PREVALENCE OF HYPERTENSION AND CARDIOVASCULAR RISK FACTORS IN HIV-1 INFECTED PATIENTS ON ANTIRETROVIRAL THERAPY

A dissertation submitted in part fulfillment of the requirements for the degree of the Master of Medicine in Internal Medicine, University of Nairobi.

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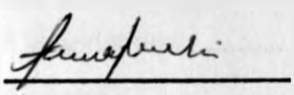

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Acknowledgements

To all who assisted and supported me in this study may God bless.

ABBREVVIATIONS

AIDS: ..... Acquired immunodeficiency syndrome

ARVS:..... Antiretrovirals

ATP III:..... Adult Treatment Panel III

BMI: .....Body mass index

BP: .....Blood pressure

CCC:.....Comprehensive care clinic

CI.....Confidence interval

CHD : .....Coronary heart disease

CKD:.....Chronic kidney disease

DAD: .....Data collection on Adverse Events of Anti-HIV Drugs

DBP: .....Diastolic blood pressure

d4t: .....Stavudine

DH:.....Diastolic hypertension

EFV: .....Efavirenz

HAART:.....Highly active antiretroviral therapy

HBA:.....Hydroxybenzoic acid

HDL-C: .....High density lipoprotein cholesterol

HIV:.....Human immunodeficiency virus

IFG:.....Impaired fasting glucose

IQR:.....Interquartile ratio

KNH: .....Kenyatta National Hospital

LDL-C: .....Low density lipoprotein cholesterol

NCEP:.....National Cholesterol Education Program

NRTI:.....Nucleoside reverse transcriptase inhibitors

NNRT: .....Non-nucleoside reverse transcriptase inhibitors

NVP:.....Nevirapine

PI:.....Protease inhibitors

SBP:..... Systolic blood pressure

SH :..... Systolic hypertension

WHO: .....World Health Organisation

3TC:..... Lamivudine

Abstract

Background: With increased use of HAART in HIV-infected individuals there is concern that antiretrovirals may be associated with hypertension, a known cardiovascular risk factor. This association could be related to duration of therapy, or the metabolic complications associated with HAART or finally to certain specific antiretrovirals.

Objective: To determine the period prevalence of hypertension in HAART experienced patients and compare this to the period prevalence of HAART naive patients and to determine the cardiovascular risk factors of these patients attending the Kenyatta National Hospital.

Design: A cross-sectional comparison study.

Setting: Kenyatta National Hospital, a tertiary health care facility.

Subjects: Consenting HIV- infected adults who where antiretroviral naive or had been on antiretrovirals for two years or more.

Outcome measures: Prevalence of hypertension; associated cardiovascular risk factors-age, gender, body mass index, dyslipidemia defined as presence of any of the following lipid abnormalities: raised total or LDL- cholesterol, low HDL cholesterol, or raised triglycerides; and dysglycemia defined as presence of any of the following: impaired fasting glucose or diabetes mellitus.

Results: Between July and November 2008, 3528 patients were screened, 1305 met the case definitions, 63% of whom were females .Of these 620 patients were recruited into antiretroviral experienced group and 615 patients were recruited into the antiretroviral naive group. Majority of the patients (95.6%) were on a non-nucleoside reverse transcriptase. At a median of 2.4 years the prevalence of hypertension was 12.9 %(95% CI 5.1-20.9) in the HAART experienced patients and 14.3 %(95%CI 5.9-22.1) in the HAART naive group (p=0.507). Dyslipidemia was the most common cardiovascular risk factor in 71.3% of the hypertensive patient on HAART. There was no statistical difference in the prevalence of dyslipidemia in HAART naive patients (p=0.299). Among the HAART experienced patients dysglycemia was noted in 35% of patients and 27.3% of HAART naive patients (p=0.23).

Conclusion: At a median of 2.4 years on HAART there was no increased prevalence of hypertension compared to HAART naive patients. Dyslipidemia and dysglycemia are important cardiovascular risk factors in hypertensive HIV populations, especially in patients on HAART. Therefore there is need to actively screen this hypertensive population for both of these risk factors.

1. LITERATURE REVIEW

1.1 INTRODUCTION

In Kenya, using population projections from the 1999 census and the general population prevalence rates from the Kenya Demographic Health Survey there are approximately 1.1 million people between 14-49years of age, another 60,000 age 50 and over, and approximately 100,000 children who are living with HIV [1]. There has been a dramatic increase in the number of patients accessing antiretroviral medication from an estimated 3,000 in 2002 to 190,000 in 2008 [2].Prior to effective antiretroviral therapy, the median duration for survival following AIDS diagnosis was about three years. Today, however, the survival times for HIV infected patients have been dramatically prolonged with the introduction of highly active antiretroviral therapy. Subsequently, AIDS related morbidity and mortality rates have dropped [3,4]. With the increasing life expectancy of HIV infected individuals under antiretroviral therapy, long term consequence of chronic infection and antiretroviral treatment will become more prevalent. These may include peripheral neuropathy, lactic acidosis and osteoporosis/osteopenia. The adverse effects of antiretroviral drugs also include cardiovascular risk factors; dyslipidemia, glucose intolerance, body fat abnormalities and possibly hypertension.

1.2 Mechanisms of vascular disease due to HIV and antiretroviral drugs

The impact of HIV and antiretroviral drugs on the cardiovascular system is under intense investigation. HIV infection causes profound functional alterations of the endothelium. The virus and its viral proteins such as glycoprotein120, Tat, and Nef are able to induce expression of several adhesion molecules and inflammatory cytokines such as E-selectin, tumour necrosis factor-α, and interleukin-6. Leukocyte adherence to the endothelium is enhanced as the expression of these cell adhesion molecules increases. Elevated circulating levels of von willebrand factor, a glycoprotein facilitating platelet adhesion, synthesized in endothelial cells and inflammatory cells, are elevated and correlate to circulating levels of inflammatory cytokines. A hypercoagulable state is induced depending on plasma HIV load. In addition, HIV

cytokines. A hypercoagulable state is induced depending on plasma HIV load. In addition, HIV and its viral proteins can also induce endothelial apoptosis and increase endothelial permeability. These effects could significantly contribute to vascular disease formation [5].

Endothelial dysfunction and reduced flow-mediated dilation in association with increased atherogenic lipoproteins has also been reported among HIV-infected adults receiving protease inhibitors [6]. The mechanisms of further vascular disease in HIV-infected patients on HAART are not known but may relate to dyslipidemia, insulin resistance, diabetes mellitus, inflammation, impaired fibrinolysis and factors specific to antiretroviral medications. Increased tissue levels of plasminogen activator and plasminogen-activator inhibitor 1 suggest that fibrinolysis is impaired in HIV-infected patients. Elevations in these substances are associated with hyperinsulinemia, lipodystrophy, and protease-inhibitor therapy [7]. High levels of protease inhibitors may promote the formation of atherosclerotic lesions by increasing CD36-dependent cholesterol ester accumulation in macrophages, a scavenger-receptor pathway that is thought to mediate the formation of atherosclerotic lesions [8].

1.3 Hypertension and antiretrovirals

Hypertension is a common cardiovascular disease in Africa and high blood pressure assumes more importance with increasing age [10]. A reasonable hypothesis is that more urban societies have a higher risk of hypertension when compared to their more rural counterparts. Connor M et al [10] in a cross sectional study done in outpatient clinics in South Africa a 55% overall prevalence of hypertension was found. More recently in 2004, in tribal villages in Ghana, the levels of hypertension (BP $\geq$140/90mmHg, measured by automatic monitoring or use of antihypertensive therapy) in those >65 years old, was ~37% versus ~50% in the semi-urban dwellers [11]. There is paucity of data on the prevalence of hypertension in Kenya.

There is continuous relationship between the level of blood pressure and the risk of cardiovascular events and hypertension has been arbitrarily defined as BP level of >140/90mmHg. Blood pressure levels both systolic and diastolic have been shown to be positively and continuously related to the risk of cardiovascular disease; for every 20mmHg systolic or 10mmHg diastolic rise in blood pressure, there is also doubling of mortality from coronary artery disease and stroke [12].

The effect of antiretrovirals on blood pressure is under debate and data is limited. There are studies that show increase in blood pressure in patients on antiretroviral therapy. Investigators have also assessed the relationship between the use of antiretroviral therapy and components of the metabolic syndrome [13] including dyslipidemia, insulin resistance and abnormal body fat distribution [14,15,16]. HAART, especially protease inhibitors seem to be associated with metabolic dysfunction which may lead to an increased risk of cardiovascular events [17].

The relationship between HAART and hypertension, another component of the metabolic syndrome, has not been well studied. Interestingly, increased blood pressure has been found to be associated with lipodystrophy. These patients have body fat changes, dyslipidemia and insulin resistance [18,23] providing evidence that HAART and hypertension may be linked via pathways involving lipodystrophy or other metabolic disorders. Other studies suggest that duration of therapy has an association with blood pressure raise and the development of hypertension [19,20,21]. Investigators have also looked at specific antiretrovirals to find those that may cause hypertension with varying results [22,24]. HIV–infected patients with a family history of hypertension appear be more vulnerable to developing hypertension when on HAART [23,24].

1.3.2 Effect of HAART on blood pressure

To study the effect of antiretroviral medication on blood pressure, Palaoss R et al [20] carried out a prospective observational study of 95 antiretroviral naïve patients. After one year of treatment the mean increase in systolic blood pressure was 7.9mmHg and increase in diastolic blood pressure was 4.9mmHg at 48 weeks of HAART. The increase in blood pressure was seen in patients both using protease inhibitors and non nucleoside reverse transcriptase inhibitors on the backbone of two nucleoside reverse transcriptase inhibitors. No relationship between the raise in blood pressure and lipodystrophic body changes were noted in this study. Their results suggest that the increase in blood pressure in HIV infected patients on HAART could be partly attributable to the HAART induced improvement in the general health of these patients. The greater increase in blood pressure was noted in patients with lower baseline CD4 counts and

lower cholesterol levels, indicating that the patients ravaged most by HIV showed significant improved health and hence increase in their blood pressure. Similarly, Chow DC et al [21] undertook a two and half year retrospective study at the State of Hawaii, USA, where blood pressure changes in 286 patients on antiretroviral treatment was compared to untreated controls. They found an increase in systolic blood pressure by 4.71mmHg/year and diastolic blood pressure by 2.26mmHg/year among patients initiating HAART. In regimes which had protease inhibitors, SBP and DBP the raise was 4.75 and 1.96mmHg/year, on NNRTIs the raise was 3.21 and 2.62mmHg/year for SBP and DBP respectively. There was no significant raise in BP in patients on NRTI only regimes. These studies suggest that with use of antiretroviral therapy there is a progressive increase in blood pressure. This increase could be in part due to the improvement in the health and subsequent weight gain of these patients.

1.3.3 Duration of HAART use and hypertension

Two studies found duration of HAART was associated with the development of hypertension. Seaberg E and colleagues [19] in a Multicenter AIDS study cohort enrolled 5622 men in the USA. Patients were enrolled during two periods, 1984-1985 and 1987-1995. Blood pressure measurements were done semi-annually. Data was analyzed in March 2003 on a total of 84,813 person visits. This study enrolled predominantly white Caucasians (83.3%). Among 4535 person visits from HIV positive men taking HAART systolic and diastolic hypertension was demonstrated in 12.0% and 9.0% respectively. Among the 49,884 person visits from HIV negative men systolic hypertension and diastolic hypertension were present in 8.3% and 9.0% respectively but even lower in HIV positive men not taking any antiretrovirals (5.0% and 6.1%). The study concluded the prevalence of systolic hypertension among HIV positive men taking HAART for < 2 years was similar to that among HIV negative men but significantly higher (51%) for a further 2-5 years (OR 1.51) and 70% > 5years (OR 1.70). This increase in systolic hypertension was noted in all classes of antiretroviral drugs.

In a study done in 542 predominantly white HIV infected patients in Norway, Baekken M et al [25] found no increased prevalence of hypertension in HIV-infected patients compared to

controls. However, cumulative of use HAART for 5 years or more was found to be associated with increasing hypertension prevalence compared those on HAART for less than 5 years.

1.3.4 Specific antiretroviral medication and hypertension

In a recent prospective American study by Crane H et al [22] looking at antiretroviral medication associated with elevated blood pressure, lopinavir/ritonavir based regimes were found to have a twofold increased risk of developing elevated blood pressure compared to efavirenz. Of significance was that, these patients were also found to have increased body mass indexes. Atazanavir showed the least effect on blood pressure. Cattelan A et al [24] studied the effect of protease inhibitors on blood pressure on 181 patients and found that indinavir was associated with development of hypertension in 31 out of 104 patients while 77 patients on nelfinavir, saquinavir and ritonavir did not develop hypertension. Patients on indinavir did not develop any renal dysfunction suggesting that the hypertension was due to another mechanism other than renal disease. It stands out that more than half of the patients in this study who developed hypertension were also noted to have a family history of hypertension. The mean blood pressures however, were not significantly elevated: systolic blood pressure was 153mmHg and diastolic blood pressure was 100mmHg.

1.3.5 Hypertension and metabolic changes in patients on HAART

In a study to evaluate the prevalence of hypertension in a group of HIV patients on HAART and investigate the relationship between hypertension, metabolic syndrome and insulin resistance, Gazzaruso C et al [23] enrolled 287 HIV positive patients on HAART and 287 age and sex matched controls. Insulin resistance was estimated using the homeostasis model (HOMA) index and metabolic syndrome defined according to the European group for the study of insulin resistance. The prevalence of hypertension was found to be higher in patients on HAART compared to controls (34.2% versus 11.1%). Metabolic syndrome was found in 31.1% versus 2.4% of controls. Insulin resistance was found in 3.3% versus 2.0% of controls. Analysis showed that family history of hypertension, metabolic syndrome, lipodystrophy and insulin resistance

were predictors of hypertension in HIV patients. Sattler F et al [18] carried out a similar case control study of 42 HIV patients with lipodystrophy and dyslipidemia and 42 HIV patients without lipodystrophy and dyslipidemia and 13 HIV negative controls. Hypertension was found in 74% of the patients with lipodystrophy and dyslipidemia. These hypertensive patients all had a family history of hypertension. This association between the effects of HAART on patients with family history of hypertension was also noted by Cattelan A et al [24]. Prevalence of hypertension was 48% in the controls enrolled. Their results found that systolic blood pressure correlated with a higher waist- hip ratio and also tended to be related to fasting triglycerides. This would therefore suggest a link between hypertension and components of the metabolic syndrome.

1.3.6 Hypertension and antiretrovirals: The DAD study

The D:A:D(Data collection on Adverse Events of Anti-HIV Drugs) [26] ,a large observational study is of note. This study involved over 16,000 patients in USA, Europe and Australia, looking at cardiovascular risk factors in HIV patients. Eight percent of the study population had hypertension. In the univariate analysis, NNRTIs and PIs were associated with increased risk of hypertension. However, after adjustment for other factors this association with antiretrovirals disappeared. The investigators found that hypertension was associated with older age, sex and higher body mass index rather than exposure to antiretrovirals. They concluded that hypertension in HAART experienced patients is therefore probably associated with the traditional hypertension risk factors.

1.4 Other cardiovascular risk factors associated with antiretroviral therapy

1.4.1 Dyslipidemia

Hypertriglyceridemia in association with low HDL and LDL cholesterol levels was commonly observed in HIV-infected patients before the era of HAART [27]. Dyslipidemia may be due in part, to the effects of viral infection, acute-phase reactants and circulating cytokines [28]. It is known that stavudine-based but not tenofovir-based antiretroviral therapy is associated with early

and statistically significant increases in triglyceride and total cholesterol levels [29]. Switch from a protease inhibitor may improve the HDL- cholesterol [30].

Protease inhibitors, especially ritonavir, can increase hepatic triglyceride synthesis and plasma triglyceride levels [31]. However, atazanavir, does not appear to have this effect [32]. Protease inhibitors also increase total cholesterol levels but this is not seen among all the protease inhibitors [33]. Changes in apolipoprotein B occur in patients receiving combination therapy with a nucleoside analogue and a protease inhibitor [34].

1.4.2 Insulin resistance and abnormal glucose homeostasis

Hyperinsulinemia, a surrogate measure of insulin resistance, is commonly seen in association with excess truncal fat, loss of fat in the limbs, an increased waist-to-hip ratio, and a buffalo hump. Among HIV-infected adults with lipoatrophy or fat accumulation, diabetes mellitus was seen in 7.0 percent, as compared with 0.5 percent of otherwise healthy control subjects matched for age and body-mass index [35].

Antiretroviral therapy may lead to altered flux of substrates, including free fatty acids, as well as to accumulation of intramyocellular lipid, alterations in adipokine levels (e.g. a low level of adiponectin)[36] . Protease inhibitors have been shown to induce insulin resistance in reducing glucose transport mediated by glucose transporter 4 [37]. Long-term effects, possibly related to changes in body composition, may affect insulin sensitivity. Atazanavir and saquinavir have minimal effects on insulin sensitivity [38]. Protease inhibitors may also reduce pancreatic beta-cell insulin secretion. The effect of nucleoside analogues on glucose metabolism may contribute to insulin resistance indirectly through changes in fat distribution [39].

1.4.3 Body-fat abnormalities and antiretrovirals.

Antiretrovirals are associated with a number of adverse effects. Between 33-75% of patients with HIV infection receiving ARTs develop lipodystropy. Many of these patients are noted to have characteristic body habitus changes associated with fat redistribution, consisting of truncal obesity with peripheral wasting. This was noted in patients with regimes containing a both protease inhibitiors and potent protease sparing combinations. It was found age, sex duration of

therapy contributed to this. These changes may be seen any time from six weeks to several years on HAART [40].

Protease inhibitors may induce lipoatrophy by inhibiting sterol regulatory enhancer–binding protein 1 (SREBP1)–mediated activation of the heterodimer consisting of adipocyte retinoid X receptor and peroxisome proliferator–activated receptor ?(PPAR?) or related transcription factors such as PPAR? coactivator 1 Protease inhibitors can inhibit lipogenesis and adipocyte differentiation, stimulate lipolysis, and impair SREBP1 nuclear localization[41,42].

The nucleoside analogue linked most strongly to lipoatrophy is stavudine, particularly when used in combination with didanosine. Lipoatrophy associated with nucleoside analogues may be due in part to mitochondrial injury resulting from inhibition of mitochondrial DNA polymerase ? within adipocytes and depletion of mitochondrial DNA. Nucleoside analogues can inhibit adipogenesis and adipocyte differentiation [41].

1.5 Local data on dyslipidemia and dysglyemia in HIV-infected patients.

In a study done in 2006 at the Comprehensive Care Centre, Kenyatta National Hospital, Manuthu E et al [43] evaluated the prevalence of dyslipidemia and dysglycemia in patients on HAART. He found that patients on HAART had a propensity to develop an atherogenic lipid profile. The investigator also noted that the prevalence of hypercholesterolemia and elevated LDL-C was four times higher in HIV infected patients on HAART compared to those not on HAART. Patients on HAART were 84% less likely to have low HDL-C compared to HAART naïve patients. The prevalence of dysglycemia was 20.7%, a low prevalence for this study population. No difference in the prevalence of dysglycemia was noted in patients on HAART compared to those not on HAART (p=0.284). This study looked at 134 patients on HAART, 41.8% of whom had been on HAART for more than 48 weeks. No significant difference in prevalence of hypertension between the two groups was found. This study however, had its shortcomings as it was not powered to detect hypertension and majority of the patients were on HAART for variable durations.

2.0 STUDY JUSTIFICATION

Increasing availability of antiretroviral medication for those who have indications to start treatment will reduce morbidity and mortality associated the HIV virus. This will translate to HIV infected patients having prolonged life. However, antiretroviral drugs are associated with lipodystropic changes and known metabolic complications such as dysglycemia and dyslipidemia. These complications can have an impact on cardiovascular events and are also known to be part of the metabolic syndrome of which hypertension is a component.

Hypertension is becoming a common cardiovascular disease in Africa and its significance increases with age.

Studies suggest a possible relationship between antiretrovirals and hypertension and this may be related to: duration on HAART, complex lipodystrophic changes due to HAART or specific antiretrovirals.

No published local or regional data exist on the impact antiretrovirals have on the development of hypertension in HIV infected individuals.

3.0 Study Objectives

3.1 Broad objective

To determine if there is any association between use of antiretroviral medication and hypertension.

3.2 Specific objective

1. To compare the prevalence of hypertension in HAART experienced patients to those who are HAART naïve.
2. To determine other cardiovascular risk factors in hypertensive patients on HAART: dyslipidemia, dysglycemia, cigarette smoking, family history of coronary heart disease, family history of hypertension and the anthropometric measures of obesity (BMI,WHR) of these patients.

4.0 MATERIALS AND METHODS

4.1 Study design

Comparative cross sectional group study.

4.2 Study site:

Kenyatta National Hospital's Comprehensive Care Centre (CCC). A dedicated outpatient HIV clinic in a tertiary national referral and teaching hospital in Kenya.

4.3 Study Population

HIV-infected adult patients (≥18years) attending the daily outpatient HIV clinic (CCC, at Kenyatta National Hospital) during the study period.

4.4 Patient selection

4.4.1 Inclusion criteria

1. HAART experienced patients who did not have a diagnosis of hypertension prior to commencing antiretrovirals.
2. Patients who were on a consistent HAART regime for duration of 2 years and more.
3. Willing and consenting to participate.

4.4.2 Exclusion criteria

1. HAART experienced patients with diagnosis of hypertension before starting antiretrovirals.
2. HAART experienced patients who have been diagnosed with hypertension at less than three months while on antiretrovirals.
3. HAART experienced patients found to have secondary hypertension from history and clinical examination.
4. Unwilling to participate in the study.

4.5 Case definitions

4.5.2 Adult

Adult patients were defined as those 18 years and older as indicated in their hospital records and /or their national identity card.

4.5.2 HIV Sero- Positive

HIV infected patients were those who have a positive HIV Elisa test recorded in their clinic files.

4.5.3 HAART

HAART was defined as combination from the three classes of antiretroviral drugs (NRTIs, NNRTIs and PIs).With: two NRTIs and one NNRTI or two NRTIs and one PI based regime or three NRTIs.

4.5.4 HAART experienced

These were defined as patients who had the diagnosis of HIV infection made and had been on antiretroviral medication for two or more years and known to be adherent to medication as determined from self report and from the patients file.

4.5.5 HAART naive

These were defined as patients who had been diagnosed with the HIV infection and were in WHO stages I or II with no indications for starting antiretroviral medication. These patients were selected because they have less co-morbidity as compared to patients in WHO stages III or IV and therefore less likely to have their blood pressure affected by underlying chronic illness such as chronic diarrhoea.

4.6 Screening and recruitment:

All new patients at the Comprehensive Care Centre undergo full evaluation including a comprehensive history, physical examination and laboratory investigations including full blood count, liver function, renal function tests and CD4/ CD8 counts.

Patients deemed eligible for HAART commence treatment and are then given individualized appointments depending on their clinical condition and are also required to return to the clinic for monthly supply of drugs.

Each day a list of patients who are HIV positive was drawn. All patients who met the case definitions for HAART experienced and HAART naïve were selected.

Patients were requested to give signed informed consent. Then targeted questions and clinical examination was carried out to exclude any possible secondary cause of hypertension. Clinical examination was focused on finding any sign suggestive of secondary hypertension. Those with a history and clinical features of secondary hypertension were not recruited but requested to undergo further work up to find any underlying cause for secondary hypertension. This was done in conjunction with the primary doctor in the HIV clinic.

4.6.1 Screening and recruitment of HAART experienced patients

These patients were screened on their visit to the HIV clinic for their regular reviews and collection of their medication. Targeted history and clinical examination was done then followed by blood pressure measurements. The study questionnaire was administered by the principal investigator with the help of two trained assistants. Those found to be hypertensive had further worked up to evaluate for any renal dysfunction that may cause hypertension. The hypertensive patients with normal renal functions then had fasting lipids and fasting blood sugars done to evaluate other cardiovascular risks. Transport was provided by the principal investigator.

4.6.2 Screening and recruitment of HAART Naive patients

Patients known to have HIV infection in WHO stages I or II with no indications to start HAART were screened as they came to the clinic for follow-up and recruited. Screening and recruitment of these patients took place concurrently with that of HAART experienced patients and was done in a similar manner to the HAART experienced patients.

4.7 Sampling

For both HAART naive and HAART experienced patients consecutive sampling technique was employed until the desired number of patients was achieved. Sampling for both groups of patients ran concurrently.

4.8 Sample size

The minimum sample size was calculated using the following formula:

$$N = \frac{\{Z_{1-\alpha}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\}^2}{(P_1-P_2)^2}$$

Where;

N = minimum sample size

P_1 = prevalence of hypertension in HAART experienced patients

P_2 = prevalence of hypertension in HAART naive patients

$Z1-\alpha$ = 95% confidence interval

$Z1-\beta$ = (0.842) 80% power

$P = \frac{P_1+P_2}{2}$

Using the prevalence of hypertension in HAART naive patients of 14.9% from a local study [43] and an estimated prevalence of 20% (to detect a 5% difference) [19], the minimum sample size required was 614 patients in each group making the total minimal sample size of 1,228 patients.

4.9 Clinical Methods

The investigator administered questionnaire was used to collect data. The principal investigator was helped by two trained assistants. The patients' age, sex, residence was recorded. Date when antiretrovirals therapy was commenced and compliance to medication were obtained. Any changes to the drug regimes and reasons for this were noted. A thorough family history of hypertension, coronary heart disease and sudden death, history of smoking and alcohol use were also sought.

A full physical examination with a targeted cardiovascular examination was done.

4.9.1 Anthropometric measures:

Body mass index, waist circumference and waist – hip ratios, were carried out.

Height

Standing height was measured to the nearest 0.5cm with the patient bare foot, the back square against the wall, with a set square resting on the scalp against the wall.

Weight

Weight was measured once to the nearest 100 grams using a lever balance, with the patient barefoot and in light garments.

BMI was taken as the weight divided by the square of the patients' height.

Waist circumference

Was measured as the widest circumference between the lowest rib and the top of the pelvis, measured in the horizontal plane and taken to the nearest mm.

Hip circumference

This was taken as the maximum circumference measured above the buttocks in horizontal plane and measures to the nearest mm.

The waist hip ratio was calculated as a ratio of the waist circumference to the hip circumference.

4.9.2 Blood pressures

Blood pressure measurements were done according to the World Health Organisation recommendations with the patient in sitting position, using a standard calibrated mercury sphygmomanometer with a cuff covering at least two-thirds of the upper arm circumference. Blood pressures were taken after an initial rest of 15 minutes or more, with the patient having not have smoked or taken coffee in proceeding 30 minutes. Blood pressure was taken in both arms and the blood pressure reading taken from the arm with a higher blood pressure if a pressure difference was noted. Systolic blood pressure was determined by the perception of the first Korotkoff sound (phase 1) and diastolic pressure determined by the disappearance of the fifth Korotkoff sound (phase 5). Two measurements were taken at five minute intervals and the average of the two readings taken as the patient's blood pressure. Patients with hypertension had their blood pressures further classified according to the WHO classification for hypertension [45].

4.9.3 Laboratory Methods

Renal functions and urinalysis were done for hypertensive patients and those with laboratory and clinical features suggestive of renal disease were excluded. Those with normal renal function had lipids and fasting sugars done after an overnight fast of 9 to 12 hours from which 8ml of venous blood was taken from the patients for measurement of lipid profiles and fasting blood

glucose. The samples collected were taken to the University of Nairobi biochemistry laboratory for analysis using the Humanlyser 2000 ^{R} machine for lipid profiles.

Triglycerides were determined after enzymatic splitting with lipoprotein lipase to free fatty acids and glycerol. The glycerol, after phosphorylation at by ATP produces glycerol-3-phosphate which is further oxidized by glycerol phosphate oxidase to produce hydrogen peroxide. The hydrogen peroxide then reacts with reagents to produce a colour change. Absorbance of this dye is proportional to the concentration of triglycerides in the sample.

Serum cholesterol levels were determined after enzymatic hydrolysis of cholesterol esters and oxidation to yield peroxide. The hydrogen peroxide then combines with HBA to form a chromophore which will be quantitated at 500nm.
HDL-cholestrol levels were determined using the precipitant method. Chylomicrons, VLDL (very low density lipoproteins) and LDL (low density lipoproteins) were precipitated by the addition of phosphotungstic acid and magnesium chloride. After centrifugation the supernatant fluid contained the HDL (high density lipoproteins) fraction which was then assayed. LDL-cholesterol was calculated from the total cholesterol concentration, the HDL-C and triglycerides using the Friedman formula [44].

Creatinine was assayed using photometric colorimetric test. Urea was determined using the enzymatic colorimetric test. Sodium and potassium levels were determined using the flame photometry method.

Fasting blood sugar was determined using the medisense Precision Q.I.D glucometer using a dry oxidation method.

Urinalysis was done on a midstream urine sample. Chemical analysis was done using a dry dipstick

Quality assurance

To ensure quality, commercial reagent kits were used for all biochemistry assays. All analysis was done as per the manufacturer's instructions by a competent technologist. Commercial quality control material was included in all analytic runs and results accepted when control samples were within normal limits.

5 DEFINITION OF OUTCOME VARIABLES

5.1 Hypertension

- Hypertension was defined as systolic blood pressure of equal to or more than 140mmHg and diastolic blood pressure of equal to or more than 90mmHg.
- Blood pressure noted as at the time of commencement of antihypertensives (if this data was available) in patients who had developed hypertension three months after starting antiretroviral medication.

5.1.1 WHO Grade of hypertension

The patients found to be hypertensive were further classified according to the WHO classification [45].

Table 1: WHO classification of Hypertension

Grade	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
I	140 -159	90 - 99
II	160 – 179	100 -109
III	>180	>110
Isolated systolic hypertension	>140	< 90

5.2 Dyslipidemia

Dyslipidemia was defined according to the NCEP ATPIII guidelines [13]. It included the presence of any one of the following:

5.2.1 Hypercholestrolemia:

Total cholesterol levels ≥ 5.17mmol/L

Categories

.>6.2mmol/L (high)

5.17-6.18mmol/l (borderline high)

5.2.2 Hypertriglyceridemia:

Triglycerides levels ≥ 1.69mmol/l

Categories

1.69-2.25mmol/l (borderline high)

≥ 2.26mmol/l (high)

5.2.3 High low density lipoprotein:

LDL- cholesterol ≥ 3.34mmol/l

Categories

3.34-4.11mmol/l (borderline high)

4.13-4.88mmol/l (high)

≥ 4.91mmoml (very high)

5.2.4 Low high density lipoproteins:

HDL ≤ 1.03mmol/l

5.3 Dysglycemia

Dysglycemia was categorized using the American Diabetic Association recommendations [46] as follows:

5.3.1 Diabetes:

Fasting blood glucose ≥ 7.0mmol/l.

5.3.2 Impaired fasting glucose:

Fasting blood glucose of 5.6-6.9mmol/l

5.4 Measure of Obesity

BMI(kg/m^2)

Normal -18.5-24.9

Overweight- 25-29.9

Obesity- ≥30

6 DATA MANAGEMENT AND ANALYSIS

All data collected was cleaned and verified and entered into a computer data base. The data was analyzed using the Statistical Package for Social Sciences (SPSS ver.12). Data was described as frequency distribution, means, percentages, proportions and ratios this was then presented as pie charts, bar charts, histograms and cross tabulations.

For comparison of continuous data, the student t-test was used while the chi-squared test was used to compare categorical data. Point prevalence was determined as a percentage of the study population. Associations were considered significant only when the p-value was equal to or less than 0.05.

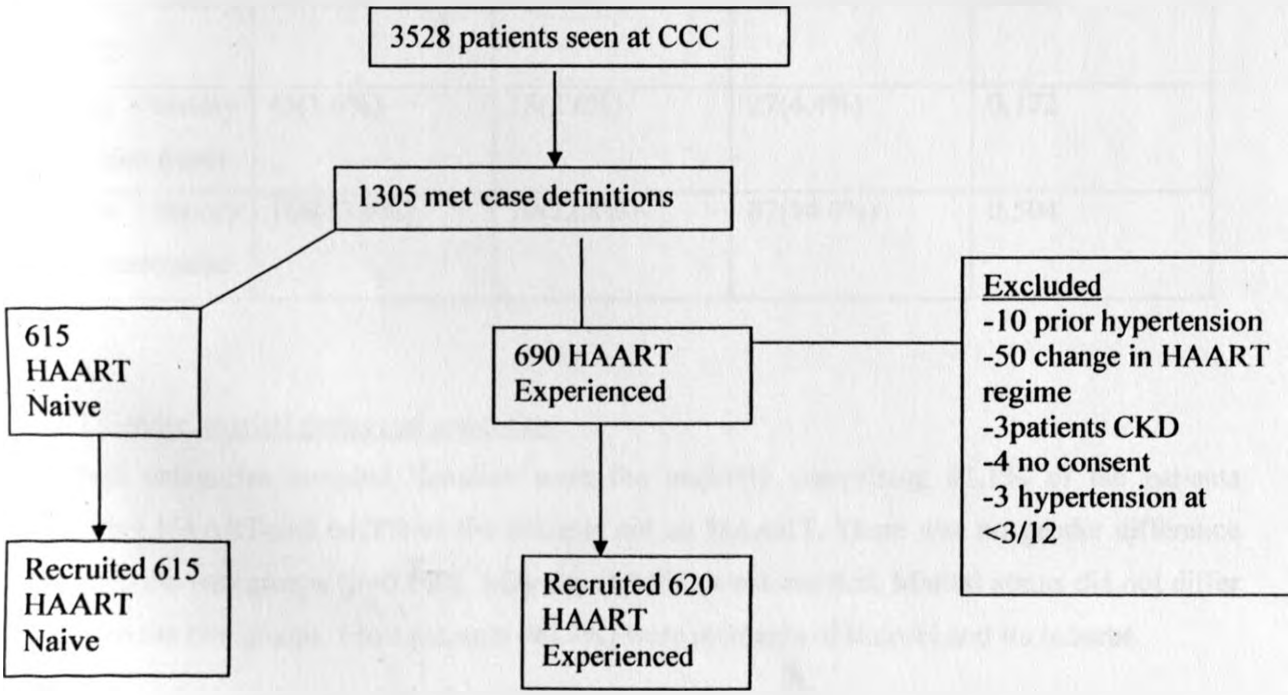
7 ETHICAL CONSIDERATIONS

Appropriate approval from the Department of Internal Medicine, University of Nairobi and Kenyatta National Hospital Ethical Committee was obtained prior to commencement of this study and informed consent was obtained from all subjects.

8 Results

During the period July 2008 to November 2008, a total of 3528 patient were seen at the CCC at Kenyatta National Hospital (KNH). 1305 patients met the case definitions. Of these, 615 patients were HAART naive, while 690 patients were HAART experienced. In the HAART experienced patient group, seventy patients were excluded because of the following reasons: 10 patients had prior history of hypertension, 3 patients had developed hypertension after less than three months of HAART, 3 patients were found to have chronic kidney disease, 4 patients declined consent, 50 patients were also excluded because they had been not been on a consistent antiretroviral regime for two years or more, it was noted that 2 of these patients were hypertensive. Thus, 620 HAART experienced and 615 HAART naive patients were recruited into the study.

Figure 1: Flow chart of screening and recruitment



8.1 BASELINE CHARACTERISTICS

The demographic characteristics are depicted in Table 2

Table 2: Study population characteristics

Variable	Totals N (%)	HAART naive n(%)	HAART experienced n(%)	p-value
Gender				
Female	778(63%)	399 (64.9%)	379(61.1%)	0.140
Male	457(37%)	216(35.1%)	241(38.9%)	
Age in years				
Mean ±S.D	40.1± 0.3	39.3±0.4	39±0.3	0.240
Median	40	39	40	
Current smoking	49(4%)	24(3.9)	25(4.0)	0.889
Family history of CHD	19(1.5%)	8(1.3%)	11(1.8%)	0.488
Family history of sudden death	45(3.6%)	18(2.6%)	27(4.4%)	0.172
Family history of Hypertension	166(13.4%)	79(12.8%)	87(14.0%)	0.504

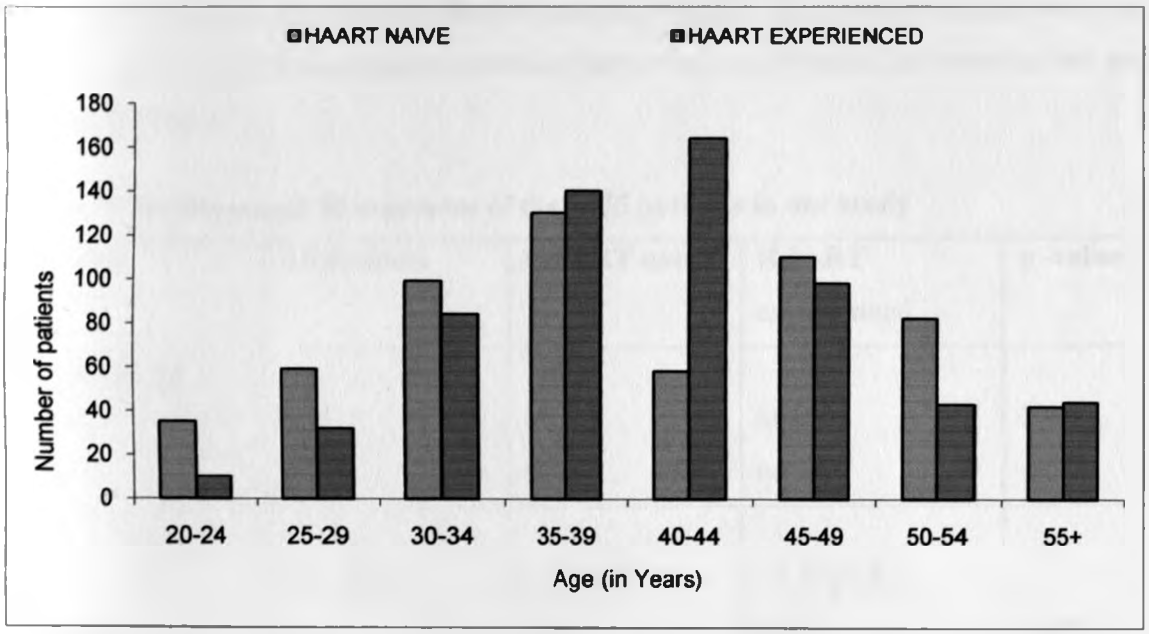
8.1.1 Gender, marital status and residence

In both categories sampled, females were the majority comprising 61.1% of the patients receiving HAART and 64.9% of the patients not on HAART. There was no gender difference between the two groups (p=0.140). Majority (68.9%) were married. Marital status did not differ between the two groups. Most patients (96.7%) were residents of Nairobi and its suburbs.

8.1.2 Age

The mean age of patients in our study was 40.1 years with a median of 40 years. The mean age of the HAART experienced patients was 39 years with a median of 40 years and in the HAART naive patients the mean age was 39.3 years with a median of 39 years. There was no statistical difference in the age of patients in both groups (p=0.240). Majority of the patients in both groups were between the ages of 30- 49 years (Figure 2).

Figure2: Age distribution in the study population



8.1.3 Cardiovascular risk factors

Overall the prevalence of smoking was low, with only 4% (n=49) of patients found to be current smokers. There was no statistical difference in the prevalence of smoking between the HAART experienced and the HAART naive group (p=0.889).

Family history of coronary heart disease had a low prevalence of 1.5% (n=19). In both groups the prevalence of family history of coronary heart disease was low and there was no difference in the two groups (p=0.488).

Only 45 patients in this study group had a family history of sudden death. There was no noted difference in the reported prevalence of history of sudden death in the family in the two study groups (p=0.172).

Family history of hypertension was reported in a total of 166 patients, 79 and 87 of whom were in the HAART naive and HAART experienced groups respectively. There was no statistical difference in the two groups (p=0.504).

8.1.4 Anthropometric measures

Both the HAART naive and HAART experienced patients had a similar median weight of 66kg. The mean BMI for the patients in this study was within normal range. The BMI in both the HAART naive and HAART experienced patients were in the normal range and there was no significant statistical difference in the two groups (p=0.109). The mean waist and waist-hip ratios were within normal in the study patients and there was no difference between the two groups in the study (Table 3).

Table 3: Anthropometric measures of the 1235 patients in our study

Variable	All patients	HAART naive	HAART experienced	p -value
Weight in kg				
Mean	67.5	67.4	66.0	0.932
Median	66	66	66	
BMI in kg/m^2				
Mean(± S.D)	23.7(±0.1)	23(± 0.2)	23.3(±0.2)	
Median	23.4	23.6	23.3	0.109
IQR	21.5-25.7	21.5-25.8	21.1-25.6	
Waist circumference (cm)				
mean	82.5	82.6	82.4	0.840
Waist – Hip ratio				
Mean				
Male	0.97	0.96	0.97	0.061
Female	0.95	0.94	0.95	0.297

8.1.5 HAART Categories

The most common NRTI regime was a stavudine-based regime with 76.2% of the patients on this regime (Figure 3). While 39.7% where on a combination of stavudine, lamuvudine and nevirapine (d4T+3TC+NVP), 36.5% of the patients were on a stavudine, lamvudine and efavirenz regime (d4T+3TC+EFV). Only 15% of the patients were on zidovudine based regimes with 7.7% on zidovudine, lamuvudine and nevirapine (AZT+3TC+NVP) regime and a similar number 7.3% on a zidovudine, lamuvudine and efavirenz (AZT+3TC+EFV) based regime. Other regimes (8.8%) represented second line regimes which were instituted in patients who had drug associated adverse effects from first line therapy or from failure of first line drugs. Of these, only 4.4% of the patients in this study were on protease inhibitors. NNRTI based regimes were the most frequently used regimes with 95.6% of the patients on either efavirenz or nevirapine.

8.1.6 Duration of HAART

In the HAART experienced patients 85.2% (n=528) of those recruited into the study had been on antiretroviral therapy for between 2 to 4 years, 11.8% (n=73) were on treatment for between 4 years to 6years and only 3% (n=19) were on treatment for more than 6 years. The mean duration of treatment was 2.8 years (SD±0.04) with a median of 2.4 years (IQR 2-3), (Figure 4).

Figure 3: HAART Categories

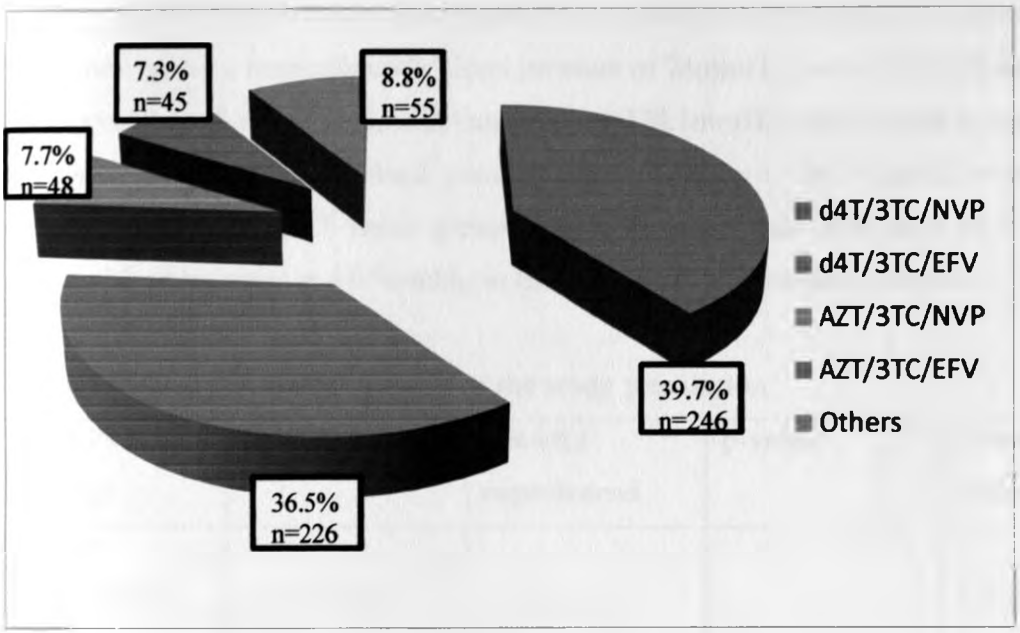
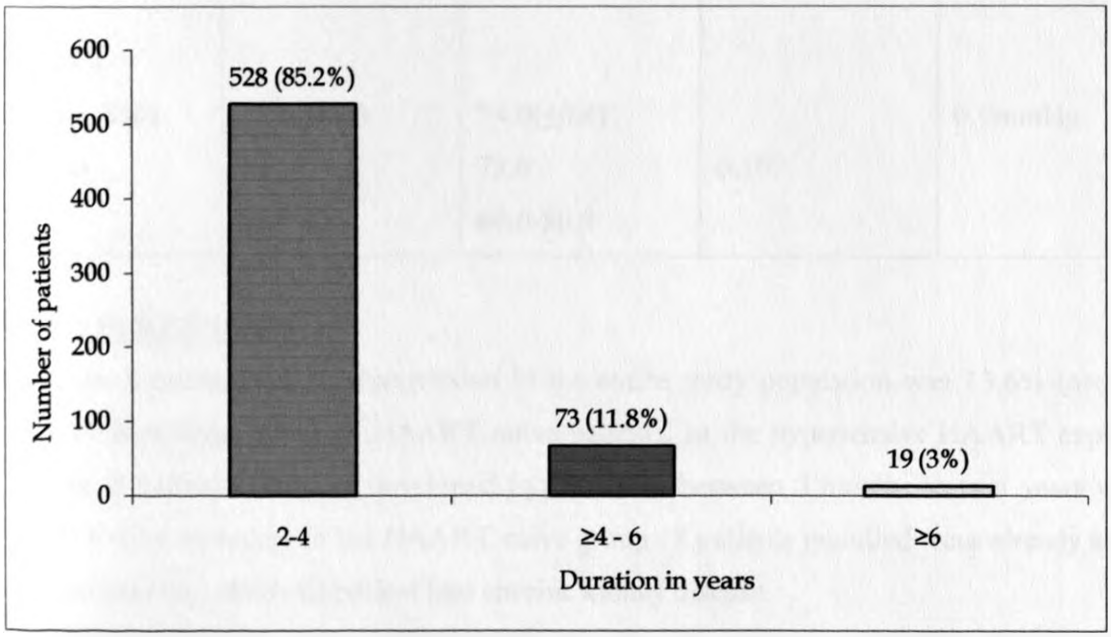


Figure 4 : Duration on HAART



8.1.7 Blood Pressures

The mean blood pressure in both the HAART experienced and the HAART naive patients was within normal range. With a mean systolic blood pressure in the HAART experienced patients of 125.6mmHg and a mean diastolic blood pressure of 74mmHg. In the HAART naive patients the mean systolic and diastolic blood pressures were 124.1mmHg and 73.1mmHg respectively. Both the systolic and diastolic blood pressures were higher in the HAART experienced group compared to the HAART naive group, with a mean pressure difference of 1.5mmHg in the systolic blood pressure and 0.9mmHg in the diastolic blood pressure (Table 4).

Table 4: Blood pressure measures of the study population

Blood Pressure (mmHg)	**HAART naive**	**HAART experienced**	**p-value**	**Mean pressure difference**
Systolic				
Mean(± S.D)	124.1(±0.7)	125.6(±0.7)		1.5mmHg
Median	122	124	0.124	
IQR	110-132.2	112-136		
Diastolic				
Mean(± S.D)	73.1(±0.5)	74.0(±0.4)		0.9mmHg
Median	70	72.0	0.109	
IQR	64.0-80.0	64.0-80.0		

8.2 HYPERTENSION

The overall prevalence of hypertension in the entire study population was 13.6% (n=168): 80 HAART experienced and 88 HAART naive patients. In the hypertensive HAART experienced patients, 3 patients who had developed hypertension between 3 months to two years while on HAART were included. In the HAART naive group 18 patients recruited were already known to be hypertensive, while one patient had chronic kidney disease.

Prevalence of hypertension in the HAART experienced patients was 12.9% (95%CI 5.1-20.9) and in the HAART naive patients the prevalence was 14.3% (95%CI 5.9-22.1). There was no statistical difference between the prevalence of hypertension in the two groups (p=0.507).

8.2.1 WHO Grade of Hypertension

Majority of the hypertensive patients in both the HAART experienced (n=54) and HAART naive patients (n=53) were found to be in WHO stage 1, we included 13 patients on antihypertensives who had inadequate blood pressure control falling into stage I , 10 patients in the HAART naive group and 3 patients in the HAART experienced group. There were 25 and 17 patients in WHO stage II in the HAART naive and HAART experienced groups respectively. With only 3 patients and 5 patients in Stage III in the HAART experienced patients and HAART naive groups respectively. Finally, 7 patients and 4 patients had isolated systolic hypertension in the HAART experienced patients and HAART naive groups respectively. Using stage 1 hypertension as reference there was no statistical difference in the WHO stages of hypertension across the other stages of hypertension (Table 5).

Table 5: WHO Grading of blood pressures of our study population

Stage	HAART naive n(%)	HAART experienced n (%)	p-value
Stage I	54(8.8)	53(8.4)	Reference
Stage II	25(4.1)	17(2.7)	0.416
Stage III	5(0.8)	3(0.5)	0.717
Isolated systolic hypertension	4(0.6)	7(1.9)	0.586

8.2.2 Antiretroviral type and Hypertension

Of the hypertensive patients on HAART, 78.8% (n=63) were on a stavudine based regime and 16.2% (n=13) were on a zidovudine based regime. Only 5% (n=4) of hypertensive patients were on a non-stavudine, non-zidovudine based regime. There was no association between hypertension and whether the patient was on a stavudine or a non-stavudine based regime (p=0.512). Majority of patients (n=593) were on non–nucleoside reverse transcriptase (NNRTIs) regimes. We found no statistical association between hypertension and whether the patient was on nevirapine or efarvienz (p=0.371).

8.2.3 HAART duration and Hypertension

There was a trend of increasing prevalence of hypertension with duration of HAART treatment: 2 to 4years ,≥4-6 years, more than 6 years were associated with prevalence of 12.3%, 15.1% and 21.1% respectively (Table 6).This was however not statistically significant (p=0.106). It is of note that we did not have sufficient power to study this association between hypertension and duration on HAART.

Table 6: Duration of HAART use and Hypertension in our study

Duration in years	No of hypertensive patients n(%)	Prevalence in (%)	95% CI
2-4	65(81.2%)	12.3%	CI(4.8-19.9)
≥4-6	11(13.8%)	15.1%	CI(6.5-23.7)
≥6	4(5%)	21.1%	CI(9.7-32.5)

*p=0.106

8.3 CARDIOVASCULAR RISK FACTORS IN HYPERTENSIVE PATIENTS

The HIV patients with hypertension were relatively young individuals with similar mean age in both groups. The mean age for the females was 44.4 years and 45.6 years in the HAART experienced and HAART naive groups respectively. While in the males it was 46.5 years in both groups. The prevalence of smoking and family history of coronary heart disease was very low, with only 2 patients found to be current smokers and 4 patients with family of CHD in the HAART experienced group (Table 7). Seven patients were current smokers and only 4 patients had a family history of CHD in the HAART naive group (Table 8). The mean BMI for the patients in both groups was just slightly overweight at 25.3kg/m^2.

Table 7: Cardiovascular risk in the 80 HAART experienced hypertensive patients

Factor	Number of patients	%	95% CI
Gender and Mean Age			
Male (mean age-46.5yrs)	32		
Female(mean age 44.4yrs)	48		
Smoking	2	2.5%	
Family history of CHD	4	4.0%	
Dyslipidemia	57	71.3%	CI(65.0-77.5)
Dysglycemia	28	35%	CI (24.6-45.5)
Impaired fasting glucose	23		
Diabetes Mellitus	5		

*BMI (mean) 25.3kg/m^2

Table 8: Cardiovascular risk in the 88 hypertensive HAART naive patients

Factor	Number of patients	%	95% CI
Gender and mean Age			
Male (mean age-46.5yrs)	33		
Female(mean age 45.6yrs)	55		
Smoking	7	8%	
Family history of CHD	4	4.6%	
Dyslipidemia	55	62.5%	CI(54.2-68.9)
Dysglycemia	24	27.3%	CI (17.7-36.3)
Impaired fasting glucose	20		
Diabetes Mellitus	4		

*BMI (mean) 25.3kg/m^2

Table 9: Types of dyslipidemia in the hypertensive patients

Type of dyslipidemia	HAART experienced patients n(%)	HAART naive patients n(%)	p-value
Hypertriglyceridemia	47(58.8%)	43 (48.7%)	0.259
Hypercholesterolemia	43(53.7%)	24(27.3%)	0.012
Elevated LDL-C	38(47.5%)	18(20.5%)	0.032
Low HDL -C	42(52.5%)	45(51.1%)	0.982

8.3.1 Dyslipidemia

The prevalence of dyslipidemia in patients on HAART was 71.3% (n=57). While the prevalence of dyslipidemia in the HAART naive patients was 62.5% (n=55). There was no statistical difference between the two groups (p=0.299).

Hypertriglyceridemia: Hypertriglyceridemia was found in 58.8% (n=47) of the hypertensive HAART experienced study patients. Majority of whom (83%) patients had borderline elevated triglycerides (1.69-2.25mmol/l), while 8(17%) had high triglyceride levels (≥ 2.25mmol). Borderline elevated triglycerides was noted in 69.8% (n=30), while high triglycerides was found in 30.2% (n=13) of the HAART naive patients. There was no statistical difference between the prevalence of hypertriglyceridemia in both groups (p= 0.259).

Hypercholesterolemia: was found in 43(53.7%) of the HAART experienced patients. Borderline high total cholesterol was found in 74.4% (n=32) of the patients, while 25.6% (n=11) had moderate to severe high cholesterol. The prevalence of hypercholesterolemia was lower in the HAART naive at 27.3%. There was a statistical difference in the two groups (p=0.012). Twenty patients had borderline high cholesterol with four patients with moderate to severe high cholesterol.

Elevated LDL cholesterol: was found in 38 patients (47.5%) of the HAART experienced patients. Of these 76.3% (n=29) had borderline high cholesterol while 23.7% had high cholesterol. We found no patient with very high cholesterol in the HAART experienced patients. HAART naive patients had lower prevalence of LDL-C (20.5%).This was statistically significant (p=0.032). In the HAART naive patients all but one patient had borderline high cholesterol.

Low HDL cholesterol: was found in 42 patients (52.5%) of the HAART experienced and 51.1% (n=45) of the HAART naive patients. There was no statistical difference between the two groups (p=0.982).

8.3.2 Dysglycemia.

The prevalence of dysglycemia was 35% (n=28) in the HAART experienced group. Five patients were noted to have diabetes mellitus, while twenty- three patients were found to have impaired fasting glucose. In the HAART naive patients 27.3% (n=24) had dysglycemia with 20 patients noted to have impaired fasting glucose and 4 patients with diabetes mellitus. There was no statistical difference between the HAART experienced and HAART naive groups (p=0.23).

9 Discussion

This study was carried out between July 2008 and November 2008 at the Comprehensive Care Centre, Kenyatta National Hospital. The study had 63% females (female to male ratio1.7:1). This is consistent with other studies done in HIV patients at the Kenyatta National Hospital [43,47].

There was no gender difference between the HAART experienced and HAART naive patients. Our study population comprised relatively young individuals. Their median age was 40 years, with majority of patients aged between 30-49 years. There was no difference in the median age between the HAART experienced and HAART naive patients. Age and gender were therefore not confounders in our study. The National AIDS and STI control Programme (NASCOP) estimates that at least two-thirds of all HIV- infected individuals in Kenya are women. Majority of them are between the ages of 14-59 years [1]. The age and gender distribution in our study is a fairly representative sample of HIV-infected patients in Kenya.

All the anthropometric measures of the HAART experienced and the HAART naive patients were within normal range. There was no difference in the anthropometric measures between the two groups. The HAART naive patients recruited had no indications to start antiretroviral therapy therefore they would not have had significant co-morbidities affecting their weight. The finding of normal anthropometric measures in HAART experienced patients is not surprising; patients on stable antiretroviral regimes are expected to gain weight as immune reconstitution occurs after suffering the ravages of immune suppression. Similar normal anthropometric findings in HAART experienced patients were found in a local study looking at lipodystrophy in patients on antiretroviral therapy [47].

Only 4% of the patients in the entire study population were current smokers. This low prevalence is consistent with other local studies [43,48,49]. An earlier local study done in a HIV- infected population found a prevalence of 9% [43] while another study done in hypertensive patients an even lower prevalence of 6.5% was found [49]. We no difference in the frequency of smoking between the HAART experienced and the HAART naive group (p=0.889). Despite this low

frequency of cigarette use, smoking remains an important cardiovascular risk factor that needs to be addressed in each individual patient who requires aggressive lifestyle modification therapy.

Overall, the family history of coronary heart disease was found in 1.5% (n=19) of patients. In a study done by Manuthu E et al [43], similar low prevalence of 2.7% in a HIV population was found. Varying prevalence's of 26.7% and 5.4% respectively have been found in non HIV-infected populations [48,49]. There was no difference in the family history of coronary heart disease between the HAART experienced and HAART naive groups (p=0.488).

Our study found the overall prevalence of hypertension in the HIV–infected patients to be 13.6%. There is no recent comparative data looking at the prevalence of hypertension in urban populations in Nairobi. Studies in other African countries have reported prevalence's of 22.4%-33.4% [50]. Our lower prevalence could be explained by our sampling of predominately young women with lower body mass indexes. In a South African study [10] of patients attending various clinics across the country, a high prevalence of hypertension of more than 55% was found. This higher prevalence could because of the difference in the study sites; we sampled patients in an exclusively HIV clinic compared to this study of attendees to general medical clinics which are likely to have a heavy hypertension burden.

The prevalence of hypertension in the HAART experienced patients was 12.9% and 14.3% in the HAART naive patients and there was no statistically significant difference in the prevalence between these two groups (p=0.507). The effect of HIV on hypertension has been studied because HIV is associated with effects on the vascular endothelium leading to arterial stiffness [54]. However, there has been no age associated increase in hypertension in HIV infected individuals [51]. Rather than HIV *per se* causing hypertension, renal failure is the major cause of hypertension in the HAART naive patients [55]. Further evidence of this lack of association between HIV and hypertension has been shown by other studies [25,52,53]. Our prevalence of hypertension is similar to a local study done by Manuthu E et al [43] who also found no statistical difference in the prevalence of hypertension between HAART naive and HAART experienced patients.

Our finding that antiretroviral therapy may not be associated with hypertension is supported by other studies [53,56,57]. In a cross-sectional study of patients with a similar comparative BMI ($24.3kg/m^2$) to our patients, Jerico C et al [56] found a similar prevalence of hypertension to our study at 13.1% and 13.5% in the HAART experienced and controls respectively. Khalsa A et al [53] found no increase in hypertension prevalence in HIV-infected women on HAART. This study had a higher group prevalence of 26% and 28% in the HAART experienced and controls respectively, which could be explained by the higher BMI of patients in this study. Seaberg E et al [19] found an increase in hypertension in HAART experienced patients. However, this study was different from ours in that it was done in men, who were predominantly white. Furthermore, blood pressures of this study group were not taken in a standardized way therefore, their findings cannot be generalised. Other studies that found a higher prevalence of hypertension had different study designs and sampled predominately white populations who already had established metabolic complications or lipodystrophy [18,23,58].

The effect of antiretroviral drugs on hypertension could have influenced the prevalence of hypertension in our study. Majority (95.6%) of our patients were on non-nucleoside reverse transcriptase inhibitors. NNRTIs have been associated with a 33% reduced incidence of hypertension in patients taking them for more than 10 months [52]. This intriguing finding could explain why we did not find an increased prevalence of hypertension. We found no association between hypertension and the various types of antiretroviral medication. This is consistent with other studies [52,53,56]. Protease inhibitors in Kenya are used as part of second line therapy. Findings of an association between protease inhibitors and hypertension [22,24] could not be addressed by our study because only 4.4% of our patients were on these drugs.

It has been suggested that a longer duration on HAART is associated with an increased prevalence of hypertension [19,25]. The median duration of use of HAART in our study was rather short at 2.4 years. A study with a similar median duration also found no increase in hypertension [52]. Cumulative use of HAART has not been associated with an increase in hypertension in women [53]. Studies [19,25] done in mainly white populations with longer follow-up durations found increasing duration on HAART is associated with higher prevalence of hypertension. Bakken M et al [25] found the highest prevalence of hypertension was

associated with cumulative use of HAART for more than five years [25]. This progressive raise in blood pressure could be as a result of "return to normality sign", in which HIV-infected patients once started on antiretroviral improve in health and subsequently gain weight with increasing BMI [20,22]. The risk for developing hypertension with increasing duration of HAART could not be satisfactorily addressed by our study as it was not sufficiently powered to detect any association between duration of HAART use and hypertension.

We looked at the grade of hypertension as a cardiovascular risk factor. Majority of the hypertensive patients (63.9%) were in WHO stage 1. This is similar to patients in the D.A.D cohort where most of the hypertensive patients on HAART were in WHO stage 1 [52]. It appears that patients with a median duration of 2.4years on HAART do not have significantly high grades of hypertension and therefore have less cardiovascular risk. This lower grade of hypertension is probably because we had younger patients who were just slightly overweight. However, this finding needs to be put in context of the fact that for every 20mmHg increase in systolic blood pressure and 10mmHg increase in diastolic blood pressure the cardiovascular risk doubles [12]. We found the mean pressure difference between the HAART experienced and HAART naive patients is not associated with an increased cardiovascular risk: with a systolic mean blood pressure difference of 1.7mmHg and diastolic blood pressure difference of 0.5mmHg.

The cardiovascular risk factors among the hypertensive patients were assessed. These patients as noted earlier were young and therefore age was not a cardiovascular risk factor. Prevalence of smoking and family history of coronary heart disease was also low. In both groups, the patients were overweight with mean a BMI of 25.3kg/m^2; this is not associated with cardiovascular risk [59].

The prevalence of dyslipidemia in the HAART experienced patients was high in our study at 71.3%. , this is similar to Mcligeyo A et al [47] but higher than the prevalence noted by Manuthu E et al[43]. This higher prevalence could be because we had a smaller highly selected group of patients who already had hypertension as a significant cardiovascular risk factor and they also had longer cumulative exposure on HAART. A similar prevalence (69.9%) was found by

Mohammed IA et al [49] in hypertensive patients attending outpatient clinics at Kenyatta National Hospital. As expected in HIV infected patients the type of dyslipidemia we found was elevated triglycerides and low HDL- C [43]. In our study it was noted that HAART experienced patients had high triglycerides, low HDL, and elevated LDL-C. This atherogenic lipid profile is worrying as it translates to possible increased cardiovascular risk. Kamotho A et al [60] found dyslipidemia was a significant cardiovascular risk factor for patients with angiographic evidence of coronary heart disease. Aggressive lipid control needs to be instituted in all hypertensive patients to reduce cardiovascular morbidity and mortality.

Dysglycemia was found in 28 patients in the HAART experienced group and in 24 patients in the HAART naive group. Our higher prevalence could be because we used a lower cut off (5.6- 6.9 mmol/l) for impaired fasting glucose compared to Manuthu E et al [43] (6.1-6.9 mmol/l). Diabetes was noted in 4 patients and impaired fasting glucose was noted in 20 patients who were HAART naive. Diabetes mellitus is coronary heart disease equivalent therefore these patients need aggressive risk factor control. Impaired fasting glucose is often associated with other cardiovascular factors and this condition is loaded with a high propensity to atherosclerosis [61].

A limitation of this study is the cross-sectional design which is only able to show association between HAART and hypertension but cannot demonstrate causality.

In conclusion, we found no increased prevalence of hypertension in patients on antiretrovirals for two years or more. The most important cardiovascular risk factor in hypertensive patients on HAART is an atherogenic lipid profile and dysglycemia. We recommend a baseline lipid profile and fasting blood sugars for hypertensive HIV-infected patients as part of their cardiovascular risk assessment with necessary steps taken to reduce any recognized risks.

10 Conclusions

1. There is no increased prevalence of hypertension in patients on antiretroviral therapy for more than two years compared to antiretroviral naive patients in our study population.
2. In hypertensive patients HIV–infected patients dyslipidemia and dysglycemia are significant cardiovascular risk factors.

11 Recommendations

1. HIV-infected hypertensive patients should have their cardiovascular risk profile determined, especially for dyslipidemia and dysglycemia, and relevant risk reduction steps taken.
2. In view of the cardiovascular risk found in the hypertensive HIV-infected patients prospective studies should be done to document any increasing morbidity or mortality from cardiovascular disease in these young patients.
3. Further follow-up of patients on HAART to document if longer duration on HAART will result in an increase in hypertension prevalence.

12 Limitations

1. By design the study is cross-sectional and therefore it's unable to show causality.
2. Intrinsic variability in blood pressure remains a confounder.
3. Patients with secondary hypertension may have been included (misclassification bias).
4. We could not determine the duration of HIV infection in our HAART naive group.
5. Recent CD4 counts of the patients were not taken.

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APPENDIX -1
STUDY PRO-FORMA DOCUMENT

Study no..... Date.....

1.Personal Data

Name of patient

Age sex

Marital Status
(single =1,married =2, divorced=3, widowed =4)

Residence

2.On ARVs Yes NO

Yes =1, No =2

If Yes, Date of beginning ARVs

3.Duration of Antiretroviral use years

A.What regime have been on
d4t-3TC-NVP(=1)

d4t-3TC-EFV(=2)

AZT-3TC-EFV(=3)

AZT-3TC-NVP(=4)

Other(=5)

B. How long was this regime used months years

C.Further history and physical examination for patients without secondary hypertension

1. Family History of
   Hypertension ☐

   Diabetes ☐

   Coronary heart disease ☐

   Sudden death ☐

2. Social History
   Smoking: Non smoker ☐

   Smoker No. of sticks per day ☐ no. of years ☐

   Former smoker No. of years of abstinence ☐

   Alcohol: Never drank alcohol ☐

   Drink alcohol ☐

3.If on ARVs ,did you develop hypertension 3 months into therapy YES ☐

   NO ☐

   BP at time of starting antihypertensives .....

4. If not on ARVS ,do you have hypertension YES ☐

   NO ☐

   BP at time of starting antihypertensives .....

B.TARGETED HISTORY AND PHYSICAL EXAMINATION

A.History and clinical findings

Renal vascular disease.....

Renal parenchymal disease.....

Endocrine Hypertension : cushings syndrome.....
Acromegally.....
Hyperthyroidism.....
Hypothyroidism.....
Pheochromocytoma.....

Coarctation of the aorta.....

Possible secondary hypertension

yes ☐

no ☐

Further work up requested.....

Results.....

Physical Examination Findings

1.Pulse rate ☐

2. 1st Blood pressure reading 2nd Blood pressure reading

Average ☐

3.Apex beat ☐

4.Heart sounds Normal ☐ abnormal ☐

5.Murmurs Yes ☐ No ☐

6. Anthropometric measures

Waist circumference ☐ Hip circumference ☐ WHR ☐

Weight ☐ Height ☐ BMI ☐

Laboratory Tests

Renal function tests

Urea.....mmol/l
Creatinine.....ummol/l
Potassium.....mmol/l
Sodium.....mmol/l

Calculated GFR.....ml/min

D.Laboratory work up for hypertensive patients on ARVs

Laboratory Findings

1. Fasting Blood sugar…….mmol/l

2.Fasting lipid profile
TG……mmol/l
TC……mmol/l
LDL-C……..mmol
HDL-C ……..mmol/l

APPENDIX-2

STUDY SUBJECT EXPLANATION

I am Dr Stanley Ngare, a postgraduate student, currently doing postgraduate studies in Internal Medicine at the University of Nairobi. I would like to introduce you to a study I am conducting, entitled the **Prevalence of hypertension and associated cardiovascular risk factors in HIV infected patients on antiretroviral therapy.**

About the study

The study involves comparing the prevalence of hypertension and any associated factors that may lead to hypertension in HIV positive patients taking anti-HIV medication. Hypertension and these factors which involve changes in blood sugar and blood cholesterol may increase the risk of heart disease. Therefore early detection can help reduce this risk.

What does the study involve?

The study will involve checking your medical records, doing a physical examination to see if any cause of hypertension can be found. Those without findings of a secondary cause of hypertension will be requested to fill the study questionnaire and also involve taking your weight, height, waist and hip measurements and blood pressure. It also involves doing laboratory tests for those who are found to be hypertensive. These tests will be for assessing renal function, fasting lipid profile, fasting blood sugar and a urinalysis. It will involve asking you to remain without eating for about 9 hours the previous night before your blood is taken. About 6-8ml of blood will be collected and a urine specimen to assess for any urinary tract disease will be taken the lab for analysis. Apart from slight pain of taking your blood there are no dangers. Transport costs to come for the lab tests will be met by me.

All information you shall provide will be kept strictly confidential.

How will you benefit from the study?

By measuring your blood pressure and doing your blood tests, we shall know the likelihood of your developing heart disease and therefore advice you accordingly and give medicine if required.

Can you withdraw from the study?

Yes, you are free to withdraw from the study and this will not affect your care or treatment in any way. However, we encourage you to remain in the study for your benefit and the benefit of other patients.

Thank you for your cooperation.

APPENDIX -3

CONSENT FORM

Name.....

Age.....

Number.....

I the above have been requested to take part in a study concerning the prevalence of hypertension and lipid and blood sugar abnormalities in patients on antiretroviral drugs. This will involve taking a full history, general examination including a full history, general examination including blood pressure, weight, height, waist and hip measurement.

If found to be hypertensive it will also involve taking of my blood (6-8ml) for assessment of lipid levels, blood sugar, renal function and also involve a providing a urine specimen. Costs for travel and laboratory costs will be met by the investigator.

All the results obtained will remain confidential

I also understand that this consent is voluntary and that I can withdraw from the study at any time without any penalties.

I therefore consent to be recruited into the study

Patient signature ..... **Date**.....

Signature.....

Dr S Ngare

Tel :0722881579