MODELLING TIME TO HYPERTENSION DEVELOPMENT AND ASSOCIATED FACTORS AMONG PATIENTS ON FIRST LINE ANTI RETROVIRAL THERAPY IN KENYATTA NATIONAL HOSPITAL

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DECLARATION

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

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ACRONYMS AND ABBREVIATIONS

ABC	-	Abacavir
AZT	-	Zidovudine
ART	-	Anti retroviral therapy
AIDS	-	Acquired immune deficiency syndrome
ARVS	-	Antiretroviral drugs
EFV	-	Efavirenz
NEV	-	Nevirapine
HIV	-	Human immune deficiency virus
KNH	-	Kenyatta national hospital
NACC	-	National Aids control council
UNAIDS	-	United Nations program on HIV/AIDS
WHO	-	World health organization
HTN	-	Hypertension
CDC	-	Centre for disease control
BP	-	Blood pressure
TDF	–	Tenofovir

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Definition of operational terms

Non communicable diseases - Diseases that can’t be passed from one person to another and can last for a long duration.

Opportunistic infections - Infections that attack HIV patients when immunity is low

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

Adherence form - Form filled when client has undergone counselling.

ABSTRACT

INTRODUCTION: Kenya is among Sub Saharan African countries facing the HIV/AIDS epidemic challenge. The introduction of ART in management of this epidemic has yielded good results in terms of viral suppression, reduction on opportunistic infections and boosting the immune system. However, there has been an increased incidence of non-communicable diseases and among them hypertension has been a key factor leading to mortality in these patients. Persons initiated on ART frequently develop hypertension but the duration patients take after being initiated on ART treatment to get hypertension and the factors that may lead to some patients becoming hypertensive earlier than others regardless of being put on same treatment remain incompletely explained.

STUDY OBJECTIVES: This study sought to estimate the probabilities of developing hypertension at different time periods in patients initiated on first line ART together with the associated factors.

METHODOLOGY: A retrospective cohort study design was applied in conducting the study at the Kenyatta national hospital comprehensive care Centre involving HIV infected patients initiated in to first line ART between 2013- 2018. A sample of 904 patients was obtained using stratified simple random sampling method and followed up for hypertension development. Demographic, clinical and laboratory data of these patients was extracted from the electronic medical records, cleaned and coded in Ms excel. Analysis was done using STATA software version 20. Kaplan Meier was applied in estimating survival functions and Log rank tests in comparison of survival functions between patients based on different ART regimes. Cox proportional model was used to evaluate the associated factors with hypertension among the participants.

RESULTS: 904 patients were included in the study, Kaplan meier estimated the median follow up time of the patients to develop hypertension to be 39 months and the log rank failure functions of patients differed significantly by age, diabetes status and smoking status while the hazard ratios of developing hypertension varied significantly with increasing age, BMI and smoking status.

CONCLUSION: Efavirenz based ART regimen was detected to have more effects on blood pressure than the Nevirapine based one. More comparative studies need to be conducted to determine the effect of each individual ART drug to blood pressure in order to come up with the right combination with less harm to the patients.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background of the study

Hypertension is a major threat for developing heart diseases that is mostly underdiagnosed and undertreated in most cases. HIV infected patients on ART have a higher risk of hypertension and other cardiovascular risk factors. The use of anti-retroviral therapy (ART) has resulted to a decline in HIV related deaths. However, use of anti-retroviral drugs has also led to a rise in the risks of acquiring cardiovascular diseases in HIV infected individuals. This high risk of cardiovascular diseases (CVD) and related mortality has been linked to continued exposure to ART (Nazisa Hajazi et.al)

Hypertensive cases are more in HIV positive population compared to their counterpart HIV negative population. Some of the risk factors thought to contribute to hypertension in PLWHIV include demographic factors, genetic, lifestyle and obesity, challenged immunity together with the anti-retroviral therapy effects.

There is a great need in improving and understanding treatment and control of hypertension as well as creating awareness on the drug interactions between the ARV's and the antihypertensive drugs.(Van zoest et.al)

A review of published literature by Bloomfield et.al, (2014) found that cardiovascular diseases like hypertension are common in low and middle income countries and commonly affect the HIV infected individuals. A study of 5563 patients initiated on ART Uganda conducted by Mateen et.al (2013) found the prevalence of hypertension to be 27.9%. Furthermore, according to Dimala, Atashili, Mbuagbaw & Wilfred 2016 Continued use of ART has been associated with metabolic complications.

According to the Kenya National guidelines for cardiovascular diseases management, Kenya in its health policy 2014 – 2030 is trying as much as possible to achieve the health needs of its people through all the best health standards means. This is because cardiovascular diseases have led to a negative impact on the social and economic development of our country through loss of our citizens on their reproductive ages which is a threat to our economic growth

1.2 Problem statement

Hypertension is one of the top causes of death worldwide. It's an increasing problem in HIV positive adults on ART whose prevalence is higher compared to HIV negative individuals. (Furrer et al. 2017). The number of individuals on ART globally and in Sub-Saharan Africa has been currently recorded as 21.7 million and 15.4 million people respectively. Due to proper use and utilization of ART, patients have been believed to have a longer lifespan but the major setback has been management of the HIV/AIDS complications associated with the continuous intake of ART.

Among the emerging challenges facing PLWH who are on ART, cardiovascular diseases account for highest number of morbidities and mortalities among these patients. (Fahme, Bloomfield, & Peck 2018). Hypertension alone accounts for Fifty percent of these heart diseases in developed countries and is reported to be higher in HIV- infected individuals than in HIV free individuals (Maya Karem, Tali Wallach, Michael Bursztyn, Shlomo Maayan and Karen Olshtain-pops)

A study done by Gerald and his colleagues in western Kenya found a prevalence of hypertension to be 9.3% among all HIV positive adult patients and this indicates that hypertension is really a threat to this population.

Hypertension among HIV individuals has been associated with the period one has lived with the infection among other risk factors (Thiebaut R, et al.) Although the use of ARV'S has improved

the lives of the victims, some individual drugs in the various ART combinations contributed to increase in blood pressures in some of the patients. How long patients on different regime types combinations can take before he/ she becomes hypertensive has not yet been well established. Despite the fact Sub Saharan Africa having recorded the highest number of HIV victims, there is still lack of adequate data on epidemiology of hypertension among PLWH. therefore, there is a need to conduct more relevant studies concerning this issue in order to get adequate knowledge which will aid in improving, having adequate preparation and hence delivery of appropriate health care for this population (Tipping B, et al.)

1.3 Study Justification

The main goal for anti-retroviral therapy among HIV positive individuals is to suppress the level of HIV virus, restore and preserve immunologic function which makes these patients live long quality life without being challenged by the HIV comorbidities.

The discovery, availability and use of ART among people living with HIV have made them live longer but the rising burden by the non-communicable diseases (NCD's) has been a challenge with hypertension (HTN) being one of the most highly reported comorbidity among this population. According to the new WHO/National guideline of testing and treating, a large percentage of patients are being put on treatment as soon as they are tested positive hence exposing the patients to this risk of developing NCD's. This has resulted to a rise in the total of patients being detected to have elevated blood pressures over time at different Comprehensive care Centre's in the country and no clear study that has been done to establish how long majority of these patients started on ART take before they develop hypertension and no clear study has been done to uncover the factors that may contribute to some patients developing hypertension earlier than other patients regardless of being put under same management and treatment.

This study sought to estimate the time patients initiated on first line ART take to develop hypertension by determining the probabilities of becoming hypertensive at different time periods and the median time from the time one is initiated to ART treatment until one is confirmed in the clinic to be hypertensive in a 3 months' time interval between January 2013 to December 2018 and the associated factors as the highest risk factor to heart disorders among patients taking ART at KNH – CCC. The findings will therefore assist policy makers in addressing the challenges of awareness, treatment and control of noncommunicable diseases including hypertension that are becoming a burden to clients being started on ART and assist in preparation and delivery of good health care for this population as well as to generate evidence for future research regarding the subject.

1.3.1 Study questions

1. What are the probabilities of developing hypertension at different time periods by patients on first line anti-retroviral therapy at Kenyatta National Hospital comprehensive care Centre?
2. How do survival functions of hypertension development time vary among different anti-retroviral therapy combinations?
3. What are the factors associated with time to development of hypertension among patients on first line anti-retroviral therapy?

1.4 Broad objective

To model time to hypertension development and the associated factors among HIV patients initiated on first line anti-retroviral therapy at Kenyatta National Hospital, comprehensive care Centre between 2013 to 2018

1.5 Specific objectives

1) To determine probabilities to hypertension development time for patients initiated on first line anti-retroviral therapy at KNH- CCC.

2) To compare time to development of hypertension among HIV patients initiated on different first line ART regime combinations at KNH- CCC.

3) To determine factors associated with time to hypertension development among patients on first line ART at KNH-CCC

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 HIV epidemiology

HIV has been a major global pandemic problem since its discovery in the past several years. At the end of 2017, 36.7 million individuals globally were infected with HIV with 1.8 million individuals recently infected and among them 21.7 million people were receiving anti-retroviral drugs Since its beginning up to date, 77.3 million people have been victims of HIV virus and about 35.4 victims have succumbed to AIDS complications. (WHO fact sheet)

In sub-Saharan Africa, the epidemic is highly spread accounting for more than 70% of the infection globally with an estimated 28.5 million people having the virus with east and south Africa being the most affected countries. Although the epidemic has been getting severe day after day, there is marked improvements that has been made towards meeting the UNAIDS 2020, 90-90-90 target.

At the end of 2018, Kenya accounted for 1.6 million infected individuals and a total of 36000 deaths from HIV/AIDS opportunistic infections and comorbidities. Currently, almost one million Kenyans are on ART and the overally the prevalence of HIV has decreased to 4.8%. According to the National Aids control council, Homabay County has reported the highest prevalence of the infection 25.7% with Wajir County having the least infection rates (0.2%).

2.2 HIV management

Proper management of HIV patients involves correct administration of ARV'S to the patients, prevention of HIV opportunistic infections and managing them if they occur, ensuring a balanced nutrition is taken by the patient and proper counseling sessions offered. HIV infection has no cure but use of anti-retroviral (ART) drugs assists in controlling multiplication of the virus hence

reducing the probability of transmission which enables the affected people together with their partners and people around them live longer and healthy. WHO recommends use of ART throughout the life for all HIV/AIDS victims regardless of CD4, clinical stage of disease including pregnant and breast feeding women. Before initiating the treatment to every patient, the health care provider should ensure the patient is willing and ready to comply to the treatment. (Gunthard HF, Aberg JA, Enron JJ et al.) The continued use of combination of different anti-retroviral drugs helps in suppressing the viral load and maintaining the functions of the immune system and preventing opportunistic infections which are major causes of death among these patients. (HIV/AIDS WHO fact sheet).

Despite the benefits of these ART drugs, it has been realized that many non-communicable diseases like hypertension has emerged as a result of day to day use of the drugs. These diseases have brought challenges in managing the HIV patients.

In management of HIV, there are different classes of HIV treatment drugs which have different targets to the virus and in any given time a patient is put on a combination of three drugs and is further grouped into three lines of treatment.

Table 1: Categories of ART treatment

Category	**Mode of action**
Protease inhibitors	Act by targeting protease protein which is an HIV protein
Nucleoside reverse transcriptase inhibitors (NRT's)	Act by targeting a protein called reverse transcriptase
Non- nucleoside reverse transcriptase inhibitors (NNRTI's)	Targets reverse transcriptase protein too
Intergrase inhibitors (INI)	Targets HIV protein known as integrase and stop the HIV virus from binding into human cell DNA
Entry inhibitors	Stops the HIV virus from entering into the human cell

2.3 Pathophysiology of hypertension in HIV ART treatment

Hypertension is a condition in which blood pressure is highly raised with a systolic blood pressure of ≥140mm/Hg and a diastolic blood pressure of ≥ 90mm/Hg (WHO international society of hypertension). The challenge of human immune deficiency virus (HIV) resulting to the continuous use of anti-retroviral therapy drugs, has contributed to high risk of developing cardiovascular disease (CVD) with hypertension occupying a prominent position. (NL Okeke 2016). The pathophysiology of hypertension in HIV has been assessed by various studies and main factors linked to it include chronic inflammation, suppression of immunity and reconstitution, lipodystrophy and renal related disease. (Sasha A. Fahme, Geralds. Bloomfield and Robert peck)

The Occurrence of hypertension in HIV patients is due to various pathogenic mechanisms in the body. (Diseases $ health, n.d). Several studies done have found that endothelial dysfunction, insulin resistance and atherosclerosis to be associated with protease inhibitors and both HIV infection and the ARV's have a negative effect on the functioning of the heart (Michael P. Dube et al)

2.4 Current state of hypertension in HIV

According to WHO, an estimated 1.13 billion people worldwide have been reported to have hypertension. Among them, HIV infected individuals on ART have been realized to have a higher prevalence of hypertension when compared to the non-infected ones. A recent meta-analysis data globally found that 35% of HIV infected individuals on ART have hypertension compared to a 30% of HIV un infected persons. A study by Brenan et al 2018 puts the prevalence of hypertension among these HIV patients on treatment at 5% to 55% in high income and 9% to 46% in low- and middle-income countries.

In sub–Saharan Africa, the burden of hypertension has currently become a widespread problem where HIV prevalence is the highest in the world. It is projected that the number of individuals generally in sub–Saharan Africa to be affected by 2025 to be 74.7 million.

In Kenya, also the prevalence of hypertension also has been reported to have been rising in the last 20 years (KDHS- 2016). A study by Joshua Nyagol et.al 2015 in Kenya found the prevalence of HTN among HIV individuals to be 23.2%.

2.5 Application of Survival Analysis in modeling hypertension development among patients on ART

Survival analysis is a field in statistics used to analyze time to event data. Time to event data refers to data generated in studies where the measure of interest is the amount of time to occurrence of a particular outcome of interest (Wienke, 2010). The event of interest is usually referred to death. However, in survival analysis, this can mean recurrence of symptoms, death or even remission. Survival time refers to the time until the event of interest is observed from a defined starting time point (Crowder, 2008). One of the advantages of this method is its ability to take into account the time.

The effect of different HIV drugs on blood pressure has been realized by several studies. Some of the studies indicate that the combination of a protease inhibitor drug to a nucleoside reverse transcriptase inhibitor drugs may lead to higher incidence of hypertension. Researchers in the past have used various methods to identify factors associated with hypertension on patients on ART treatment. Peck et al. (2015). for instance conducted a study on the prevalence of hypertension on ART patients in Tanzania and found that patients on ART for duration greater than one year had a higher probability of developing hypertension.

Another study by Massimo Galli et al. consisting of 655 patients followed up for hypertension development after initiation to ART indicated a median time of developing hypertension to be 86 weeks. Different ART regimes have been reported of having this negative impact in patient's blood pressures. Protease inhibitors have been reported to have the highest impact although non-nucleoside reverse transcriptase and nucleoside reverse transcriptase have also been associated with incidences of hypertension (Thiebaut R et al.)

More studies have explored on the issue of hypertension prevalence and its associated factors but only few have focused on the duration patients may take before they become hypertensive and the likelihood of the same among patients put on different ART regime combinations. Therefore, there is still need for gathering more evidence on how long after initiation to ART most patients may take before they are confirmed to be hypertensive and also to be able to ascertain the safer regime type combination for our patients.

2.6 Factors associated with hypertension in HIV patients on ART

Well known risk factors like increased age, male gender higher BMI, obesity, chronic kidney disease and dyslipidemia have been linked to hypertension in both HIV negative and positive persons.

A study done in South Africa by Alana T. Brennan et al. on determining the prevalence and incidence of hypertension among HIV positive adults on ART in public clinic found that 13% of individuals with normal BP when started on treatment, developed hypertension while on ART. This was noted to be more common on patients with ≥ 40 years of age and with BMI ≥ 25 Kg/m^2. Male patients had higher hazard of hypertension over the follow up period and patients on Nevirapine based regime had 27% increased risk of developing hypertension compared to those on efavirenz based regime.

Another study done in rural Tanzania by Eduardo Rodriguez – Arboli at al. on incidence and risk factors for hypertension among HIV patients showed that age, Body mass index and estimated glomerular filtration rate were also risk factors for hypertension on these patients. Therefore, the relation between hypertension and HIV infection and use of ART is still a subject of interest.**2.5**

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study site

The study was carried out at Kenyatta National Hospital comprehensive care Centre clinic in Nairobi which is an HIV clinic whose clientele is from rural and urban populations and opens from Monday to Friday. Patients who attend the clinic for the services are registered and proper clinical care, nursing care and psychosocial services are given to the patients. Also nutritional and physiotherapy services are offered when necessary. Then lifetime follow up of patients is ensured. By the end of 2018, the clinic had registered a total of 9915 active patients on follow up with 9063 adults (≥ 20 years) and 362 young adults (15- 19 years). Among these patients, 8262 adults were on first line ART and 284 young adults as well.

3.2 Study design

It involved use of a retrospective cohort study design to investigate factors associated with development of hypertension among HIV patients enrolled on first line ART at KNH-CCC

The outcome of interest was time a patient on ART took to develop hypertension. Legible patients were enrolled and followed up from 1st January 2013 up to 31st December 2018.

3.3 Study population

The study involved HIV/AIDS positive patients aged 15 years and above who were started on first line ART between January 2013 to December 2018, All patients enrolled to the study met the inclusion criteria.

3.3.1 Inclusion criteria

Participants were all confirmed HIV positive patients aged 15 years and above, for patients below 18 years, consent and assent was sought from parents / guardians. All participants were

also confirmed non-hypertensive during initiation on ART and had been initiated on ART treatment between 1st January 2013 and 31st December 2018.

3.3.2 Exclusion criteria

Patients who were below 15 years, those below 18 years whose consent / assent was not sought from parents/ guardians, patients who were confirmed hypertensive during enrollment and those transferred into the clinic while already on ART treatment were excluded from the study.

3.4 Sample size determination

The main outcome for this study was time to hypertension development. The sample size for this study was determined using the formula for comparing the hazard ratio by Collett (2004) and Shao, Chow and Wang (2003);

$$n = \frac{1}{P_A P_B P_E} * \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\ln(HR)}\right)^2$$

$$HR = \frac{\ln(1-P_1)}{\ln(1-P_2)}$$

$$P_E = {}^{(P_1 + P_2)}/_{2}$$

Where;

HR- the hazard ratio (expected HR ratio= 1.40)

P_A- Proportion allocated to group of male HIV positive patients (0.5)

P_B- Proportion allocated to group of Female HIV positive patients (0.5)

P_B- Overall probability of hypertension in the population

P1= probability of hypertension development among male HIV positive patients on ART (0.82 based on a study by Eduardo Rodriguez et.al)

P2- probability of hypertension development among female HIV patients on ART (0.18 based on study by Eduardo Rodriguez et al.)

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

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

n= Total sample size

Based on the parameter defined above and the sample size formula, the minimum sample size for the study was n= 904

3.5 Sampling procedure

The prevalence for hypertension varies differently among HIV positive male and female individuals on ART. To ensure that a representative sample was attained, a stratified random sampling technique was employed. Sampling population was all HIV positive patients aged 15 years and above initiated on first line ART between 2013 and 2018 which formed the sampling frame. Stratification was then done by gender then a simple random sampling method with equal allocation was applied. Within each stratum, the individual units were numbered then random numbers were generated using STATA statistical package to help in selecting the participants. Patients were then followed up for hypertension development starting from 1st January 2013 to 31st December 2018.

3.6 Variables

3.6.1 Dependent variable

The outcome variable was time to hypertension development in HIV victims on first line anti-retroviral therapy. Hypertension was diagnosed when a systolic blood pressure measurement was (SBP) ≥ 140 mm/ Hg and a diastolic blood pressure measurement of (DBP) ≥ 90 mm/ Hg. (Handler J, et al.)

3.6.2 Independent variables

Age: Was a continuous variable of patients aged 15 years and above.

Gender: Categorized in to two (male and female)

BMI: Was categorized in to four (underweight, normal weight, overweight and obese) according to WHO classification.

Renal failure status: Was denoted as present or absent.

Diabetes status: Categorized as whether positive or negative.

ART regime type: Was in to two groups Nevirapine based and Efavirenz based.

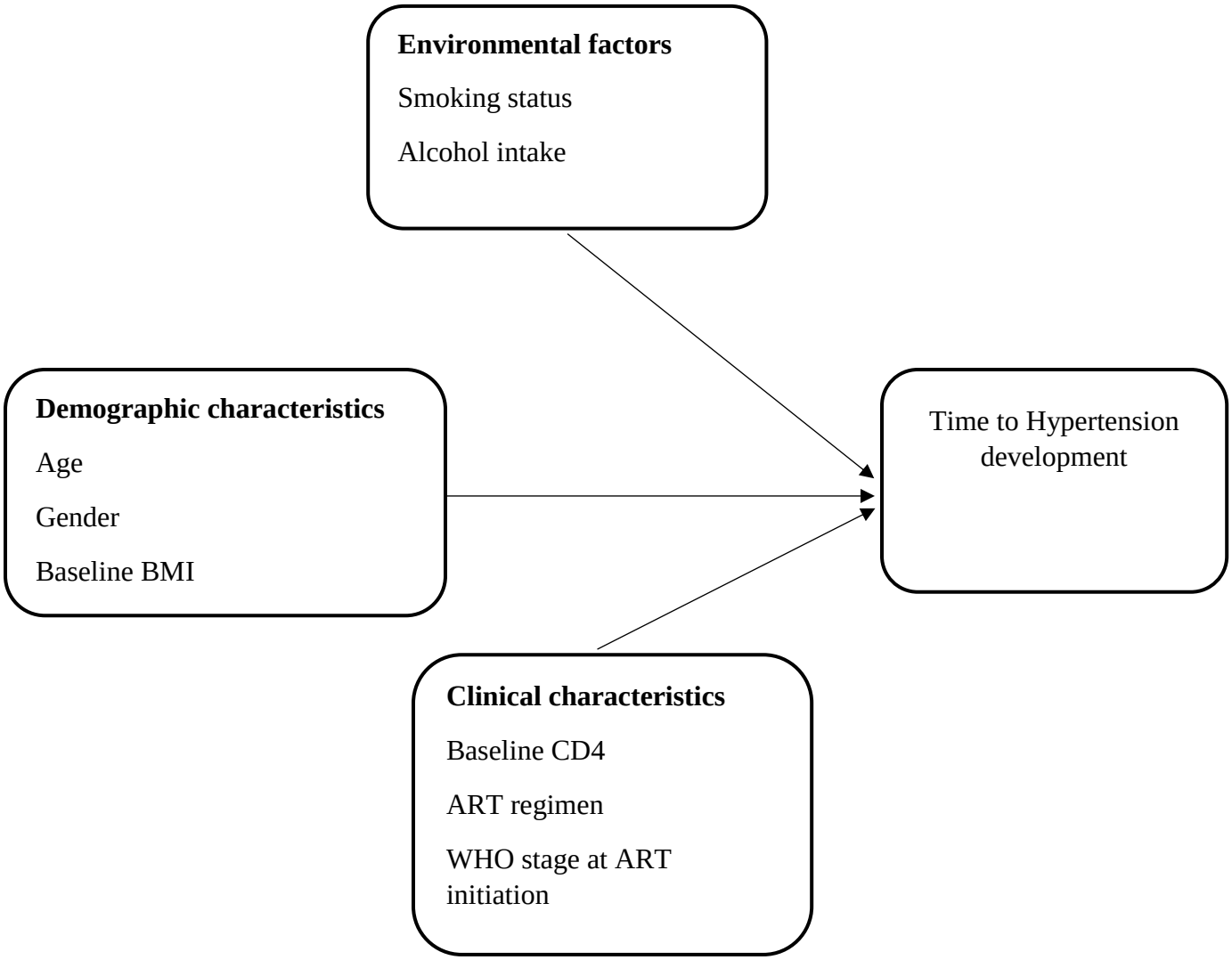
Baseline CD4 Count: Was a categorical variable with 4 categories (< 100, 100-250, 250-350 and above 350)

WHO stage at ART initiation: Comprised of four stages (Stage1, stage2, stage3 and stage4)

Smoking status and Alcohol intake: Categorized as either yes or no

Conceptual frame work

Figure 1: Conceptual framework



3.7 Data collection procedures

Baseline clinical, pharmaceutical, laboratory and hypertension status data of every study participant was retrieved from the KNH-CCC electronic medical records (IQ-CARE) first during recruitment to the study. Then each patient was followed up from the time he/she was started on ART treatment until he/she developed hypertension in a three-month time interval (every visit to clinic) until the end of the study period. Patients were censored in case of loss to follow up, death or end of the study. The retrieval of the entire patient's information was done through a query that was run from IQCARE data extraction tool and then stored in a Microsoft Excel data base. This was done with the aid of personnel from the medical records at KNH- CCC with the authority from the head of KNH Comprehensive care Centre.

The system consists of all data from different departments of each patient monitored in each visit to the clinic from time the patient is registered in the clinic up to the current status.

3.8 Data management and analysis

Data was imported and stored to MS excel where cleaning and coding was done. Analysis was done using STATA software version 20. Histograms were done to show distribution of continuous variables. Bar charts and tables were used to demonstrate the distribution, frequencies and proportions of categorical variables.

Kaplan Meier method was used to estimate the hypertension development function in all patients receiving first line ART aged 15 years and above at a quarterly time interval (3 months' interval)

Log rank tests were used to compare hypertension development functions or probabilities by Gender, ART regime type and BMI. The chi square statistic together with the corresponding p. value was reported.

Cox proportional hazard regression model was fitted to determine the effect of the patient's baseline characteristics on the risk of developing hypertension at the next time. The P.values, hazard ratios and 95% confidence intervals was reported for all the risk factors.

Cox proportional Hazard model

$$\boldsymbol{h_1(t) = h_0(t) * e^{(\beta 1 X1 + \beta 2 X2 \ldots\ldots\ldots + \beta 9 X9)}}$$

Where;

$h_{1(t)}$ = Hazard rate for patient 1 at time t

$\boldsymbol{h_0(t)}$ = Baseline Hazard rate at time t

$\boldsymbol{X_1 X_2 \ldots\ldots X_9}$ Are Prognostic factors/Covariates

$\boldsymbol{B_1, B_2, \ldots\ B9}$ are Coefficients representing the effect of each covariate

3.8.1 Ethical considerations

Ethical approval was sought from the University of Nairobi / Kenyatta National Hospital ethics research committee through submission of the proposal. Permission was also sought from the Kenyatta National hospital comprehensive care Centre management health system and head of the unit from which the data was drawn. To ensure confidentiality, data was encrypted and stored in a password protected computer and a backup copy stored in an external hard drive that was kept in a lockable cabinet. The study data was only accessed by the study personnel. Change of identifiers was done before analysis.

3.9 Study Limitations

The main setback in this study was failure of clinic attendance of some of the patients at the exact due dates given by the clinicians and some missing observations from some of the patients. To address this, analysis was done based on patients with complete recorded data.

CHAPTER FOUR

4.0 RESULTS

A total of 904 patients were randomly sampled from the database of all patients enrolled into first line ART between 2013 and 2018. The primary outcome of interest was hypertension development time. The median follow-up time was 23 months (IQR: 23-30 months), with a minimum of 1 month and a maximum of 54 months. Sociodemograpic and clinical characteristics of the patients are presented first. Thereafter, the failure functions of the patients are compared by key predictor variables. Finally, the determinats of time to hypertension development are presented.

4.1 Socio-demographic characteristics of patients in the study

The distribution of patient's age was right-skewed. The median age was 41.9 years (IQR: 34.9-50.3 years), implying that the majority were generally of middle-age. The youngest was 15.0 years while the eldest was 88.9 years. See figure 1.

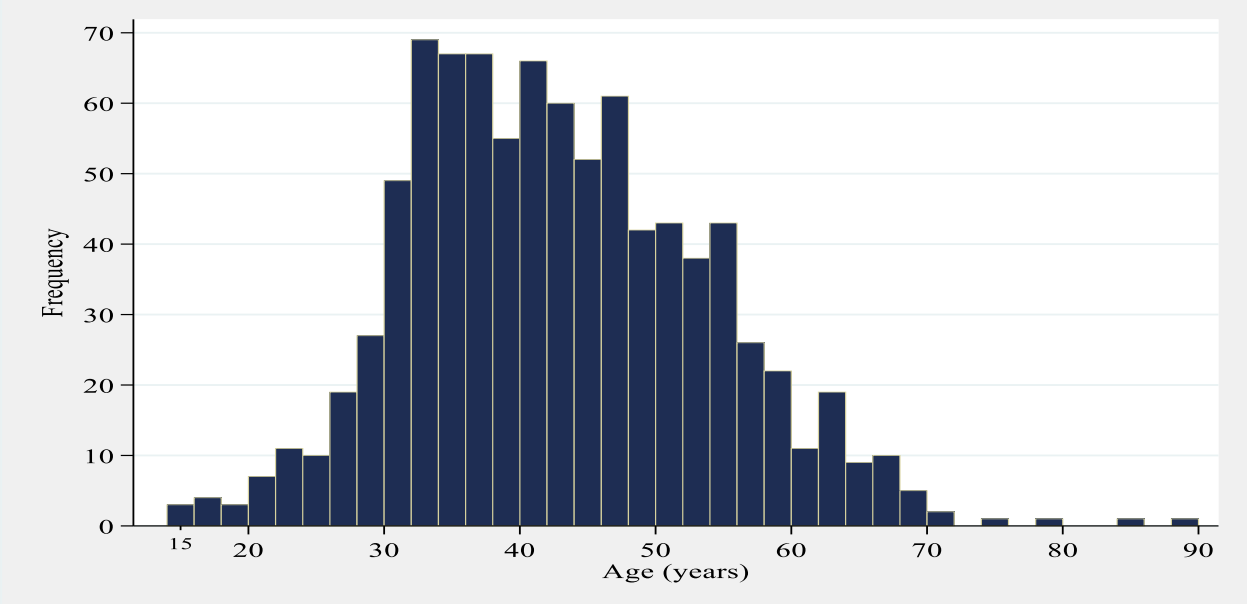


Figure 2: Distribution of patients' age in years

Socio-demographic characteristics are presented in Table 1. There were about as many females (49.0%) as there were males. Half (50.3%) of the patients in the study were aged between 30 and 44 years. More than half (52.7%) were overweight while about one-tenth (11.4%) were obese. Smoking (9.0%) and alcohol consumption (12.1%) were not common among the patients in the study.

Table 2: Socio-demographic information of patients (N=904)

Variable	Category	Frequency	Percent
Gender	Female	443	49.0
	Male	461	51.0
Age group	<30 years	84	9.3
	30 to 44 years	455	50.3
	≥45 years	365	40.4
BMI	Underweight	102	11.3
	Normal	476	52.7
	Overweight	223	24.7
	Obese	103	11.4
Alcohol use	No	795	87.9
	Yes	109	12.1
Smoking status	No	823	91.0
	Yes	81	9.0

4.2 Clinical profile of patients in the study

The distribution of baseline CD4 count was right-skewed as shown in Figure 2. The least count was 2 cells/ml while the most was 2076 cells/ml. The median cell count was 194 cells/ml (IQR: 94-324 cells/ml) and 90% of the patients had CD4 count of less than 456 cells/ml.

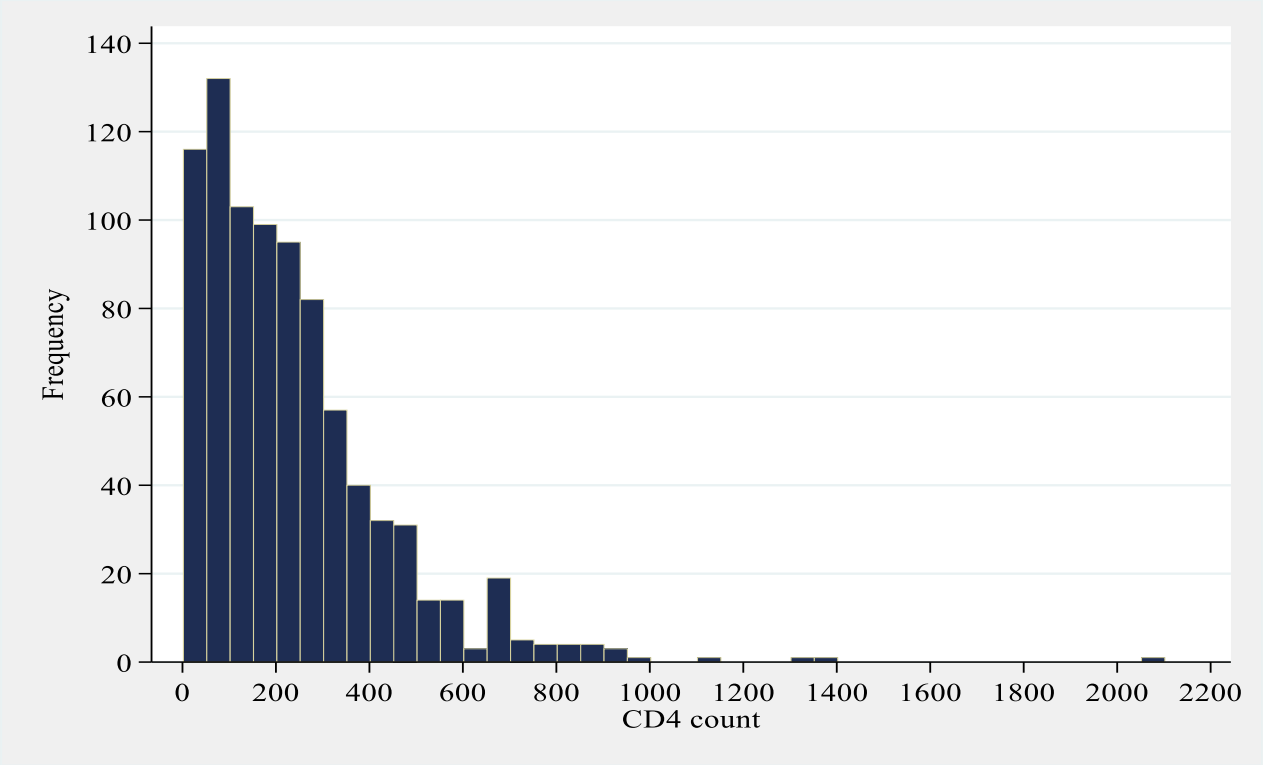


Figure 3: Distribution of baseline CD4 count (cells/ml)

Based on the WHO guidelines on HIV staging, nearly half (45.1%) of the patients were enrolled at stage 1, while just over one-tenth (12.9%) were enrolled at stage 4. Also at enrolment, about two-thirds (63.0%) had CD4 count of 250 cells/ml and below. More than three-quarters (82.3%) of the study population were initiated into efavirenz regimen. Diabetes (8.9%) and renal failure (1.9%) were uncommon among patients at baseline. See Table 2 for more details.

Table 3: Baseline clinical profile of patients

Variable	Category	Freq.	Percent
Baseline HIV stage (WHO)	Stage 1	408	45.1
	Stage 2	195	21.6
	Stage 3	184	20.4
	Stage 4	117	12.9
Baseline CD4 count (cells/ml)	<100	253	28.0
	100-250	316	35.0
	250-300	147	16.2
	>350	188	20.8
Initiated ART regimen (general)	Nevirapine (NVP)	160	17.7
	Efavirenz (EFV)	744	82.3
Initiated ART regimen(specific)	ABC+3TC+EFV	20	2.2
	ABC+3TC+NVP	13	1.4
	AZT+3TC+EFV	60	6.6
	AZT+3TC+NVP	72	8.0
	TDF+3TC+EFV	664	73.5
	TDF+3TC+NVP	75	8.3
Has diabetes at baseline	No	824	91.2
	Yes	80	8.9
Has renal failure at baseline	No	887	98.1
	Yes	17	1.9

4.3 Estimation of failure time (time to development of hypertension) among first line ART patients

Estimation of time to development of hypertension of patients was done using Kaplan-Meier curve. Through visual inspection of Figure 3, the failure fucntion rose steadily from diagnosis time (time=0) to 39 months after which it rose sharply until the end of follow-up time (54 months). At 39 months of follow-up, the probability of failure (hypertension development) was

50%. The confidence interval progressively becomes wide since the number of patients at risk decreases with time leading to more and more unstable estimates.

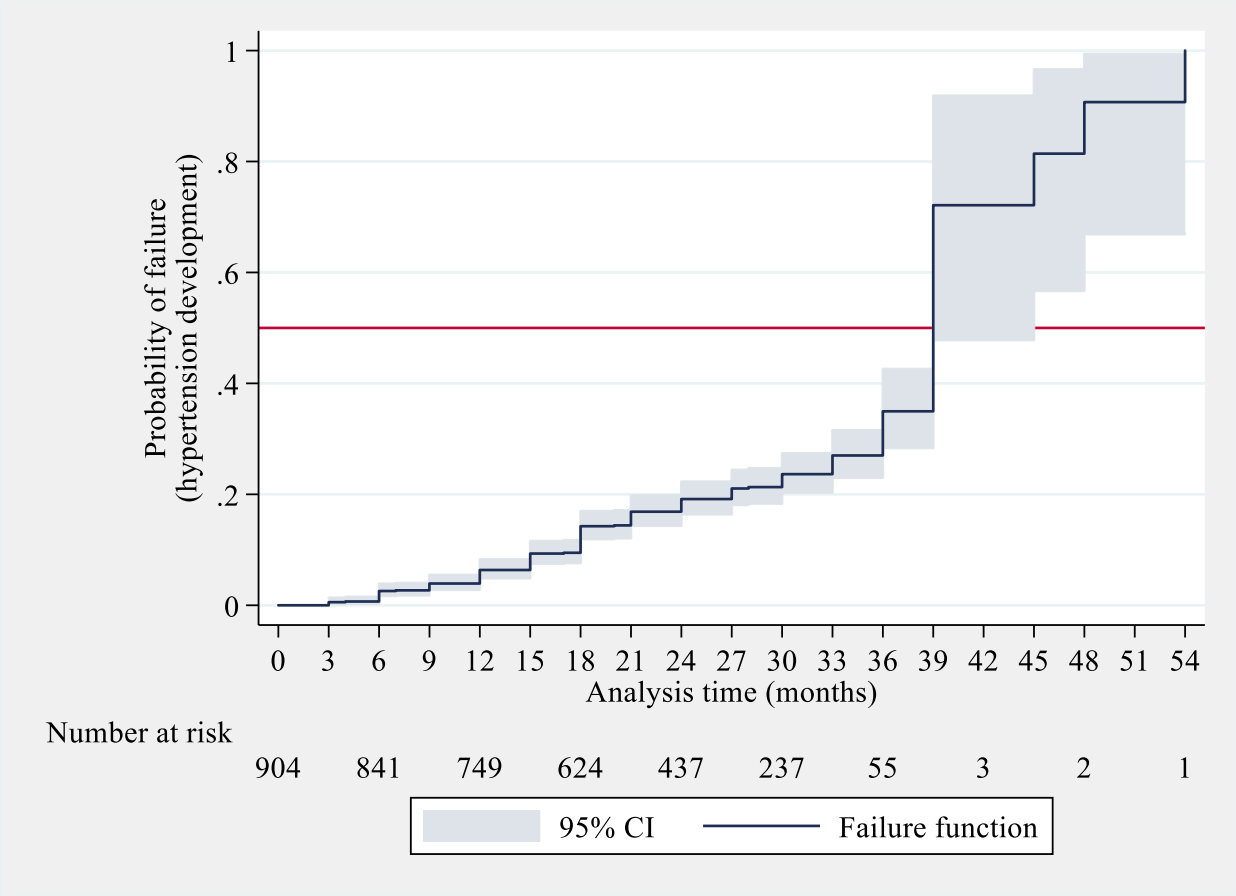


Figure 4: Estimation of failure time of patients- overall

Curves were also plotted by ART regimen type (Figure 4) and by gender (Figure 5). Failure was defined as hypertension development. Regarding ART regimen type, patients in the boths groups seemed to have similar failure functions since their failure curves ran close to each other most of the time and their confidence intervals overlapped for most of the follow-up time (Figure 4). This observation was augmented by the result of the statistical test of the significance of the difference in the survival experience, which revealed no significant difference (P=0.135). There

was a 50% probality of failure (developing hypertension) at 39 months for those under EFV and at 54 months for those under NVP (golden line).

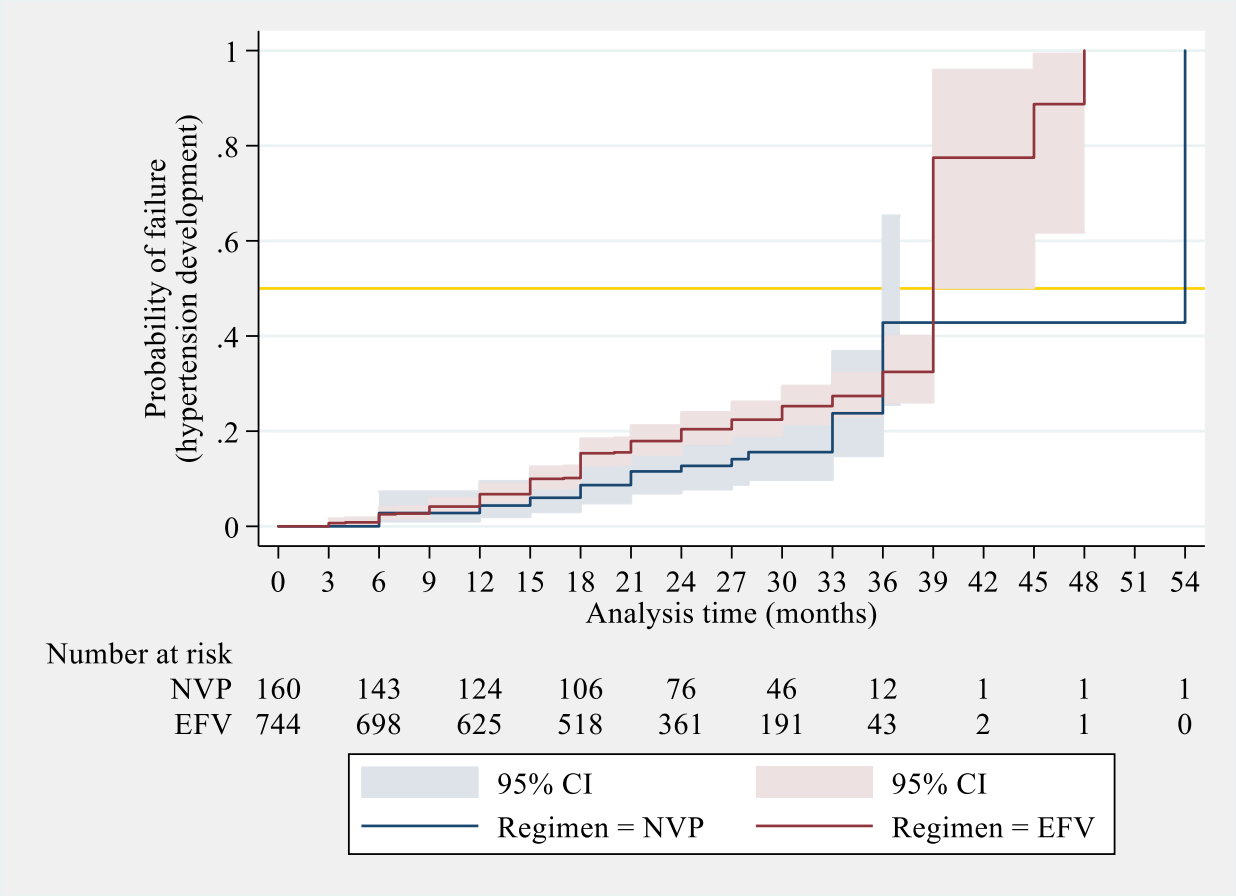


Figure 5: Estimation of failure time by ART regimen

Patients grouped by gender appeared to have similar failure functions as shown by curves with overlapping confidence intervals. For males, the curve rose gradually up to 30 months while that of females was gradual up to 36 months after which both curves rose drastically. At 39 months, there was a 50% probability of failure for both males and females (golden line). There was no significant difference in the failure functions of the two groups at 5% significance level (P=0.087). See Figure 5.

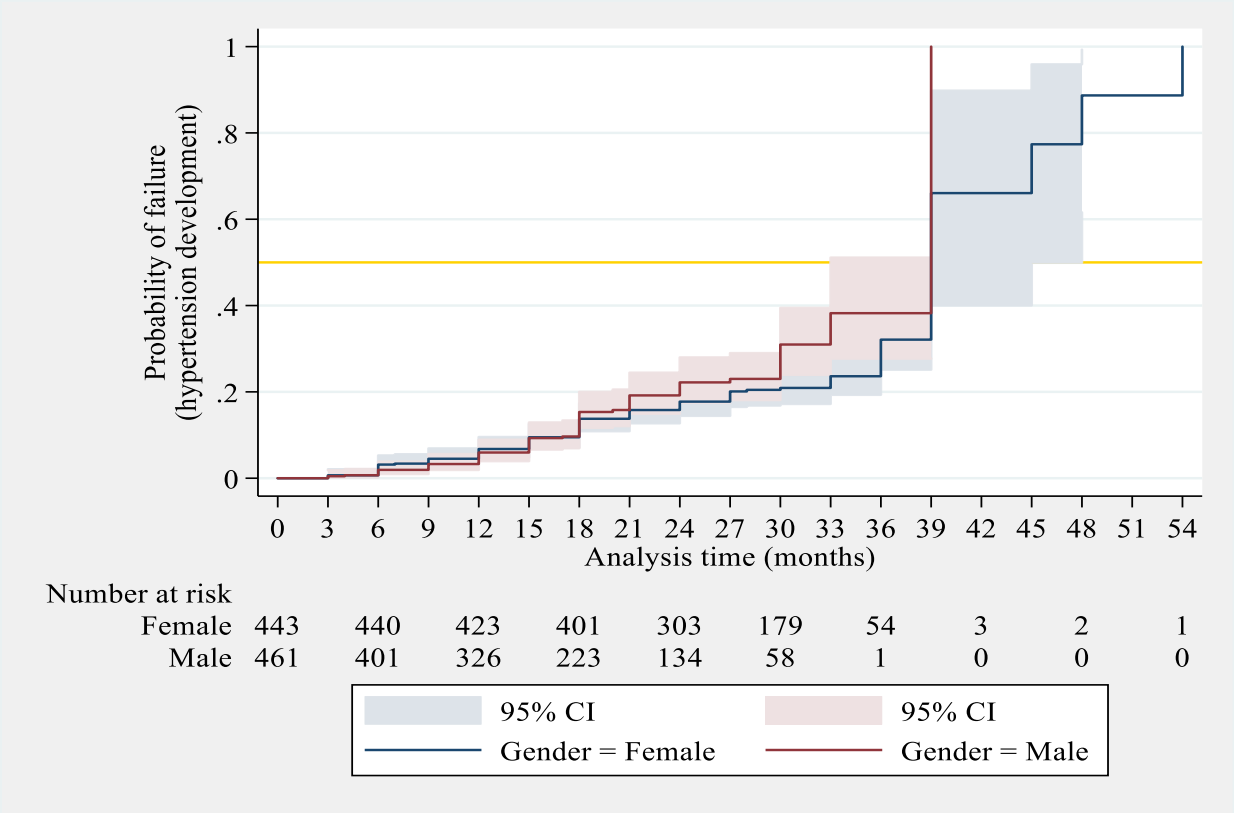


Figure 6: Estimation of failure time by gender

Log-rank test was used to compare the failure functions of patients by key factors at 5% level of significance (Table 3). Failure functions of patients differed significantly by age group (P<0.001), by BMI (P<0.001), by diabetes status at enrollment (P<0.001), by smoking status (P<0.001) and by alcohol intake behavior (P<0.001). See Table 3 for more details.

Table 4: Comparison of hypertension development functions

Variable	Observed events	Log rank test Chi^2	P-value
ART regimen			
NVP	24	2.2	0.135
EFV	148		
Gender			
Female	102	2.9	0.087
Male	170		
Age group			
<30 years	1	108.2	**<0.001**
30-44 years	35		
≥45 years	136		
HIV stage			
Stage 1	69	3.2	0.362
Stage 2	40		
Stage 3	37		
Stage 4	26		
Baseline CD4			
<100	53	3.0	0.400
100-250	62		
250-350	28		
>350	29		
BMI			
Underweight	10	42.9	**<0.001**
Normal	78		
Overweight	40		
Obese	44		
Diabetes			
No	144	11.4	**<0.001**
Yes	28		
Renal failure			
No	169	0.2	0.66
Yes	3		
Smoking			
No	141	29.4	**<0.001**
Yes	31		
Alcohol			
No	135	22.7	**<0.001**
Yes	37		

Note: P-values in bold are significant at 5% level of significance.

4.4 Determinants of time to hypertension development among first line ART patients

Cox proportional hazards regression model was used in assessment of determinants hypertension development time i.e. the adjusted effect of the patients 'characteristics on the time to development of hypertension. Patient's age, BMI and smoking behavior were significant predictors of time to development of hypertension at 5% significance level.

Adjusting for other predictors in the model, for every additional year in a patients age, there is 8% increase in the hazard of hypertension development (HR=1.08; 95% CI: 1.06-1.09). This implies that older patients had a higher risk of hypertension development. Controlling for the effects of other factors in the model, obese patients had 71% higher hazard of hypertension development compared to the normal weight patients (HR=1.71; 95% CI: 1.13-2.59). In other words, obese patients were more susceptible to hypertension than normal weight patients. A smoking patient had 2.33 times higher hazard of hypertension development compared to a non-smoking patient (HR=2.33; 95% CI: 1.47-3.71) after adjusting for other predictors in the model. This means that smoking patients were more likely to get hypertension than non-smoking patients. See Table 4 for more details.

Table 5: Factors associated with hypertension development - Cox proportional regression

Variable	Hazard Ratio	P-value	95% Confidence Interval
Regimen type			
Nevirapine (NVP)	Ref.		
Efavirenz (EFV)	1.22	0.393	0.77 - 1.92
Age (years)	1.08	**<0.001**	1.06 - 1.09
Gender			
Female	Ref.		
Male	1.10	0.582	0.79 - 1.51
HIV stage (WHO)			
Stage 1	Ref.		
Stage 2	1.23	0.315	0.82 - 1.86
Stage 3	1.05	0.823	0.68 - 1.63
Stage 4	0.70	0.201	0.41 - 1.21
Baseline CD4 count			
<100	Ref.		
100-250	0.82	0.339	0.54 - 1.24
250-349	1.06	0.820	0.63 - 1.78
>350	0.90	0.686	0.53 - 1.51
BMI			
Normal	Ref.		
Underweight	0.67	0.246	0.34 – 1.32
Overweight	1.02	0.915	0.69 – 1.51
Obese	1.71	**0.011**	1.13 – 2.59
Smoking			
No	Ref.		
Yes	2.33	**<0.001**	1.47 - 3.71
Use Alcohol			
No	Ref.		
Yes	1.19	0.440	0.76 - 1.87
Has diabetes			
No	Ref.		
Yes	1.18	0.462	0.75 - 1.86

Note: Ref. – Reference group

CHAPTER FIVE

5.0 DISCUSSION

It is now well known that use of anti-retro viral drugs boosts the immunity of HIV/AIDS positive patients despite of the different reactions and side effects they also manifest to the patient's body after use. (Jobert Richie N Nansseur et al).

The main goal towards this study was to evaluate what determinants influence the time a patient receiving care at Kenyatta national hospital comprehensive care Centre take to have high blood pressure. The study assessed how baseline characteristics i.e (Age, Gender, regimen type, BMI, HIV stage, renal status, diabetes status, smoking and alcohol intake) will have an effect on the patient's risk of developing hypertension using the Cox proportional hazards model. Some of well recognized risk factors to majority of heart disorders such as Age, BMI, and cigarette smoking were found to have a significant association with the time patients took to develop hypertension. The median time to failure in the whole population was estimated at 39 months in which was almost similar to a similar study conducted in Tanzania which indicated a median time of 36 months (Eduardo Rodriguez Arboli et al).

Increased BMI readings were noted to have an association with higher risks of developing hypertension in which was in support with a study done in the western part of the country (Chepchirchir et al) and other studies elsewhere (Eduardo Rodriguez Arboli et al) showing that HIV positive victims and on ART categorized as overweight and obese had higher risk of having high blood pressures just like normal HIV negative population with high BMI. This therefore suggests that it is important for all health care workers to do mandatory screening to these patients together with close and frequent monitoring as well as offering knowledge to them

mainly on life style modification majorly on diet and adequate exercise as the basis of healthy living.

Although most of the few studies that have been conducted on ART use and its effects in increasing blood pressures have noted a positive association, the exposure to ART has been found to have minimal effect on blood pressure in a large South African population-based survey although failure to adjust for immunological status, disease stage and duration of treatment may support these findings. (Abraham malaza et al) In this study, baseline CD4 count and baseline stage of the disease of the patients were not found to have any significant association with development of hypertension.

Majority of the patients were initiated on Efavirenz based regimen (82.3%) whereas the remaining 17.7% where on Nevirapine based regimen. Nevertheless, none of the regimens was found to significantly be associated with failure time in this study although in a similar study done in Cameroon founds that the odds of hypertension to be higher on patients put on efavirenz based regimen compared to the Nevirapine regimen. (Pepanze jill pangmekeh et al).

The high risk of hypertension detected among older HIV patients on ART in this study is also in agreement with previous study in the country (Chepchirchir et al) and therefore it's a clear indication that older patients should be keenly monitored and screened of hypertension frequently together with guidelines on their lifestyles though this should apply to the other patients as well. This study also didn't find a significant association between baseline diabetes status, gender and baseline renal insufficiency with increased odds of developing hypertension contrary to other similar studies (Eduardo Rodriguez et al).

Clinically majority of the patients (45%) initiated on ART at the facility were in WHO stage 1, This indicates that there is an improvement on awareness among people on their HIV and

majority tend to seek treatment on early stage of the disease hence preventing the severe effects of the opportunistic infections. However, the clinical staging of the disease was not significantly associated to the hypertension development risks

5.1 CONCLUSION AND RECOMMENDATIONS

The study found that the patient's age, regimen type (efavirenz/ Nevirapine), BMI of the patient and smoking status had a significant association with the time to hypertension development.50% of the patients were noted to start failing after 39 months from the time of initiation of the treatment. Patients on Nevirapine base regimen took longer time before they started failing compared to those on efavirenz based regimen. There is a need to alert healthcare workers attending to HIV patients to embark on continued frequent screening and monitoring of these patients on their blood pressure as well as offering adequate advice to the patients on the importance of proper nutrition and lifestyle in routine HIV care. There is also a need to conduct more studies to detect the association between each individual ARV drug and the risk of developing hypertension in order to come up with the conclusion on the safest ART drug to use on our patients with minimal side effects.

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APPENDIX III: DATA COLLECTION TOOL

Demographic characteristics

1. Questionnaire no ----------

2. Age in years----------

3. Sex Male ☐ Female ☐

4. Vital measurements of the client

Weight in kgs ---------- Height in CM---------- BMI----------

5. Marital status

☐ Married

☐ Single

6. Education level

☐ Primary education

☐ Secondary education

☐ College/University

☐ None

6. Religion

☐ Christian

☐ Muslim

☐ Others

7. Employment status

☐ Employed

☐ Not employed

History of treatment

8. Year of being initiated to ART ----------DD/MM/YYYY

9. Duration of first line ART use in months ----------

10. Initial ART regime used

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. Any history of change to another regime

☐ Yes ☐ No

If yes, which regime type ----------

12. WHO stage at enrollment----------

13. Presence of diabetes before ART initiation

☐ Yes ☐ No

14. Presence of renal disease before ART initiation

☐ Yes ☐ No

Medical report of the patient

15. Initial Cd4 count----------

16. Initial BP measurements ----------

17. BP measurements after every 3 months of treatment ----------

Psychosocial history

18. History of defaulting follow up clinic appointment

☐ Yes ☐ No

19. Was treatment initiated in this clinic or elsewhere

☐ Yes ☐ No

20. Any reported history of substance abuse/use

☐ Yes ☐ No

If yes, which one

☐ Smoking ☐ Alcohol

APPENDIX IV: ETHICAL APPROVAL

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6th December , 2019

Jackline Muendo
Reg.No.W62/7446/2017
Institute of Tropical and Infectious Diseases (UNITID)
College of Health Sciences
University of Nairobi

Dear Jackline

RESEARCH PROPOSAL: A SURVIVAL ANALYSIS APPROACH TO MODEL TIME TO HYPERTENSION DEVELOPMENT AND ASSOCIATED FACTORS AMONG PATIENTS ON FIRST LINE ANTI RETROVIRAL THERAPY IN KENYATTA NATIONAL HOSPITAL (P594/07/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 6th December 2019 – 5th December 2020.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

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