tables.

Multivariate (examining whether there were associations among all the independent variables to ensure every impact of one factor or variable is detached from others to circumvent distorting results) was also used in the analysis of the data.

Six hundred and ninety five (62.05%) of the patients were female and 425 (37.95%) were male. Most patients were married 456 (43.02%), while the single patients account for 290 (27.36%) of the patients. A significant number of the patients had attained secondary and post secondary 146 (37.44%) and 98 (25.13%) respectively.

Majority of the study patients 146 (37.44%) had secondary level of education, 132 (33.85%) had primary level, 98 (25.13%) had post-secondary level of education, and 12 (3.08%) had no education at all.

Lost to follow up was the most common exit reason 98 (50.0%).

The commonest medication service area with the highest number of patients was the ART clinic 1045 (93.30%), with routine VL being the most common justification for high viral load failure accounting for 237 (75.48%) of study patients.

The current status of the patients was mostly active 863 (77.05%) patients, while transfer accounted for 70 (6.25%) of the patients. Lost and lost- not care-ended account for 98 (8.75% and 61 (5.45%) respectively.

Survival analysis revealed that generally patient viral load suppression (viral load less than 1000) was during the first 80 days after enrollment.

Only education level and enrollment duration were significantly related to viral load suppression. Each day spent in the centre will increase the chance to get viral load suppression to 14%.

Compared to those without any education level (no education), other patients are less likely to have viral load suppression.

STUDY LIMITATION

Missing of data not captured in the electronic data base.

CONCLUSION

1. Only education level and enrollment duration were significantly related to viral load suppression. Each day spent in the centre increased the chance to get viral load suppression to 14%. Compared to those without any education level (no education), other patients were less likely to have viral load suppression.

2. Lost to follow up was a significant exit from follow up reason.

RECOMMENDATION

1. A retrospective study is needed to delve into the reasons for lost to follow up which has an impact on 2nd line ART treatment failure.

2. Offer counselling on clinic follow-up especially to patients with no education.

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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 second line ART treatment ----------DD/MM/YYYY

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

10. **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

11. **History of changing ART drug**

Yes ☐ No ☐

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

13. Reason for changing ----------

14. **History of adherence counselling due to defaulting**

Yes ☐ No ☐

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

16. 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 ☐ ☐

APPENDIX 2: DATA ANALYSIS DUMMIES

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		

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		
Viral load before changing to 2nd line	Yes No		
Baseline CD4	< 100 100-250 250-350 350-500		

Multivariate factors influencing virological failure

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/LPV/R TDF/3TC/LPV/R TDF/3TC/ATV/R ABC/3TC/LPV/R AZT/3TC/ATV/R ABC/3TC/ATV/R		