

**ELECTROCARDIOGRAPHIC ABNORMALITIES AMONG  
HIV INFECTED ADULTS ATTENDING THE  
COMPREHENSIVE CARE CENTER AT KENYATTA  
NATIONAL HOSPITAL**

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## **DECLARATION**

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## LIST OF ABBREVIATIONS

<b>AIDS:</b>	Acquired immune deficiency syndrome
<b>ART:</b>	Anti-retroviral therapy
<b>BMI:</b>	Body mass index
<b>CCC:</b>	Comprehensive Care Center
<b>CHD:</b>	Coronary heart disease
<b>CI:</b>	Confidence interval
<b>CIMT:</b>	Carotid intima-media thickness
<b>CRP:</b>	C-reactive protein
<b>CVD:</b>	Cardiovascular disease
<b>DAD:</b>	Data collection on adverse events of anti-HIV Drugs
<b>ECG:</b>	Electrocardiography
<b>HAART:</b>	Highly active antiretroviral therapy
<b>HDL:</b>	High-density lipoprotein
<b>HIV:</b>	Human immunodeficiency virus
<b>HOPS:</b>	HIV outpatient study
<b>ICAM:</b>	Intercellular adhesion molecule
<b>KNH:</b>	Kenyatta National Hospital
<b>LBBS:</b>	Left bundle brunch block
<b>LDL:</b>	Low-density lipoprotein
<b>LVH:</b>	Left ventricular hypertrophy
<b>MACS:</b>	Multicenter AIDS Cohort Study
<b>MI:</b>	Myocardial infarction
<b>NNRTI:</b>	Non-nucleoside reverse transcriptase inhibitor
<b>NRTI:</b>	Nucleoside reverse transcriptase inhibitor
<b>OR:</b>	Odd ratio
<b>PAD:</b>	Peripheral arterial disease
<b>PEP:</b>	Post-exposure prophylaxis
<b>PI:</b>	Protease inhibitor
<b>RBBB:</b>	Right bundle brunch block
<b>RHD:</b>	Rheumatic heart disease
<b>SD:</b>	Standard deviation
<b>SMART:</b>	Strategies for Management of Antiretroviral Therapy
<b>TNF:</b>	Tumour necrosis factor
<b>UNAIDS:</b>	Joint United Nations Programme on HIV/AIDS
<b>US:</b>	United States of America
<b>VCAM:</b>	Vascular cell adhesion molecule
<b>WHO:</b>	World health organization
<b>WIHS:</b>	Women's Interagency HIV Study

## ABSTRACT

**Background:** Cardiovascular disease is a growing concern among the HIV infected population. HIV positive individuals have a greater risk of both traditional cardiovascular risk factors and cardiovascular events than non-HIV individuals. Various ECG abnormalities have been shown to be predictor for adverse cardiovascular outcomes. Resting ECG testing can be a convenient tool for cardiovascular screening and risk stratification. There is no data in Kenya on the prevalence and types of ECG abnormalities amongst HIV infected adults.

**Objectives:** The primary objective was to describe the prevalence and types of ECG abnormalities among HIV positive adults attending the Comprehensive Care Center at Kenyatta National Hospital. The secondary objective was to determine the association between the presence of ECG abnormalities and demographic characteristics, selected cardiovascular risk factors (hypertension, diabetes mellitus, smoking, obesity) and HIV related factors (the nadir CD4 cell count and antiretroviral therapy status) of the patients.

**Methodology:** This was a cross sectional study conducted at the Comprehensive Care Center at KNH. Patients meeting the inclusion criteria and giving written consent were enrolled in the study. A resting 12 lead ECG was recorded for each patient by standard procedure. The ECGs were interpreted as per the *AHA/ACC recommendations for the standardization and interpretation of the electrocardiogram*.

**Results:** 200 participants were included. Mean age was 44 years, 69.5% were female. Mean duration of HIV infection was 101 months (SD 68.3). 99% were on HAART and 12.7% on second line HAART. Mean nadir CD4 cell count was 283.7 (SD 239.8). Mean BMI was 26.3 (SD 5.6). Hypertension and type 2 diabetes were present in 20% and 2.5% respectively. An abnormal ECG was found in 68 (34%) participants. Arrhythmias were seen in 37 participants, T wave abnormalities in 15 participants, LVH and QTc prolongation were both present in 7 participants. Conduction abnormalities were seen in 9 participants. ST segment abnormalities and pathological Q waves were observed in 3 and 2 participants respectively. There was no association between any demographic and HIV factors with any ECG abnormality.

**Conclusion:** One in 3 HIV participants had at least one ECG abnormality. Minor abnormalities had the highest prevalence. Clinical significance of these ECG abnormalities among our HIV population still needs to be established.



## INTRODUCTION

Sub-Saharan Africa carries a huge burden of HIV infection (1) . Kenya has the fourth largest epidemic in the world according to UNAIDS 2017 report (2).

Non communicable diseases especially cardiovascular disease have become the leading cause of morbidity and mortality globally. Growing concern with regards to cardiovascular disease in people living with human immunodeficiency virus (HIV) has emerged. With the access to antiretroviral therapy, AIDS-related mortality has significantly reduced. HIV positive people live longer and cardiovascular disease has become one of the most common cause of morbidity and mortality. Both traditional risk factors, HIV related risk factors such as viral replication and opportunistic infections, as well as metabolic toxicity of antiretroviral drugs have been implicated in the development of cardiovascular disease. Hence, the importance of a regular cardiovascular screening in this population.

The spectrum of cardiovascular disease in HIV ranges from atherosclerotic cardiovascular disease, higher in the Western countries, to cardiomyopathy, pericardium disease, pulmonary arterial hypertension, arrhythmias due to autonomic dysfunction which are predominant in Africa.

Various modalities of screening for cardiovascular disease have been described such as resting ECG, exercise stress ECG, echocardiography and measurement of the carotid intima media thickness. Despite the superiority of other modalities, resting ECG is cheaper and readily available. In developing countries where the resources are limited, resting ECG has been proposed to be a useful screening tool especially in asymptomatic heart disease. Studies have shown that up to 11% of silent myocardial ischemia among HIV positive patients can be seen on a resting ECG (3). Resting ECG is also a good predictor of cardiovascular mortality. Major ECG findings have been shown to be best predictor of cardiovascular mortality than cardiovascular risk factors (4).

This study aims to describe the prevalence and types of resting ECG abnormalities among ambulant HIV positive patients and to determine their association with demographic characteristics, selected cardiovascular risk factors and HIV related clinical factors.

## **1.0 CHAPTER ONE: LITERATURE REVIEW**

### **1.1 Global Burden of Human Immunodeficiency Virus**

More than thirty years after its discovery, infection due to HIV is still a major global public health problem. World health organization (WHO) reports 36.9 million people living with HIV globally at the end of 2017 with a global prevalence of 0.8 % among adult population (1). The highest rate is observed in sub-Saharan Africa where 25.5 million people live with HIV infection. Southern and East Africa regions are the most affected with 19.4 million HIV infected people. These two regions accounted for 44% of new HIV infections globally in 2016. Kenya's disease burden is the fourth largest epidemic in the world. In Kenya, UNAIDS reports a prevalence of HIV infection of 5.9% in 2016 and there was 1.5 million people living with HIV in 2015 (2).

### **1.2 Antiretroviral Therapy**

Highly active antiretroviral therapy (HAART) was introduced in 1996 as a standard of care for the treatment of HIV. It has a high efficacy in suppressing viral replication. Six classes of antiretroviral agents currently exist:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Integrase inhibitors
- Fusion inhibitors
- Entry inhibitors

The preferred regimen is a combination of two NRTIs with a NNRTI or a PI (1). The national guidelines in Kenya on the use of antiretroviral drugs (5) recommends Tenofovir, Lamivudine and Efavirenz as the first line regimen of choice in adults. The second line regimen of choice should include two NRTIs and ritonavir boosted Atazanavir or Lopinavir. Alternative combinations can be used in case of contraindication and intolerable side effects. Although HAART is generally well tolerated, some adverse drug reactions are still observed. The older PIs and NRTIs such as lopinavir, didanosine and stavudine are known to cause metabolic complications such as dyslipidemia, lipodystrophy and insulin resistance (6). These complications may increase the risk of cardiovascular diseases (CVD) in HIV positive patients (7) .

### **1.3 The Epidemiological Transition**

With the improved access to HAART, morbidity and mortality due to HIV infection have significantly reduced and non-AIDS defining diseases have become the main cause of mortality.

An analysis of the HIV outpatient study (HOPS) cohort which was a prospective observational study in 10 HIV clinics in the United States of America (US) demonstrated a rise in deaths due to non-AIDS defining illnesses from 13.1% to 42.5% ( $P < 0.001$ ). The most common non-AIDS related illnesses were cardiovascular, hepatic and pulmonary diseases as well as non-AIDS defining malignancy. Patients who died from non-AIDS defining illness were likely to have been on highly active antiretroviral therapy (HAART) longer and had higher CD4 count than those who died from AIDS (8,9).

Other studies, such as the Data collection on Adverse events of anti-HIV Drugs (DAD) study which was a prospective multi-cohort study and a national survey in France showed the same trend of reduction of AIDS-related cause of deaths with an increase in cardiovascular deaths (10,11).

The rate of cardiovascular deaths in HIV infected populations is significant and accounts for 6% to 15% of total deaths (8,11–13).

### **1.4 Traditional Cardiovascular Risk Factors**

It is known that people infected with HIV have a high calculated risk for coronary heart disease (CHD). The Framingham risk score was used in two large US-based cohorts of HIV positive women and men (the Women's Interagency HIV Study [WIHS] and the Multicenter AIDS Cohort Study [MACS]) to estimate the 10-year risk for developing CHD compared to non-HIV individuals. High predicted risk of CHD (10-year risk  $\geq 25\%$ ) was found in 17% of HIV positive men and 12% of HIV positive women compared to 11% and 12% in uninfected men and women respectively. In this analysis, high risk of CHD was associated with exposure to HAART, overweight and obesity (14).

HIV infected patients are at higher prevalence of cardiovascular risk factors such as smoking and dyslipidemia compared to their non-infected counterparts. In the DAD study (10), smoking, hypertension and diabetes were associated with an increased risk of myocardial infarction. In a small hospital based study in Cameroun that included HIV infected patients presenting with heart disease ( $n=44$ , mean age 48, ART 70%), hypertension, dyslipidemia and smoking were the most frequent cardiovascular risk factors among HIV positive patients (15).

In the United States, the prevalence of smoking among people living with HIV is 2 to 3 fold higher than that in the general population and higher in HIV positive men than HIV positive women (16,17). As in the general population, smoking is an important risk factor for CVD. In a cohort study of HIV infected patients in Denmark, non-drug users (n=2921), current smoking was associated with an increased prevalence in both cardiovascular and all-cause mortality (RR: 4.3 and 4.4 respectively) compared with never smoking (18).

Dyslipidemia is also common in HIV-infected populations regardless of antiretroviral therapy (ART). The prevalence ranges from 23% to 63% compared to a prevalence of 17.6% in non-HIV cohort (19,20). High levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-c) are observed with a normal or a decreased level of high-density lipoprotein cholesterol (HDL-c) (21). These abnormalities have been linked with increased apolipoprotein E levels, increased hepatic production of very low density lipoprotein as well as reduced clearance of triglycerides (7).

Prevalence of diabetes among HIV infected individuals is between 7% and 20.7% compared to 6.6% in non-HIV counterparts with a higher prevalence observed among HIV infected patients on HAART (14,19,20).

The reported prevalence of hypertension among HIV patients ranges from 13 % to 21%. Although, data on hypertension are conflicting and some studies have demonstrated no difference among HIV compared to non-HIV infected individuals. Hypertension seems to be more related to other classical CVD risk factors such as dyslipidemia, obesity and existing kidney disease rather than ART (21).

Obesity is another risk factor for CVD which is prevalent in the HIV population as both HIV itself and ART affect fat metabolism (21). Visceral fat accumulation especially pericardial adipose tissue has been assessed as an independent marker of cardiovascular risk in HIV infected patients (22).

In addition to the traditional cardiovascular risk factors, HIV patients are also exposed to the side effects of antiretroviral drugs which can increase their risk of developing CVD.

### **1.5 Effects of antiretroviral therapy on cardiovascular disease risk**

Some antiretroviral drugs are known to cause metabolic toxicity such as fat redistribution. Lipodystrophy occurs 6 to 12 months after HAART initiation in patients on NRTIs and PIs based ART(21). Prolonged use of NRTIs especially thymidine analogues (stavudine, didanosine and zidovudine) cause mitochondrial toxicity and are associated with peripheral lipodystrophy (23). Conversely, PIs cause central lipohypertrophy. Fat redistribution leads to

ectopic fat accumulation especially in the heart and the liver. This is thought to eventually increase the risk for CVD (22). Fat redistribution also causes dyslipidemia, insulin resistance and dysglycemia through inhibition of apolipoprotein B degradation, disruption of insulin signaling pathways and blockade of glucose transporter 4 (21).

A study including 840 HIV/AIDS patients who were followed up for a median of 6 years reported a prevalence of 69.2 % of lipodystrophy (24). NRTIs and PIs based regimens were associated with a higher risk of developing lipodystrophy (OR: 2.1, 95% CI=1.7-3.3,  $p<0.01$ ; OR: 6.1, 95% CI=4.1-9.7,  $p<0.01$  respectively). Another study found higher levels of cholesterol, triglycerides, glucose and body fat in patients on HAART regardless of PI or PI sparing based regimen compared with HAART naïve patients. And the 10-years CVD risk increased linearly with the severity of lipodystrophy score (25). Old NRTIs and PIs such as didanosine, stavudine and lopinavir may exacerbate the risk of CVD compared to newer regimens (26,27). With regards to abacavir, its effect on the CV system is still controversial (28–32).

From the literature, the association of HAART and cardiovascular events is still not well established. The DAD study group (28) reported a relative risk of MI per year of PI use to be 1.10 (95%CI, 1.04-1.18) after controlling for traditional risk factors. A study done in US veteran population (n=24510, 42% blacks, median age of 46, 47% smokers, 12% diabetics) looked at the association between antiretroviral combination therapy and the risk of cardiovascular events: MI, stroke, percutaneous coronary intervention and coronary artery bypass. Both individual drugs and combination therapy were associated with an increased risk of CVD. Current exposure to abacavir, efavirenz, lamivudine, and zidovudine was significantly associated with increased risk of a cardiovascular event, with odds ratios ranging from 1.40 to 1.53. Efavirenz, lamivudine, and zidovudine was the second most commonly used combination and was associated with a 1.60 fold higher risk of cardiovascular event that of patients not currently exposed to the combination (OR = 1.60, 95% CI, 1.25–2.04) (30). The SMART trial (33) assessed the incidence of cardiovascular events among HIV individuals on continuous versus intermittent ART. The rate of major cardiovascular events was higher in the intermittent ART group compared to the continuous ART group HR=1.57 (95% CI, 1.0-2.46,  $p=0.05$ ). These findings suggest that HIV infection itself may play an important role in the pathogenesis of CVD besides the use of ART.

## **1.6 Pathogenesis of HIV associated coronary artery disease**

HIV infection is an independent risk factor for CVD. HIV increases the risk of developing an MI by 44-48%, independent of the traditional risk factors (34). Immunodepression with a CD4 cell count less than 200 is associated with a higher risk of MI (34,35). There are various mechanisms by which HIV contributes to the pathogenesis of CVD.

First, HIV causes dysregulation of intracellular lipid cholesterol. Immunosuppression has been associated with reduced clearance of LDL cholesterol particles, lower levels of apolipoprotein B and a decrease in HDL cholesterol leading to dyslipidemia observed in HIV infection (21).

Secondly, HIV causes premature atherogenesis via an interplay between inflammation, endothelial dysfunction and coagulation disorders (36). The inflammatory state which is mediated by the direct action of HIV RNA and HIV proteins Tat and Gp120 provokes endothelial damage, dysfunction and apoptosis. Endothelial dysfunction is evidenced by upregulated markers of endothelial activation such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin and Von Willebrand factor (37). These mechanisms lead to hypercoagulability and atherosclerosis. HIV infected individuals have higher levels of inflammatory markers such as interleukins 6, 8, tumor necrosis factor (TNF) alpha and C-reactive protein (CRP) than HIV negative individuals (38–40). HIV positive patients with high CRP levels have a 4 fold increase risk of MI compare to HIV negative patients (39). High levels of interleukin 6 and D-dimers have been associated with MI and stroke events (40). In the SMART trial (33), high levels of interleukin 6 was significantly associated with CVD (OR=2.8,  $p<0.03$ ). Plasma levels of interferon gamma is also elevated in HIV and it is thought to be responsible for reduced HDL cholesterol and increased triglycerides (36). In addition, it is currently known that there is a persistent low level of immune activation and an ongoing chronic inflammation even after suppression of the viral load (41) which constitutes a residual risk for CHD.

Coagulation abnormalities are common in HIV infection. D-dimers, fibrinogen, factor VII, Von Willebrand factor, soluble thrombomodulin and Tissue Factor are all increased making HIV infection a prothrombotic state (42,43). HIV protein gp120 activates smooth muscle cells through CXCR4 and CCR5 causing them to express tissue factor thus initiating the coagulation cascade (36). Higher D-dimer levels have been independently associated with CVD deaths among HIV infected patients (38). Chronic platelet activation also plays a role in the development of thrombosis and atherosclerosis (44).

The chronic inflammation and the prothrombotic state caused by HIV favors the acceleration of atherogenesis. HIV stimulates the proliferation of vascular smooth muscle cells thereby promoting atherosclerosis (45). Studies using carotid intima-media thickness (CIMT) and coronary computed tomography angiography (CCTA) as a screening tool for subclinical atherosclerosis found that the prevalence of subclinical atherosclerosis was higher in HIV positive compared to HIV negative people (46–48). A local study including 162 HIV patients majority on HAART found a prevalence of 27.2% of subclinical carotid atherosclerosis using CIMT. All of the 27.2% were on HAART, were older than those without subclinical atherosclerosis and were hypertensive with high total cholesterol and LDL cholesterol (49). The type of atherosclerotic plaque is a noncalcified plaque and thus more susceptible to rupture. HIV infected patients with a low CD4 count have more vulnerable plaques (47). This finding suggests that disease severity may increase the risk of CVD. Another observation made is that CIMT increases in children on HAART suggesting that the risk of CHD in HIV is already strong at a young age (50).

### **1.7 Pattern of cardiovascular disease in HIV**

The spectrum of HIV related CVD comprises atherosclerotic disease and non-atherosclerotic disease such as cardiomyopathy, myocarditis, pericardial disease and pulmonary arterial hypertension.

HIV-related atherosclerotic disease is the most common CVD among HIV population in developed countries. Silent myocardial ischemia has been reported in up to 10% of HIV patients in some European studies (51,52). It seems to be more prevalent in HIV than the non-infected population and it has been associated with central fat accumulation (53). Silent myocardial ischemia represents an important risk for acute MI, stroke and sudden death.

In Sub Saharan Africa, data suggest a higher prevalence of non-atherosclerotic CVD. The largest data are from the Heart of Soweto study cohort which looked at the implication of HIV in the novo presentation of CVD (n=5328, 9.7% were HIV positive) in patients presenting to the cardiology unit in one of the hospital in Soweto (54). Among HIV infected patients, coronary artery disease represented only 2.4%. Patients presenting with acute MI were young (mean age  $41\pm 13$  years), smoker with low HDL and no influence of HAART was found.

The most frequent heart disease associated with HIV was cardiomyopathy which accounted for 38% (54). The prevalence in Africa ranges between 9 to 57% (55). HIV associated cardiomyopathy is thought to be caused by the immune dysregulation, effects of viral HIV

proteins on the cardiac myocytes, endothelial dysfunction, opportunistic infections (Toxoplasmosis gondii, Cryptococcus neoformans and mycobacterium) and malnutrition (55). Zidovudine has been also incriminated in cardiac myopathy. Cardiomyopathy carries a poor prognosis in HIV infected patients (56).

Pericardial disease (pericardial effusion and pericarditis) was the second common cause accounting for 12.5% of CVD. Although, it was described as the most common cause in other publications (15,57). Pericardial effusion confers a 2.2 relative risk for mortality compared to CD4-matched controls (55). Almost 90% of pericardial effusion are due to mycobacterium tuberculosis. It was noted that 25% of patients with TB pericardial effusion have atrial fibrillation which reverts with treatment (58).

Another common cardiovascular manifestation of HIV is pulmonary arterial hypertension either it is secondary or primary. In the Heart of Soweto study, it accounted for 8.1% of CVD (54). Pulmonary arterial hypertension decreases the long term survival in HIV positive patients (1.3 Vs 2.6 years in HIV negative controls). The pathogenesis is an HIV proteins and cytokines mediated endothelial cell proliferation and vasoconstriction in the pulmonary vasculature (54–56).

Autonomic dysfunction has also been described in HIV populations. Patients at high risk are those with nervous system disease. Cardiac autonomic dysfunction exposes patients to arrhythmia and it does not appear to correlate with the immunological status (56).

### 1.8 Resting ECG changes in HIV

There is a variety of electrocardiographic (ECG) abnormalities that have been described in the general population. These ECG abnormalities have been classified into major and minor abnormalities according to the Minnesota code. Minnesota code is the mostly used ECG classification method especially in population-based studies (59).

**Table 1:Minnesota code classification of ECG abnormalities (59)**

<b>Major</b>	<b>Minor</b>
Severe or moderate ST segment depression	Borderline Q waves
Deep or moderate T wave inversion	Left or right axis deviation
Complete left bundle branch block	High voltage QRS complex
Frequent premature beats	Borderline ST depression
Atrial fibrillation	T-wave flattening
Atrial flutter	Low voltage QRS



According to a general population study done in Belgium, any ECG abnormalities range from 16 to 32% in the general population. ECG abnormality increases with age and are more frequent in men than women at a rate of 6% and 10.4% for major and minor ECG abnormalities respectively (60).

Studies have shown higher rate of ECG abnormalities among HIV positive patients compared to healthy individuals. In the SMART study (n=4518, 29% blacks, multicenter), 51.5% of the participants had either a minor or major ECG abnormalities. Minor abnormalities were the most frequent accounting for 48.6%. Major abnormalities accounted for 7.7% and the commonest abnormalities were major ventricular conduction defects, major Q/QS abnormalities, and major isolated ST/T abnormalities (61).

Compared to Western countries, few studies on the prevalence of ECG abnormalities among HIV positive patients have been done in Africa. These studies were hospital based with smaller population study.

In Zambia, a study analyzed the prevalence of subclinical CVD among 243 asymptomatic HIV patients. Using the Minnesota code, the prevalence of any ECG abnormalities was 54% with major ECG abnormalities accounting for 29%. The most common abnormalities in this study were: LVH (27%) and abnormal T wave. Major ECG abnormalities included: LVH, complete LBBB/RBBB, atrial fibrillation/flutter, major QT prolongation and second and third degree heart blocks. A high rate of ECG abnormalities was observed among patients with a CD4 cell count  $\leq 350$  (62).

A study in Nigeria (63) found a prevalence of any ECG changes of 81% in AIDS patients (n=100), 61% in asymptomatic HIV patients (n=78) and 37.5% in healthy controls (n=80). The most common abnormalities were sinus tachycardia (51%), prolonged QTc (41%) and T wave inversion (27%). A second study (64) in Nigeria including young patients (mean age=35 years) with no known CVD, HIV positive on HAART at least for 3 months (n=100), HAART naïve (n=100) and healthy controls (n=100) reported a prevalence of ECG abnormalities of 93%, 73% and 38% respectively. T wave inversion, prolonged QTc, sinus tachycardia were the most frequent abnormalities seen in HIV individuals. Left axis deviation was seen in both groups with a higher rate in the control group. A hospital based study in south India (65) reported a prevalence of 14.7% (n=150). The ECG abnormalities were as follow: 27% low voltage complexes, 18% of poor progression of R wave, 13% non-specific ST/T changes, 13% atrial ectopic, 9% right bundle branch block, 9% sinus tachycardia and 9% ventricular ectopic.

Prolonged QT duration among HIV infected individuals has been well described. The prevalence ranges from 11% to 20 % and can go up to 65% in patients with autonomic dysfunction (66–69). The prevalence seems to be higher in women and among patients with risk factors for ischemic heart disease but does not correlate with the use of ART (61).

Myocardial ischemia is usually silent in people living with HIV. In the SMART study, ECG findings of asymptomatic ischemia (Q wave or ST depression) were presents in 10.9 % of HIV patients with no prior ischemic heart disease (n=4831). This occurred in older, hypertensive and diabetic patients (3). Njoku et al did not find ECG changes of ischemic heart disease in a Nigerian cohort of 200 HIV patients (64).

### **1.9 Prognostic Significance of Resting ECG Abnormalities**

ECG abnormalities have been related to cardiovascular and all-cause mortality. ST segment depression, LVH, bundle branch block, T wave flattening, ischemic changes and arrhythmia are the most predictive ECG findings for cardiovascular mortality [RR 4.71, 2.79, 2.58, 2.47, 2.35, 2.15 respectively] (4).

In HIV population, any major ECG abnormalities are associated with increased risk of cardiovascular events (acute MI, coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, sudden death and cardiovascular death) as observed in the SMART study (61). In this study, a cardiovascular event was observed in 3.4% of HIV infected patients. The presence of ECG abnormalities was a significant predictor of CVD events in the study treatment group. The hazard ratio for major and minor ECG abnormalities was 2.76 and 1.58 respectively. After adjustment for demographic, clinical and HIV characteristics, major ECG abnormalities were still the strongest predictor of CVD events (HR 1.83, 95%CI 1.12-2.97, p=0.015). Individual ECG abnormalities with a significant predictive value were minor or major isolated ST/T abnormalities, major prolongation of QT and minor isolated Q/QS abnormalities. In the presence of a major ECG abnormality, there was a cumulative risk of CVD event over time p<0.001.

Prolongation of QT interval is associated with increased risk of ventricular arrhythmias especially torsade de pointe and can lead to sudden death. It is associated with an increase in 5-year risk for cardiovascular event independent of the cardiovascular risk factors, immunological status and viral suppression (61).

## **CHAPTER TWO**

### **2.1 JUSTIFICATION OF THE STUDY**

Cardiovascular disease is an important cause of morbidity and mortality among HIV population. Hence, there is need for screening for cardiovascular risk factors in this population as part of their comprehensive management. ECG abnormalities have been shown to be predictor for adverse cardiovascular outcomes. Resting ECG testing can be a convenient screening tool especially in resource limited settings. Despite suggestions from the literature on the prognostic value of resting ECG testing among HIV positive individuals, it is not routinely done in this population.

In Africa, very few studies have looked at the spectrum of electrocardiographic abnormalities in HIV patients and in Kenya none has been done. This study aims to fill this gap by giving a local prevalence and characteristics of ECG changes in our HIV infected population.

### **2.2 RESEARCH QUESTION**

What is the burden of resting ECG abnormalities in ambulatory patients with HIV attending the Comprehensive Care Center at Kenyatta National Hospital?

### **2.3 BROAD OBJECTIVE**

To describe the prevalence and types of resting ECG abnormalities in HIV infected adults attending the Comprehensive Care Center at Kenyatta National Hospital.

### **2.4 SPECIFIC OBJECTIVES**

#### **2.4.1 Primary Objectives**

1. To determine the prevalence of resting ECG abnormalities in HIV infected adults attending the Comprehensive Care Center at Kenyatta National Hospital.
2. To describe the types of abnormalities found on resting ECG in HIV infected adults attending the Comprehensive Care Center at Kenyatta National Hospital.

#### **2.4.2 Secondary Objectives**

To determine the association between the prevalence of ECG abnormalities and demographic characteristics, selected cardiovascular risk factors (hypertension, diabetes mellitus, smoking, obesity) and HIV-related clinical factors (nadir CD4 cell count, antiretroviral status).

## **CHAPTER THREE**

### **3.0 STUDY DESIGN AND METHODOLOGY**

#### **3.1 Study Design**

This was a descriptive cross-sectional study

#### **3.2 Study Site**

The study was undertaken at the Comprehensive care center (CCC) at Kenyatta National Hospital (KNH). KNH is a public and teaching hospital located in Nairobi, Kenya. KNH is a national hospital for almost all parts of the country and also serves as a primary care center for residents in Nairobi. CCC is an outpatient clinic dedicated to HIV infected patients. It runs from 8 am to 4 pm from Monday to Friday. The clinic offers many services such as daily medical care, psychosocial support, nutritional counseling and physiotherapy. The clinic has its own pharmacy that supplies ARVs and usual antimicrobial drugs to enrolled patients. The clinic also has a laboratory that runs required baseline tests for HIV infected patients. An average of 65 new patients are enrolled in the clinic every month and between 1500 and 2000 patients come for their follow-up visit per month.

#### **3.3 Study Population**

Adult HIV positive patients on follow up at the Comprehensive Care Center.

##### **3.3.1 Case Definition**

Any adult patient  $\geq 18$  years with a confirmed diagnosis of HIV from the patient's medical records.

##### **3.3.2 Inclusion Criteria**

- Patient of 18 and above
- Patient consenting to participate in the study

##### **3.3.3 Exclusion Criteria**

- Pregnant women and women in the postpartum period
- Patients with a known cardiac abnormality prior to the diagnosis of HIV

#### **3.4 Sample Size Determination**

To determine the minimum sample size required for the prevalence of ECG abnormalities in HIV infected patients, the following formula (70) was used to calculate the sample size;

$$n = \frac{Z^2 x P(1 - P)}{d^2}$$

Where

$n$  = Desired sample size

$Z$  = value from standard normal distribution corresponding to desired confidence level ( $Z=1.96$  for 95% CI)

$P$  = The prevalence of any ECG abnormalities ranges from 13.6 to 83% in sub-Saharan African studies.  $P$  was considered as a prevalence of 13.6% from a study done by Danbauchi et al in Nigeria (71).

$d$  = desired precision (0.05)

$$n = \frac{1.96^2 x 0.136(1 - 0.136)}{0.05^2} = 178$$

### 3.5 Sampling Technique

A consecutive sampling was used until the desired sample size was achieved.

### 3.6 Recruitment procedure

The recruitment was done at CCC/KNH. On each day of recruitment, patients awaiting their doctor's appointment were consecutively sampled. Information about the study was given verbally and in written. A screening proforma (Appendix I) was used to assess eligibility of the subjects. Subjects meeting the inclusion criteria and who had given a written consent were recruited in the study.

### 3.7 Clinical Variables

- Age: in years
- Gender: male or female
- HAART naïve was defined as an individual who has never been exposed to HAART.
- HAART was defined as an individual who had been at least for one month on combination therapy of at least 3 drugs from the four classes of antiretroviral drugs (NRTI, NNRTI, PI and integrase inhibitors).
- Duration of HAART: indicated in months from the date of initiation of HAART.
- CD4 count: was considered the lowest recorded absolute CD4 cell count and was categorized into  $<200$  and  $\geq 200$ .
- Duration of HIV: time (indicated in months) from the date of diagnosis.

- Hypertension was defined as a documented elevated blood pressure  $\geq 140/90$ mmHg or as being on antihypertensive treatment
- Diabetes as either reported by the patient, documented or use of hypoglycemic agents.
- BMI (in kg/m<sup>2</sup>) was categorized as:
  - Underweight: BMI < 18.5
  - Normal: BMI ranging between 18.5 and 24.9
  - Overweight: BMI ranging between 25 and 29.9
  - Obesity: BMI  $\geq 30$
- Cigarette smoking was categorized as:
  - Non-smokers: those who had smoked less than 100 cigarettes in their lifetime or who had never smoked.
  - Former smokers: those who had smoked at least 100 cigarettes in their lifetime and who at the time of the study had not smoked at all for at least one year.
  - Current smokers: those who had smoked at least 100 cigarettes in their lifetime and were still smoking.

### **3.8 ECG Variables**

Heart rate, P wave (presence, amplitude, duration), frontal plane QRS axis, PR interval, QRS complex (duration), QT interval, Q wave, T wave, R and S waves and ST segment changes were examined.

The ECG abnormalities were classified as follow:

#### **1. Arrhythmias:**

- a. Supraventricular
  - Sinus tachycardia
  - Sinus bradycardia
  - Atrial fibrillation
  - Atrial flutter
  - Premature atrial contractions
- b. Junctional rhythms
- c. Ventricular
  - Premature ventricular contractions
  - Ventricular tachycardia

#### **2. Conduction delays**

- a. Atrioventricular blocks
  - First degree AV block
  - Second degree AV block
  - Third degree AV block
- b. Intraventricular conduction defects
  - Left bundle branch block
  - Right bundle branch block
  - Left anterior fascicular block
  - Left posterior fascicular block
  - Bifascicular block

### **3. Cardiac chamber enlargement**

- Left ventricular hypertrophy
- Right ventricular hypertrophy
- Left atrial enlargement
- Right atrial enlargement

### **4. Mean QRS axis**

### **5. QT abnormalities**

- Prolonged QT
- Short QT

### **6. Repolarization abnormalities**

- ST segment changes
- T wave changes

### **7. Pathological Q waves**

## **3.9 Clinical Methods**

A face to face interview using a study proforma (Appendix II) was conducted with the recruited participants to obtain socio-demographic data and their medical history. Additional data such as duration of HIV since diagnosis, ART duration and regimens, viral load and CD4 counts were obtained from the patients' medical records. The PI then conducted a physical examination including anthropometric measurements. Weight (to the nearest 0.5 kg) was measured using a step on digital weighing scale (Seca®). Height (in meters to the nearest 0.5cm) was measured using a standard stadiometer. Body mass index (BMI in kg/m<sup>2</sup>) was calculated as weight (kg)/ [height (m) X height (m)].

### 3.10 ECG Methods

The ECG procedure was performed at CCC in a consultation room reserved for this purpose. Adequate information about ECG test was given to the patient. The test was conducted in a screened and quiet consultation room. The privacy, dignity and comfort of the patient were preserved as much as possible. The option of having a chaperone was proposed to the patient. The patient was requested to remove clothing over the chest area and to lie supine on a couch with clean linen.

The 12-lead ECG recording was done by the principal investigator. The same ECG machine model MEM3 was used throughout the study. The ECG was recorded following the British Society for Cardiological Science and Technology (SCST) guidelines (72) to record a standard 12-lead ECG. The ECG was recorded at a paper speed of 25mm/s and voltage gain of 10mm/mv. All the ECGs were inspected by the PI to ensure the authenticity of the patient's details and for artefacts. Subsequently, the ECGs were interpreted by the PI and a second interpretation by a cardiologist was obtained. ECG findings were interpreted as per the *AHA/ACC recommendations for the standardization and interpretation of the electrocardiogram* and recorded on a data tool (appendix 2).

#### 3.10.1 Criteria for interpretation of ECG abnormalities

The following definitions as per the “*American heart association/American college of cardiologists (AHA/ACC) recommendations for the standardization and interpretation of the electrocardiogram*” were used:

**Heart rate:** tachycardia was defined as a heart rate >100 beats/min and bradycardia as a heart rate <60 beats/min.

**QRS deviation:** Left axis deviation was  $-30^{\circ}$  to  $-90^{\circ}$ . Right axis deviation was  $90^{\circ}$  to  $120^{\circ}$ .

**Ventricular conduction abnormalities (73)**

##### **Complete RBBB**

1. QRS duration greater than or equal to 120 ms.
2. Rsr', rsR', or rSR' in leads V<sub>1</sub> or V<sub>2</sub>. The R or r deflections usually wider than the initial R wave.
3. S wave of greater duration than R wave or greater than 40 ms in leads I and V<sub>6</sub>.
4. Normal R peak time in leads V<sub>5</sub> and V<sub>6</sub> but greater than 50 ms in lead V<sub>1</sub>.

Of the above criteria, the first 3 had to be present to make the diagnosis. When a pure dominant R wave with or without a notch was present in V<sub>1</sub>, criterion 4 had to be satisfied.

##### **Incomplete RBBB**



Defined as by a QRS duration between 110 and 120 ms in addition to the criteria for complete RBBB.

### **Complete LBBB**

1. QRS duration  $\geq$  to 120 ms.
2. Broad notched or slurred R wave in leads I, aVL, V<sub>5</sub>, and V<sub>6</sub>.
3. Absent Q waves in leads I, V<sub>5</sub>, and V<sub>6</sub>, but in the lead aVL, a narrow Q wave may be present in the absence of myocardial pathology.
4. R peak time greater than 60 ms in leads V<sub>5</sub> and V<sub>6</sub> but normal in leads V<sub>1</sub>, V<sub>2</sub>, and V<sub>3</sub>, when small initial r waves can be discerned in the above leads.
5. ST and T waves usually opposite in direction to QRS.

The presence of the first 2 criteria will make the diagnosis.

### **Incomplete LBBB**

1. QRS duration between 110 and 119 ms.
2. Presence of left ventricular hypertrophy pattern.
3. R peak time greater than 60 ms in leads V<sub>4</sub>, V<sub>5</sub>, and V<sub>6</sub>.
4. Absence of q wave in leads I, V<sub>5</sub>, and V<sub>6</sub>.

### **QT interval abnormalities (74)**

QT interval was adjusted for heart rate using Bazett's formula. QTc prolongation was defined as  $\geq 460$ ms in women and  $> 450$ ms in men.

### **T wave abnormalities (74)**

Inverted T waves: amplitude  $> -0.1$  mv in leads I, II, aVL, and V<sub>2</sub> to V<sub>6</sub>

Flat T waves: amplitude between 0.1 and -0.1 mv in leads I, II, aVL V<sub>4</sub> to V<sub>6</sub>

### **ST abnormalities (75)**

Myocardial infarction: ST-segment elevation (convex upwards)  $> 0.08$  s, associated with T wave inversion

Ischemic heart disease: ST-segment depression  $> 1$  mm in more than one lead

### **ST-T changes**

Acute pericarditis: ST/T ratio  $\geq 0.25$  in V<sub>6</sub> or  $\geq 0.24$  in V<sub>4</sub>, V<sub>5</sub> (76)

### **Cardiac chamber abnormalities (77)**

**Left ventricular hypertrophy:** defined according to Sokolow-Lyon criteria. S wave in V<sub>1</sub>+R wave in V<sub>5</sub>  $> 35$ mm

**Right ventricular hypertrophy:** defined as R wave in V<sub>1</sub>+S wave in V<sub>5 or 6</sub>  $> 10.5$ mm or R wave in V<sub>1</sub>  $\geq 7$ mm or R/S ratio in V<sub>1</sub>  $> 1$

**Left atrial abnormality** defined as a P wave duration  $\geq 120$  ms or notched P wave  $\geq 40$ ms

**Right atrial abnormality** defined as a P wave amplitude  $> 2.5$ mm in lead II

### **Arrhythmias (78)**

**Atrial fibrillation:** absence of consistent P waves; presence of rapid oscillations or fibrillatory waves that vary in size, shape and timing and associated with an irregular ventricular response.

**Atrial flutter:** Atrial flutter was described as presence of a ‘saw tooth’ pattern of atrial activity.

### **Ectopic beats**

**Atrial premature beats:** A reduced RR interval of 25% or more, the presence of a P wave, and a QRS width of less than 0.12 seconds.

**Ventricular premature beats:** widened QRS complex with QRS duration  $> 0.16$  seconds, absent p wave before the premature complex or if present the PR interval is shorter than the native sinus beat.

## **3.11 Quality Assurance**

The research assistant was trained by the PI. The SCST guideline was followed to avoid lead misplacement and artefacts. All the equipment was calibrated before their use. Interpretation of all the ECG recordings was confirmed by a cardiologist and was done according to the ACCF/AHA guidelines. Where there was uncertainty in the interpretation, a second collaborator cardiologist was consulted and a consensus opinion was obtained from both cardiologists.

## **3.12 Ethical Consideration**

The study protocol was approved by the department of Clinical Medicine and Therapeutics as well as the Ethical committee of KNH (approval number P14/01/2018). Participating in the study was voluntary and every participant had to give an informed written consent. Patient identifiers were not mentioned in the data to maintain confidentiality. The results were explained to the patients and in case of further intervention; this was communicated to the primary physician.

### **3.13 Data management and analysis**

Data collected was recorded on the study proforma sheet and stored by the PI awaiting data analysis. Study proforma sheets and ECG recording were kept in a secure and lockable place only accessible to the PI. Data was entered, cleaned and analyzed by use of Statistical Package for Social Science (SPSS; Version 21.0, Chicago-Illinois).

Continuous data was analyzed and summarized as means and standard deviation. Categorical data was analyzed and displayed by use of frequencies and proportions. The overall prevalence of ECG abnormalities was calculated as the proportion of patients with at least one abnormality on the ECG and presented as a percentage and 95% confidence interval was determined. The type of ECG abnormalities was calculated as the proportion of patients with abnormal ECG and presented as a percentage. Bivariate analysis was used to test the association between the presence of ECG abnormalities and the demographic characteristics, selected cardiovascular risk factors, nadir CD4 cell count and ART status respectively. P-values and 95% confidence intervals (CIs) were calculated where applicable. A P value <0.05 was considered statistically significant.

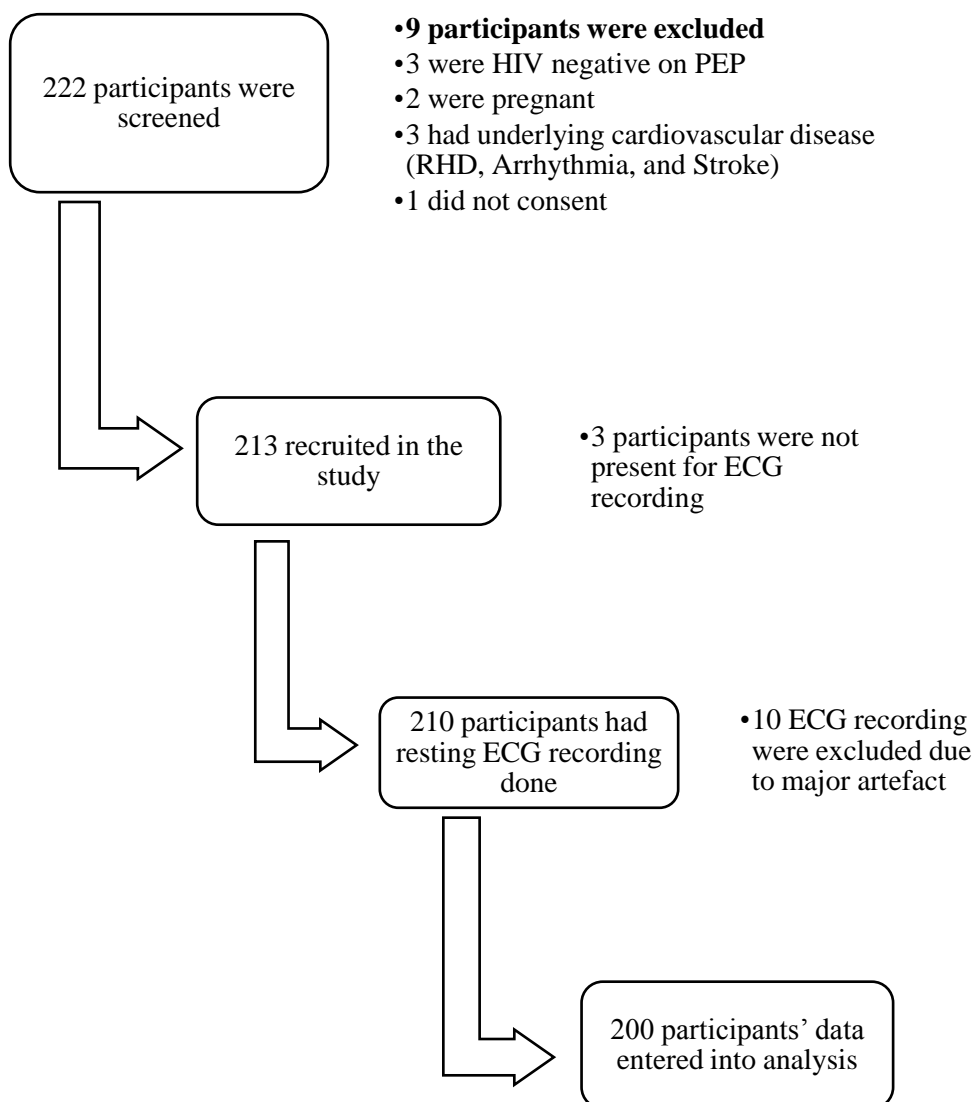
## CHAPTER FOUR

### 4.0 RESULTS

#### 4.1 Characteristics of study participants

Between April and May 2018, a consecutive sampling was done until the desired sample size was reached. A total of 222 adults were screened from the HIV outpatient clinic in KNH. 213 participants met the inclusion criteria and were recruited in the study. 210 were enrolled for resting ECG recording and the final analysis of the study included 200 participants.

**Figure 1: Flow diagram of patient recruitment**



#### 4.1.1 Socio-demographic characteristics of the study participants

A total of 200 participants were evaluated for this study. The mean age of all participants was 44.0 years (SD 10.1 years) and ranged from 20 to 73 years. Majority of the participants (64%) were between 30 and 50 years of age. The median age of female participant was 42 years (range 24-72 years) and 48 years (range 20-73 years) for male participants. One hundred and thirty nine participants (69.5%) were female. Majority of the participants were married 56.5%, had a secondary and tertiary education (70.5%) and 77.5% had a source of income as they were either employed or self-employed. A summary of socio demographic characteristics is illustrated in table 2 below.

**Table 2: Socio demographic characteristics of the study participants**

<b>Variable</b>	<b>Total (%) n=200</b>	<b>Women n=139</b>	<b>Men n=61</b>
<b>Age Groups (years)</b>			
20 – 29	15	8	7
30 – 39	54 (27.0)	46	8
40 – 49	74 (37)	56	18
50 – 59	43 (21.5)	20	23
60 – 69	11 (5.5)	8	3
70 – 79	3 (1.5)	1	2
<b>Marital Status</b>			
<i>Married</i>	113 (56.5)	64	49
<i>Single</i>	37 (18.5)	29	8
<i>Widowed</i>	29 (14.5)	26	3
<i>Divorced</i>	16 (8.0)	16	0
<i>Separated</i>	5 (2.5)	4	1
<b>Occupation</b>			
<i>Self employed</i>	78 (39.0)	54	24
<i>Employed</i>	77 (38.5)	50	27
<i>Unemployed</i>	38 (19.0)	32	6
<i>Retired</i>	4 (2.0)	3	1
<i>Student</i>	2 (1.0)	0	2
<i>Prisoner</i>	1 (0.5)	0	1
<b>Education</b>			
<i>Tertiary</i>	61 (30.5)	35	26
<i>Secondary</i>	80 (40.0)	54	26
<i>Primary</i>	50 (25.0)	41	9
<i>None</i>	9 (4.5)	9	0

#### **4.1.2 Clinical Characteristics of the Study Participants**

The mean duration of HIV infection since date of diagnosis was 101 months (SD 68.3). One hundred and ninety seven participants (98.5%) had been initiated on HAART with a mean duration since initiation of 84.4 months (SD 60.4). One hundred and seventy two participants (87.3%) were on first line regimen with a mean duration of 80.7 months (SD 59.0) and 12.7% were on second line with a mean duration of 33.8 months (SD 24.9). For 163 participants whose nadir CD4 cell counts were available, the mean nadir CD4 cell count was 283.7 (SD 239.8) and nadir CD4 cell count was  $<200$  cells/mm<sup>3</sup> in 44.2%. Viral load results were available for 179 participants and 90% of them had achieved viral suppression.

The mean BMI was 26.3kg/m<sup>2</sup> (SD 5.6) in women and 25.1 kg/m<sup>2</sup> (SD 5.1) in men. Thirty percent of participants were overweight, 25% were obese and 4.5% underweight. Forty individuals (20%) had either a recorded high blood pressure or were on antihypertensive drugs (11/40). Five individuals (2.5%) were known to have type 2 diabetes. A total of 16 individuals reported history of cigarette smoking and 3 were active smokers. Twenty eight participants reported consuming alcohol. Table 3 below gives a summary of the baseline clinical and HIV related characteristics of the study participants.

**Table 3: HIV related characteristics and cardiovascular risk factors of the study participants**

<b>Variable</b>	<b>Total (%)</b>	<b>Women (%)</b>	<b>Men (%)</b>
<b>Mean BMI Kg/m<sup>2</sup></b>	26.3 (SD 5.5)	26.9 (SD 5.6)	25.1 (SD 5.1)
<b>BMI category n (%)</b>			
<i>Underweight (&lt;18.5Kg/m<sup>2</sup>)</i>	9 (4.5)	6 (4.3)	3 (4.9)
<i>Normal (18.5-24.9Kg/m<sup>2</sup>)</i>	81 (40.5)	50 (36)	31 (50.8)
<i>Overweight (25-29.9Kg/m<sup>2</sup>)</i>	60 (30)	46 (33.1)	14 (23)
<i>Obesity (≥30Kg/m<sup>2</sup>)</i>	50 (25)	37 (26.6)	13 (21.3)
<b>Mean duration of HIV infection (months)</b>	101 (SD 68.3)	106.2 (SD 65.8)	89.3 (SD 72.8)
<b>Mean duration of HAART (months)</b>	84.4 (SD 60.4)	86.7 (SD 56.4)	79.2 (SD 68.7)
<b>Smoking status n (%)</b>			
<i>Non smoker</i>	181 (90.5)	136 (97.8)	45 (73.8)
<i>Former smoker</i>	16 (8)	3 (2.2)	13 (21.3)
<i>Current smoker</i>	3 (1.5)	0	3 (4.9)
<b>Alcohol use n (%)</b>	28 (14.0)	14 (10)	14 (22.95)
<b>Type 2 diabetes n (%)</b>	5 (2.5)	3 (2.15)	2 (3.3)
<b>Hypertension n (%)</b>	40 (20.0)	26 (18.7)	14 (22.95)
<b>Recent viral load</b>			
<i>&lt;1000</i>	162	118	44
<i>&gt;1000</i>	17	9	8
<b>Nadir CD4 cell count</b>			
<i>&lt;200</i>	72	46	26
<i>≥200</i>	91	68	23
<b>Current HAART regimen</b>			
<i>First line</i>	172	119	53
<i>Second line</i>	25	17	8

## **4.2 Prevalence of ECG Abnormalities**

Two hundred resting ECG recordings were adequate for analysis. Any ECG abnormalities were observed in 68 (34% CI 27.8-40.8) participants.

Arrhythmias were documented in 37 (18.5%) of participants. The pattern was as follows: 32 participants had supraventricular arrhythmias, 1 had a junctional rhythm and 4 had ventricular arrhythmia (single unifocal premature ventricular beats). Of the supraventricular arrhythmias, sinus bradycardia accounted for 90.6%. Only 2 participants had a sinus tachycardia and 1 had premature atrial contraction.

QRS axis deviation was present in 7 (3.5%) participants. Left axis deviation was present in 3 participants and right axis deviation in 4 participants.

Chamber enlargement was observed in 8 (4%) of participants. Only 1 participant had right ventricular hypertrophy. There was no atrial enlargement observed.

Atrioventricular conduction abnormalities were documented in 7 (3.5%) of participants. The types of atrioventricular block were as follows: 6 participants had a first degree AV block and 1 had Mobitz type II AV block. Intraventricular conduction abnormality was recorded in 2 participants. One had a bifascicular block and another a complete left bundle branch block.

Repolarization abnormalities were present in 18 (9%) individuals. These abnormalities comprised of T wave changes in 15 participants and ST segment abnormalities in only 3 participants. T wave changes included T wave inversion in 8 participants and T wave flattening in 7 participants. ST segment elevation and ST segment depression were observed in 2 and 1 participants respectively.

Prolonged QTc was observed in 7 participants. Pathological Q waves were present in 2 participants.

Table 4 illustrates the prevalence of ECG abnormalities among the entire study population and Table 5 summarizes the proportion of each type of ECG abnormalities among the population with at least one ECG abnormality.



**Table 4: Prevalence of ECG abnormalities among 200 HIV infected adults at CCC/KNH**

<b>Variables</b>	<b>Total (%) N=200</b>
<b>Any ECG abnormality</b>	<b>68 (34) [CI 27.8-40.8]</b>
<b>Arrhythmia</b>	37 (18.5)
<b>QRS axis deviation</b>	7 (3.5)
<b>Chamber enlargement</b>	8 (4)
<b>Atrioventricular block</b>	7 (3.5)
<b>Intraventricular block</b>	2 (1)
<b>QTc prolongation</b>	7 (3.5)
<b>T wave changes</b>	15 (7.5)
<b>ST segment changes</b>	3 (1.5)
<b>Pathological Q waves</b>	2 (1)

**Table 5: Types of ECG abnormalities among 68 HIV infected adults with any ECG abnormality**

Type of ECG abnormalities	Category prevalence N=68	Women	Men
<b>Arrhythmias</b>	37 (54.4)	21(56.8)	16 (43.2)
Supraventricular	32 (47.0)	18 (56.3)	14 (43.7)
Sinus bradycardia	29 (42.6)	15 (51.7)	14 (48.3)
Sinus tachycardia	2	2	0
Premature atrial contraction	1	1	0
Ventricular (premature ventricular contraction)	4	3	1
Junctional	1	0	1
<b>Axis deviation</b>	7	3	4
Left axis deviation	3	2	1
Right axis deviation	4	1	3
<b>Chamber enlargement</b>	8	4	4
Left ventricular hypertrophy	7	4	3
Right ventricular hypertrophy	1	0	1
Atrial enlargement	0	0	0
<b>AV conduction abnormality</b>	7	3	4
First degree AV block	6	2	4
Mobitz type II block	1	1	0
<b>IV conduction abnormality</b>	2	1	1
Bifascular block	1	1	0
Left bundle branch block	1	0	1
<b>ST segment abnormality</b>	3	1	2
ST depression	1	1	0
ST elevation	2	0	2
<b>T wave abnormality</b>	15	11	4
T wave flattening	7	7	0
T wave inversion	8	4	4
<b>Pathological Q waves</b>	2	1	1
<b>QTc prolongation</b>	7	6	1

### 4.3 Factors associated with ECG abnormalities

Using ECG abnormality as the dependent variable, we tested for association between the dependent variable and socio demographic (gender), cardiovascular risk factors (obesity, cigarette smoking, diabetes and hypertension) as well as HIV related factors (HAART experience, nadir CD4 cell count). Of all participants with any ECG abnormality, 43 (63.2%) were female and 25 (36.8%) were male and this difference was not statistically significant.

Table 6 gives a summary of the different associations.

**Table 6: Association of ECG abnormalities with demographics, selected cardiovascular risk factors and HIV-related clinical characteristics.**

Variable	ECG abnormal (%)	ECG normal (%)	COR (95% CI)	p-value
Gender				
Female	43 (63.2)	96 (72.7)	0.65 (0.35 – 1.20)	0.22
Male	25 (36.8)	36 (27.3)		
HAART Experienced				
Yes	68 (100%)	129 (97.7)	Undefined	
No	0	3 (2.3)		
Lowest CD4 Count				
<200	26 (38.2)	46 (43.8)	1.04 (0.55-1.99)	1.00
≥200	32 (61.8)	59 (56.2)		
Diabetes				
Yes	1 (1.5)	4 (3.0)	0.48 (0.05 – 4.36)	0.57
No	67 (98.5)	128 (97.0)		
Hypertension				
Yes	10 (14.7)	30 (22.7)	0.59 (0.27 – 1.29)	0.24
No	58 (85.3)	102 (77.3)		
Obesity (BMI≥30.0)				
Yes	15 (22.1)	35 (26.5)	0.78 (0.39-1.57)	0.61
No	53 (77.9)	97 (73.5)		
Smoking status				
Ever smoked	7 (10.3)	12 (9.1)	1.15 (0.43 – 3.06)	0.98
Non smoker	61 (89.7)	120 (90.9)		

## CHAPTER FIVE

### 5.0 DISCUSSION

This study examined the prevalence of ECG abnormalities among HIV infected adults attending their routine clinic at CCC/KNH. One third of the participants had at least one ECG abnormality and majority was minor abnormalities: sinus bradycardia, non-specific ST-T changes, LVH and QTc interval prolongation.

Of all participants with any ECG abnormality, 42.6% had sinus bradycardia. This high prevalence of sinus bradycardia could be either physiologic, drug induced or as a result of cardiac autonomic dysfunction which is common in HIV infected population. However, none of the participants were symptomatic. Major arrhythmias such as atrial fibrillation, atrial flutter, supraventricular and ventricular tachycardia were absent. Our population had a low rate of comorbidities and some of these arrhythmias are paroxysmal in nature.

Repolarization abnormalities and pathological Q waves represented 29.4% (20/68) of all ECG abnormalities. The most common type of abnormality was T wave changes (22.1%). ST elevation was found in 2 participants and this could be attributed to early repolarization. Repolarization abnormalities in our study were mostly non-specific and could have also been associated with electrolytes disturbances. There were no abnormalities suggestive of ischemic changes or pericarditis. Minor and major ST/T abnormalities have been shown to be a significant predictor of cardiovascular events among HIV population [HR 1.58, 1.91 respectively](61).

Left ventricular hypertrophy, using Sokolow-Lyon criteria, was the most common type of chamber enlargement. Four out of 7 participants who had LVH were hypertensive. Hypertension is a significant correlate of LVH. LVH has been shown to be a strong predictor of cardiovascular events and mortality in the HIV infected population [RR 1.37] (61).

QTc prolongation, using Bazett's formula, represented 10.3% of all ECG abnormalities. QTc prolongation is common in HIV population and it seems to be related to common factors such as female gender, increasing age, hypertension (LVH), diabetes, duration of HIV; with a significant prolongation after the 4<sup>th</sup> year of HIV infection and medications (68). QTc prolongation has been shown to be an independent risk of ventricular arrhythmias and sudden cardiac death.

Studies have shown that being either on NRTI especially the older drugs such as stavudine, didanosine and zidovudine or being on a PI based HAART regimen was associated with a significant increased risk of cardiovascular events (26,27,30). Severe immunosuppression also put HIV infected patients at a high risk of cardiovascular events especially when the CD4 cell count is less than 200 cells/mm<sup>3</sup> (34,35). In our study, although age and gender were suggestive of a trend towards a higher risk of having ECG abnormalities, none of the associations were statistically significant. Being a prevalence study, it was not powered enough for associations.

A study done in Zambia (62) evaluated subclinical CVD in 243 asymptomatic HIV infected patients, mean age of the participants was 42 years, females 58.5%, hypertension 16%, diabetes 3%, current smokers 3%, chronic kidney disease 39.5% and dyslipidemia 23%. The prevalence of any ECG abnormalities using the Minnesota code was 54% (major abnormalities 33% and minor abnormalities 21%). There was a correlation between CD4 cell count less than 350 and an increasing risk of ECG abnormalities. Diabetes, smoking, duration of HIV and exposure to PIs did not show any association. The high prevalence of kidney disease and dyslipidemia in addition to the different method of ECG analysis (Minnesota code) could explain the higher prevalence of ECG abnormalities compared to our study.

Our prevalence of 34% was higher compared to 14.7% found in a study done in south India among 150 HIV positive patients (65). This study had strict inclusion criteria that could explain the low prevalence of ECG abnormalities. The participants were HAART naïve, were between 18 and 55 years with no comorbidities as hypertension, diabetes, dyslipidemia, any heart disease and family history of CVD were excluded.

### **5.1 Conclusions**

One in 3 participants had at least one ECG abnormality. Majority of these abnormalities were minor. There was no factor that was found to be associated with ECG abnormalities.

### **5.2 Strengths of the study**

This is the first study done in Kenya that described the prevalence of resting ECG abnormalities among HIV infected adults. It will serve as a baseline for future studies.

### **5.3 Limitations**

1. Paroxysmal ECG abnormalities may have been underreported.
2. This was a cross-sectional study, the risk for having ECG abnormalities cannot be established.
3. We did not have a comparison group for this study to determine the role of HIV infection in increasing the risk of ECG abnormality in this population.

### **5.4 Recommendations**

From this study, we recommend that a prospective study is needed to define the clinical significance of ECG abnormalities among HIV population. Secondly, further studies are needed to identify risk factors that are associated with ECG abnormalities among HIV population. Thirdly, a study doing serial ECG testing or a 24 hour holter monitoring might have a role due to the paroxysmal nature of some ECG abnormalities.

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## APPENDICES

### Appendix I: Screening Proforma

Study N° .....

Age .....

Date of birth.....

Gender:    Male         Female, LMP.../.../....

Year of HIV diagnosis .....

Are you willing to participate in the study *Electrocardiographic abnormalities among HIV infected adults attending the Comprehensive Care Center at Kenyatta National Hospital?*

YES

NO

*Tick where appropriate:*

Have you ever been told by a doctor that you have coronary artery disease?

Have you ever had a heart attack?

Have you ever had a heart surgery?

Have you delivered in the last 6 weeks?

## Appendix II : Study Proforma

Study N°

1. Date

2. Patient's contact

### SOCIO-DEMOGRAPHICS

3. Date of birth ..... Age.....

4. Gender  Male  Female

5. Marital status  Single  Married  Widowed  Divorce

Separated

6. Occupation  Student  Self-employed  Employed  Unemployed

Retired

7. Education level  None  Primary  secondary  Tertiary

Other

### HIV HISTORY

8. Year of HIV diagnosis.....

9. Duration of HIV since diagnosis.....

10. HAART naïve:  YES  NO

11. Year of initiation of HAART.....

12. Duration of HAART.....

13. Current regimen  first line  second line  third line

Specify the regimen.....

14. Duration of first line .....

15. Duration of second line .....

16. Duration of third line.....

17. Lowest CD4 count.....

18. Recent CD4 count .....

19. Recent Viral load.....

20. WHO stage of HIV.....

### MEDICAL HISTORY

21. Hypertension  YES  NO Duration (yrs).....

22. Diabetes  YES  NO Duration (yrs).....

23. Cardiovascular disease  YES  NO Specify.....

24. Chronic kidney disease  YES  NO Duration (yrs).....

25. Chronic pulmonary disease YES NO Specify.....

26. Tuberculosis  Current Past

**SMOKING**

27. Smoking status  Current smoker  Former smoker  Non smoker

**ALCOHOL**

28.  YES  NO

**MEDICATIONS**

29. Hypoglycemic agents  YES  NO

30. Antihypertensive agents  YES  NO

**PHYSICAL EXAMINATION**

31. Weight (kg).....

32. Height (m).....

33. BMI (kg/m<sup>2</sup>)

Underweight (<18.5)  Normal (18.5-24.9)  Overweight (25-29.9)  Obese  
(≥30)

## ELECTROCARDIOGRAPHIC ABNORMALITIES

Question		Response /interpretation
34	Is the ECG recording normal?	1=Yes 2=No. If NOT proceed to
A	Does the ECG recording show an arrhythmia?	1=Yes 2=No If YES specify in part B below
B	If yes to (A) above what is the origin of the arrhythmia?	1=Supraventricular.....Go to C 2=Junctional 3=Ventricular.....Go to D
C	If supraventricular,what type of arrhythmia is it ?	1=Atrial fibrillation 2=Atrial flutter 3=Premature atrial contraction 4=Sinus bradycardia 5=Sinus tachycardia 6=Others
D	If ventricular what type of arrhythmia is it	1=Premature ventricular contraction 2= Others (specify)
E	Does the ECG show chamber enlargement?	1=Yes .....Go to F and specify 2=No
F	What is the type of chamber enlargement? For each indicate the response 1= yes, 2=No	1=Left ventricular hypertrophy 2=Right ventricular hypertrophy 3=Left atrial abnormality 4=Right atrial abnormality
G	Does the ECG show atrioventricular conduction abnormality	1=Yes.....Go to G below 2=No .....Go to I
H	What is the specificity of the atrioventricular conduction abnormality	1=First degree AV block 2=Mobitz type I AV block 3=Mobitz type II block 4=Third degree AV block
I	Does the ECG show intraventricular conduction abnormalities?	1=Yes 2=No



J	What is the type of Intraventricular conduction abnormality	1=Left Bundle Branch Block 2=Right Bundle Branch Block 3=Left anterior fascicular block 4=Left posterior fascicular block 5=Bifascicular block 6=Incomplete left bundle branch block 7=Incomplete right bundle branch block
K	Does the ECG show any ST segment changes?	1=Yes 2=No
L	What type of ST segment abnormality does the ECG show?	1= ST elevation 2= ST depression
M	Does the ECG show any T wave abnormalities?	1=Yes 2= No
N	What type of T wave abnormality does the ECG show?	1= T wave inversion 2= T wave flattening 3= other T wave abnormality
O	Does the ECG show any QTc prolongation?	1=Yes 2=No
P	Does the ECG show any Q waves abnormalities	1=Yes 2=No
Q	Does the ECG show any axis deviation?	1=Yes 2=No
R	What type of axis deviation does the ECG show?	1=Right 2=Left

### **Appendix III: Consent Explanation Form**

I am Dr. Erica Cimpaye, a postgraduate student in the department of Clinical Medicine and Therapeutics at the University of Nairobi.

I would like to invite you to participate in a study that I am conducting on *Electrocardiographic abnormalities in HIV infected adults on follow up at the Comprehensive Care Center at Kenyatta National Hospital.*

An electrocardiogram (ECG) is a test that measures the electrical activity of the heart. The heart is an important organ that pumps blood through the body. In order to do so, the heart has to generate an electrical impulse that stimulates its muscles to contract and pump blood. This can be recorded by a machine attached to the body by means of electrodes. The electrical impulse of the heart is then visualized as a graphic representation that can be printed out on paper. The ECG is able to detect different abnormalities with the heart's rhythm, the size of the heart chambers and the conduction of the heart impulse. These abnormalities can be seen in patients infected with HIV.

The aim of this study is to determine the prevalence and types of electrocardiographic abnormalities in HIV infected adults. The study will also correlate these electrocardiographic abnormalities with the CD4 cell counts of the patients and their medications.

Your participation in this study is voluntary and there is no compensation for participating. Refusal to participate will not impact on the medical management you are already receiving.

If you accept to participate in the study, you will be required to answer few questions about yourself and your medical condition. We will also be requested to expose your chest when the ECG test is performed but this will be done in privacy.

There is no harm to participate in this study. You may benefit from this study by getting free screening for heart disease. In case you are found to have any ECG abnormality, this will be communicated to your doctor and you will receive appropriate management.

All information collected from you will be kept confidential. Any publications arising from this study will not identify you in person.

If you have understood the information I have given you and you are willing to participate in this study, I will require you to sign a form indicating your willingness to participate.

For further information, you may contact any of the following:

1. Dr. Erica Cimpaye.

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0719-766-236.

2. Professor M.D. Joshi.

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0722-516-904

3. The Secretary KNH-UON Ethics and Review Committee.

Telephone number: 2726300 Ext 44102

Email: [uonknh\\_erc@uonbi.ac.ke](mailto:uonknh_erc@uonbi.ac.ke)

## Appendix IV: Consent Form

I \_\_\_\_\_ do confirm that I have read/ been explained to the above study, understood the information presented to me and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw from this study at any time without giving reason. I confirm that I have agreed to have an electrocardiogram (ECG) be recorded on me.

I agree to take part out of my own free will and no coercion or incentive has been offered.

Signature of participant \_\_\_\_\_ Date: \_\_\_\_\_

Signature of investigator \_\_\_\_\_ Date: \_\_\_\_\_

## **Appendix V: Fomu Ya Maelezo Kuhusu Utafiti**

### **Kitangulizi:**

Jina langu ni daktari Erica Cimpaye , mwanafunzi wa shahada ya uzamili kwenye somo la udaktari wa magonjwa ya undani katika wa chuo kikuu cha Nairobi .

Ningependa kukualika uhusike katika utafiti ambao naufanya kuhusu ‘Hitilafu za umeme ya moyo zinazopatikana kwa wagonjwa walioathiriwa na virusi vya Ukimwi kwenye hospitali kuu ya Kenyatta.

Kipimo cha *‘electrocardiogram’* ni aina maalum ya picha inayokagua umeme wa misuli ya moyo. Moyo ni kiungo cha mwili ambacho kazi yake huwa ni kusambaza damu kwenye maeneo yote ya mwili. Ili kufanikisha kazi hii, umeme unaotoka kwenye sehemu speshelesli ya moyo lazima isisimue misuli ya moyo ndipo iweze kusambaza damu mwilini. Kwenye kipimo cha ECG, aina hii ya umeme wa moyo huwa unasajiliwa kwenye kifaa cha ECG kisha kuandikisha ujumbe huu kwa njia ya mchoro kwenye karatasi. Walioathirika na virusi vya ukimwi huwa wanaweza kuwa na hitilafu ambazo zinaweza kuathiri umeme wa moyo.

### **Lengo la utafiti huu**

Lengo la utafiti huu ni kutathmini kiwango na aina ya hitilafu zinazoathiri umeme wa moyo kwa walioathirika na virusi vya ukimwi. Utafiti huu pia utalinganisha hitilafu za umeme wa moyo na viwango vya CD 4 vya wagonjwa pamoja na madawa wanayotumia.

### **Hiari ya Kujiunga na Utafiti**

Kuhusika kwako kwa utafiti huu ni kwa hiari yako. Hakuna malipo yoyote ambayo mtafiti atakupea ili uweze kushiriki. Una hiari ya kukataa kushiriki na hilo haliwezi kuathiri zile huduma zako za matibabu za kawaida kwa njia yoyote ile.

### **Jinsi utafiti utakavyofanywa**

Iwapo utakubali kushiriki kwenye utafiti huu, utahitajika kujibu maswali kuhusu nafsi yako na pia maradhi ambayo unatibiwa. Pia, tutakuomba utoe nguo kwenye sehemu ya kifua ili tuweze kufanya kipimo cha ECG. Kipimo hiki kitafanyiwa sehemu faraghani.

Kakuna athari yoyote ya kuhusika katika utafiti huu. Utaweza kufaidika kutokana na utafiti huu kwa kupata huduma ya kupimwa moyo bila malipo. Iwapo utapatikana na hitilafu yoyote ya umeme wa moyo, daktari wako wa kawaida atajulishwa ili aweze kukuhudumia ipasavyo.

### **Faragha yako**

Ujumbe utakaokusanywa kwenye utafiti huu utahifadhiwa vizuri ili kulinda faragha yako. Machapisho yatakayoambatana na utafiti huu hayatachapisha majina yako, yale ya jamaa wako wala taarifa yoyote ambayo itaweza kufanya utambuliwe.

Iwapo umeelewa haya maelezo kuhusu huu utafiti, nitakuhitaji uweke sahihi kwenye fomu ya ridhaa.

Iwapo ungependa kuuliza maswali yoyote kuhusu utafiti huu, unaweza kuwasiliana na wafuatao

1. Daktari Erica Cimpaye. Chuo kikuu cha Nairobi. ANWANI 19676, Nairobi.  
Nambari ya simu: 0719-766-236
2. Professor M.D. Joshi. Chuo kikuu cha Nairobi. ANWANI 19676, Nairobi.  
Nambari ya Simu: 0722-516-904
3. Katibu Mkuu, Kamati cha Kuhariri Utafiti cha Hospitali Kuu ya Kenyatta na Chuo Kikuu Cha Nairobi.  
Nambari ya simu: 2726300 Ugani 44102. Ama barua pepe: uonknh\_erc@uonbi.ac.ke

## Appendix VI: Fomu Ya Ridhaa

### Hitilafu za umeme wa moyo kwa watu wanaouguua ugonjwa unaoletwa na virusi vya ukimwi

Mimi \_\_\_\_\_ nathibitisha ya kwamba nimesoma/ nimepewa maelezo kuhusu huu utafiti, nikaelewa na nikapata fursa ya kuuliza maswali. Naelewa kuwa kushiriki ni kwa hiari yangu na kwamba niko na uhuru wa kujiondoa kwenye utafiti wakati wowote bila kutoa sababu yoyote. Nathibitisha kwamba nimekubali nifanyiwe kipimo cha ECG.

Nimekubali kuhusika kwa hiari yangu mwenyewe na sijalazimishwa wala kuhongwa.

Sahihi ya mhusika \_\_\_\_\_ Tarehe: \_\_\_\_\_

Sahihi ya mtafiti \_\_\_\_\_ Tarehe: \_\_\_\_\_



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11<sup>th</sup> April 2018

Dr. Erica Cimpaye  
Reg. No.H58/74149/2014  
Dept. of Clinical Medicine and Therapeutics  
School of Medicine  
College of Health Sciences  
University of Nairobi

Dear Dr. Cimpaye

**RESEARCH PROPOSAL - ELECTROCARDIOGRAPHIC ABNORMALITIES AMONG HIV INFECTED ADULTS ATTENDING THE COMPREHENSIVE CARE CENTER AT KENYATTA NATIONAL HOSPITAL (P14/01/2018)**

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 11<sup>th</sup> April 2018 – 10<sup>th</sup> April 2019.

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) 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*).
- f) 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.

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

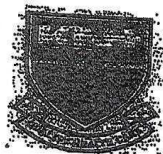
Yours sincerely,



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

c.c. The Principal, College of Health Sciences, UoN  
The Deputy Director, CS, KNH  
The Chairperson, KNH-UON ERC  
The Assistant Director, Health Information, KNH  
The Dean, School of Medicine, UoN  
The Chair, Dept. of Clinical Medicine and Therapeutics, UoN  
Supervisors: Prof. Mark D. Joshi, Dr. Jared O. Mecha

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KNH/R&P/FORM/01

**Study Registration Certificate**

1. Name of the Principal Investigator/Researcher  
..... ENICA CIMPAYE .....
2. Email address: ..... [enica.cimpaye@gmail.com](mailto:enica.cimpaye@gmail.com) ..... Tel No. 0719766936 .....
3. Contact person (if different from PI) ..... PI .....
4. Email address: ..... PI ..... Tel No. ..... PI .....
5. Study Title  
..... Electrocardiographic abnormalities among HIV infected adults attending the comprehensive care center at Kenyatta National Hospital .....
6. Department where the study will be conducted (Please attach copy of Abstract)  
..... Comprehensive care center - KNH .....
7. Endorsed by Research Coordinator of the Department where the study will be conducted.  
Name: ..... Signature ..... Date .....
8. Endorsed by Head of Department where study will be conducted.  
Name: DA PETER MURRAY ..... Signature ..... Date 17/4/18 .....
9. KNH UoN Ethics Research Committee approved study number (Please attach copy of ERC approval)  
..... PI4/10/2018 .....
10. I ENICA CIMPAYE ..... commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.  
Signature ..... Date 16/04/2018 .....
11. Study Registration number (Dept/Number/Year) (To be completed by Research and Programs Department)  
..... CCC 172/2018 .....
12. Research and Program Stamp



All studies conducted at Kenyatta National Hospital must be registered with the Department of Research and Programs and investigators must commit to share results with the hospital.