PREDICTORS, INCIDENCE OF HYPERTENSION AND TRAJECTORIES OF BLOOD PRESSURE DURING A FIVE YEAR PERIOD AMONG HIV-INFECTED AND UNINFECTED RWANDAN WOMEN

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In Epidemiology and Biostatistics

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DECLARATION

I, Christine MUTAGANZWA, declare that the work contained herein is my own original work, and that where I have made use of others' ideas, I have referenced accordingly. This work has never been submitted before for any degree or qualification, certificate or publication.

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ABSTRACT

Introduction:

The Human Immunodeficiency Virus (HIV) and Acquired Immune-deficiency Syndrome (AIDS) epidemic is one of the most devastating health crises of the modern time, affecting mostly the African continent. Non-communicable diseases such as hypertension (HTN) are also becoming increasingly important health threats in Sub-Saharan Africa (SSA) linked to a rapid epidemiological transition. In this study, the incidence of HTN and risk factors associated with blood pressure (BP) changes in HIV+ and uninfected (HIV-) Rwandan women were determined.

Method:

Participants were recruited in 2005 as an observational cohort, and measurements taken every six months to assess the effectiveness and toxicity of HAART in HIV+ women in Kigali, Rwanda. Clinical examination was conducted and socio-demographic information, blood pressure readings, anthropometric and laboratory risk factors were collected in 710 HIV+ and 224 HIV- women aged 22 – 78 years. Of these, 662 HIV+ and 202 HIV- women met the inclusion criteria for this study. HTN incidence rates were estimated from 2005 to 2011. Generalized estimating equations were used to determine risk factors associated with systolic and diastolic blood pressure (SBP/DBP) changes over time.

Results:

In this analysis of 864 women, 202 (23%) were HIV- and 662 (77%) were HIV+ HAART-naïve at recruitment. Of the HIV+ participants, 497 (75%) were initiated on treatment by the end of the study in February, 2011. HIV- participants were significantly older than the HIV+ participants (median age 43 (33.8-49.4) vs. 35 (30.6-39.5) years; $p < 0.001$) and had on average higher SBP (119 SD (15) versus 116 SD (10) mmHg, $p = 0.012$) and higher DBP (73.3 SD (10.4) versus 71.2 SD (7.5) mmHg, $p = 0.0013$) measurements at recruitment.

The incidence rate (IR) of HTN from 2005 to 2010 in HIV + participants on antiretroviral treatment was 7 cases per 1000 per person-years at risk (95% CI 4.2 – 10.9); for HIV- women the IR was 23 cases per 1000 person-years (95% CI 15.3 – 36) and for HIV + patients HAART naive the IR was 3 cases per 1000 person-years (95% CI 0.47 – 23.72).

Being underweight was associated with a 3.1 mmHg decrease in mean SBP compared to being normal weight (95% -5.48 – (-0.68); p = 0.012) for HIV + participants on HAART. For every unit increase in monthly income, SBP increased by 2.34 mmHg (95 % CI 0.077- 4.75; p = 0.058) for the HIV + HAART naïve and by age (p < 0.0001) and income (p < 0.0001) for the HIV-. Being underweight decreases DBP by 1.59 mmHg compared to being normal weight (95% CI -3.17 – (-0.013); p = 0.048) for the HIV+ on HAART. Being employed was associated with 5.1 mmHg decrease in DBP (95% CI -9.06 – (-1.14); p = 0.012) compared to not being employed for the HIV+ HAART naïve and for every year increase in age the HIV-, DBP increased by 0.2 mmHg (95 % CI 0.018 – 0.327; p = 0.028) and with every unit increase in depression score, DBP decreased by 0.02 mmHg (95 % CI -0.35 – (-0.02); p = 0.025).

Conclusion:

Incidence rates of HTN were higher in HIV- compared with HIV+ participants, most likely due to the older age of the HIV- study participants. The findings also show that socio-economic factors such as income and employment status and lifestyle factors such as BMI and depression were also associated with blood pressure changes. Therefore, efforts should be made in raising the awareness of potential modifiable risks, such as lifestyle factors, for prevention of HTN and blood pressure control.

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I dedicate this study to the RWISA participants and staff.

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LIST OF ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome

ANOVA: Analysis of variance

BP: Blood pressure

CI: Confidence interval

CVD: Cardiovascular diseases

DBP: Diastolic blood pressure

GEE: Generalized estimating equations

HAART: Highly active antiretroviral therapy

HDL: High density lipoprotein cholesterol

HIV: Human immunodeficiency virus

HTN: Hypertension

IQR: Inter-quartile range

IR: Incidence rate

LDL: Low density lipoprotein cholesterol

OCP: Oral contraceptive pill

RASD Rwanda: Regional Alliance for Sustainable Development Rwanda

RWF: Rwandan Francs

RWISA: Rwandan Women's Inter-association Study and Assessment.

SBP: Systolic blood pressure

SD: Standard deviation

US$: United States Dollars

WE-ACTx: Women Equity and Access to Care and Treatment

WHO: World Health Organisation

SSA: Sub-Saharan Africa

CHAPTER ONE

BACKGROUND AND INTRODUCTION

1.1. BACKGROUND

The Human Immunodeficiency Virus (HIV) and Acquired Immune-deficiency Syndrome (AIDS) epidemic is one of the most devastating health crises of modern times, affecting families and communities in all nations of the world (1). Sub-Saharan Africa (SSA) is home to 13% of the global population, but carries a disproportionate burden of HIV prevalence worldwide, with about 68% of all persons living with HIV being Africans. In Africa, about 60% of infected adults are women (1). Gradually, highly active antiretroviral therapy (HAART) medications have become available in most African countries due to price reductions and increased availability of generic drug formulations (2). Availability of HAART gives new hope for optimal health for HIV-infected persons who have access to HAART medications in developed and most developing countries (3, 4). As access and availability to HAART improves in most African countries including Rwanda, HIV infection will become a chronic illness. In some countries, life expectancy has started to increase significantly in HIV infected patients (5-8). Since the introduction of Zidovudine in 1987, antiretroviral medication has improved the wellbeing of HIV infected persons due to durable virologic suppression (9). For instance, the median survival for a person diagnosed with HIV infection was 10 years in 1990 (8), but is now close to the life expectancy in the general population (5).

However, it is of concern that HAART use has recently been repeatedly reported to increase the occurrence of metabolic and cardiovascular complications during the course of treatment (10-13). The metabolic syndrome has been defined by the International Diabetes Federation (IDF) as a cluster of central obesity, raised triglycerides, reduced HDL cholesterol, raised

fasting plasma glucose and increased blood pressure (14). The National Cholesterol Education Program (Adult Treatment Panel III) defines metabolic syndrome as the presence of three out of five of the following characteristics: abdominal obesity, elevated triglycerides, raised HDL cholesterol, elevated blood pressure and raised fasting glucose (15).

Some of the cardiovascular complications that are, repeatedly reported in patients with HIV on HAART are elevated blood pressure or hypertension reported as an emerging new threat to the health and well being of people living with HIV (16). . and have become the focus of scientific debate (17-19). However, this debate remains controversial. Some studies have shown HAART use for HIV treatment to be associated with an increase in prevalence of cardiovascular diseases (CVD) (20). Furthermore, studies suggest that HTN with HAART use may be related to specific antiretroviral agents such as NNRTIs and longer term use of HAART (21-23).

Raised blood pressure means that the arterial blood pressure is continually higher than the recommended level, 120/80 mmHg. One may have high blood pressure if just one of the two numbers is higher than it should be, in that case it is called isolated SBP (i.e 140/80 mmHg) or isolated DBP (i.e 120/100 mmHg) (24). For most people, there is no single cause for their high BP. Causes of raised BP are not exactly known; however, it is known that some lifestyle and / or environmental factors can affect one's risk of developing it. For example eating too much salt, physical inactivity, and being overweight, and drinking alcohol and now HAART use. HTN is an independent risk factor for myocardial infarction, stroke, heart failure and kidney disease (25).

The aim of this research was to examine the development of HTN, a contributor to the burden of heart disease, stroke and kidney failure and premature death and disability, in the era when access to HIV treatment and rapid scale-up of HAART became evident in Rwanda (26) and

life expectancy has improved. This study does not assess the effect of specific HAART regimens on the outcomes of interest, but has assessed the effects of commencing HAART on incidence of HTN among the studied population; it concentrates on socio-economic and lifestyle non-pharmacological modifiable risk factors that may be changed in order to prevent HTN occurrence. Although there are still geographical barriers to effective access to some healthcare programs, Rwanda's health care services have improved within the last 10 years. This has led to a decline in HIV prevalence in Rwanda, attributed to strong political will and a leadership committed to improving health care infrastructure.

1.2. LITERATURE REVIEW

Although enormous challenges persist in the control of infectious diseases, non-communicable diseases are increasingly becoming important health threats in SSA, linked to a rapid epidemiological transition (27). Since the beginning of the HIV epidemic in 1981, 25 million people have died of AIDS globally until 2009 (WHO 2009). Untreated HIV infection was also found to be associated with pericardial disease and cardiomyopathy, which worsened as the infection progressed (28). Prendergast reported that 10 to 20% of HIV positive patients were affected by significant cardiac diseases, which were the causes of death for 5% of the patients (29).

Following implementation of HAART in 1996 in developed countries, mortality due to AIDS decreased substantially as a result of the effectiveness of the therapy in providing sustained suppression of viral replication and preservation of immune system function (9, 30). With HAART use, complications of HIV infection such as cardiomyopathy and pericarditis have been remarkably reduced (31). Since then, considerable progress has been achieved worldwide, and the increased availability of therapeutic agents has led to about 5.2 million (36%) of the 15 million people in need of treatment in low and middle income countries

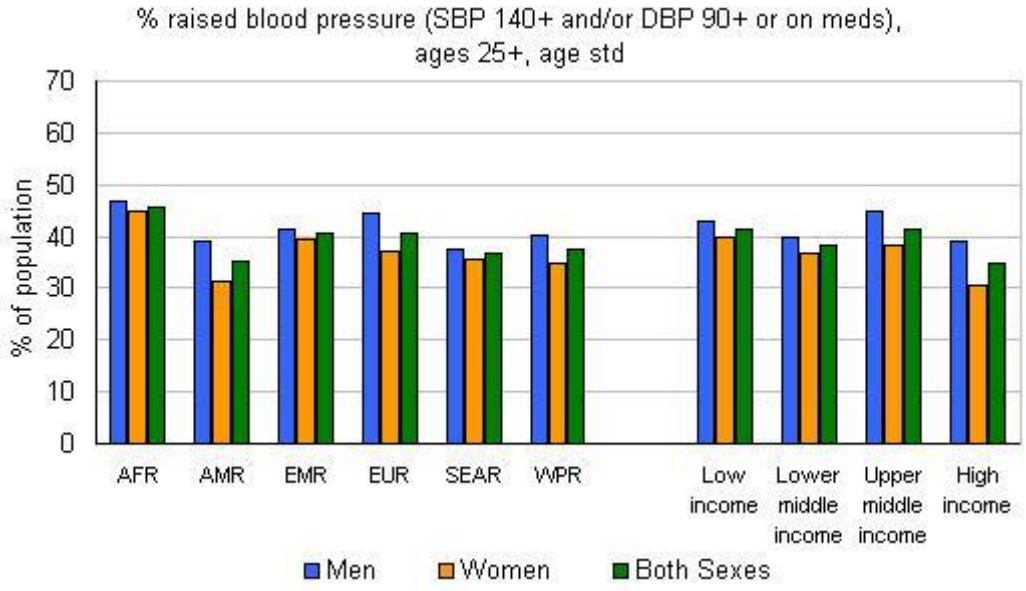
receiving HAART compared to 30% in 2008 (UNAIDS 2011). Most countries in SSA are working towards universal access to HAART, and Rwanda is among the top ten low and middle income countries (Botswana, Cambodia, Chile, Croatia, Cuba, Guyana, Namibia, Nicaragua, Rwanda and Slovakia) in achieving universal access to antiretroviral treatment by December 2010 (UNAIDS 2011). The Rwandan national guidelines eligibility criteria for ART initiation have recently changed twice. The first change was in 2007/2008, where eligibility was expanded from CD4+ counts <200 cells/µL and/or WHO stage III or IV with 200-350 cells/µL, to CD4+ counts <350 cells/µL irrespective of WHO stage. In late 2012, eligibility was expanded further to include all persons with CD4+<500 cells/µL.

As demonstrated in the paragraphs above, the significant benefit of HAART in decreasing morbidity and mortality is indisputable. As life-expectancy increases, HIV infected individuals have become gradually exposed not only to the effects of aging itself, but also to the influence of other environmental risk factors, which are known to act in the general population.

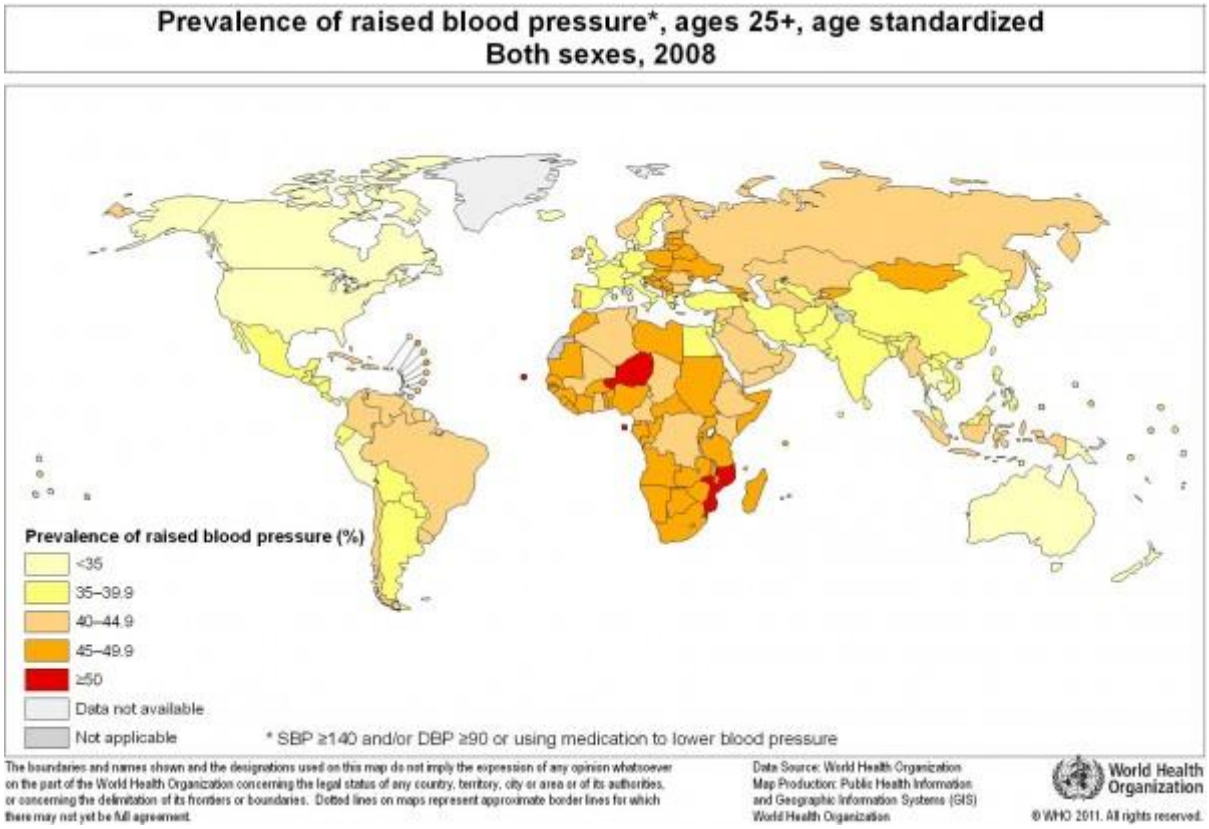
HIV infected individuals, like the rest of the population, are living long enough to experience chronic diseases such as HTN, also known as high or raised blood pressure, an increasingly important medical and public health issue worldwide. HTN is a well-known risk factor for cardiovascular diseases (CVDs) such as myocardial infarction, heart and kidney failure, and stroke. It has been identified as the primary cause of around half of all deaths from stroke and heart disease (32) and was ranked recently as the third-highest global cause of disability in terms of disability-adjusted life years (33) and the second leading cause of death in Africa (WHO 2013) Global Health estimates 2013 http://www.who.int/healthinfo/global_burden disease/en/)

According to WHO, in 2011NCDs accounted for 30% of the 9.5 million deaths, and 25.8% of the 65.4 million disability adjusted life years (DALYs) recorded in Africa. it has been projected that by 2030 NCDs will exceed communicable diseases as the most common cause of death in Africa (32).

Every year, 9.4 million people die from HTN related complications (WHO 2013). Worldwide, the prevalence of HTN is highest in the African region at 46% of adults being from 25 and above years of age (WHO 2013).



The graph above shows HTN proportions across the globe according to WHO continents. The African continent shows the highest rates in both male and female population. http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/



The map above also depicts the prevalence of HTN across the world and per country. Most SSA countries are in orange and red, showing HTN prevalence greater than 40%.

In 2000, 639 million people with HTN were living in developing countries, and the predicted number of adults with HTN by 2025 was estimated to increase to 1.15 billion in developing countries (33). Apparently, the expected number for 2015 might already have been reached. In 2008, the estimated number of HTN cases in SSA was 75 million, and thus about four times higher as compared to 2005 (34). From African countries there is evidence that few patients, irrespective of their HIV status, seem to have adequate knowledge of hypertension (35).

HTN, as it is explained by the pathophysiology of HTN an area of active research attempting to explain its causes, is a chronic disease characterized by elevation of arterial blood pressure (diastolic and/or systolic). HTN can be classified as either essential or secondary. Essential HTN indicates that no specific underlying medical cause can be found to explain the patient's

condition. Secondary HTN indicates that high blood pressure is a result of another underlying condition. In this study, secondary HTN will be dealt with.

Hypertension is thought to be caused by both genetic and environmental factors, with varying combinations in different individuals. Proposed environmental factors include exposure to chronic stress, obesity, alcohol and salt intake and physical inactivity. It is likely that environmental and lifestyle factors operate interactively rather than independently to promote HTN (36).

Also recent little information on genetic variations or genes that are over or under expressed as well as the intermediary phenotypes that they regulate to cause high BP (37) shows that a number of factors increase the BP including obesity, insulin resistance, high alcohol intake, high salt intake, aging and perhaps sedentary lifestyle, stress, low potassium intake and low calcium intake. Furthermore, many of these factors are additive such as obesity and alcohol intake (38).

Effective combination antihypertensive therapies include combined agents from the following pharmacological classes: thiazide diuretics, beta blockers, Angiotensin- converting enzyme (ACE inhibitors), Angiotensin II receptor blockers (ARBs), Calcium channel blockers and renin inhibitors. Other medications sometimes used to treat HTN are Alpha blockers, these medications reduce nerve impulses to blood vessels, reducing the effects of natural chemicals that narrow blood vessels. Alpha- beta blockers, in addition to reducing nerve impulses to blood vessels, they slow the heartbeat to reduce the amount of blood that must be pumped through the vessels. Other medications are central acting agents and vasodilators. The latter, works directly on the muscles in the walls of arteries preventing them from tightening and narrowing. The former prevent the brain from signalling the nervous system to increase the heart rate and narrow the blood vessels.

Thiazide diuretics act on the kidneys to help the body eliminate sodium and water, thus reducing blood volume. Beta blockers reduce the workload of the heart and open blood vessels causing the heart to beat slower and with less force. ARBs relax blood vessels by blocking the action not the formation of a natural chemical that narrows blood vessels. Persons with chronic kidney disease may benefit from having an ARB as one of their hypertensive regimens. Calcium channel blockers help relax the muscles of blood vessels and some slow the heartbeat. Calcium channel blockers may work better for older people and blacks than ACE inhibitors do alone. Renin inhibitors slows down the production of renin, an enzyme produced by kidneys that starts a chain of chemical steps that increases blood pressure. In a study that assessed the prevalence, awareness, treatment and control rate of HTN in HIV infected patients from Italy, it was found that nearly 30% of HIV adult out patients had HTN, more than the 1/3 of this population were unaware of their condition and more than 2/3 were uncontrolled (39). In another systematic review of the studies done in the general population from urban areas of SSA, in most studies it was found that less than 40% of people with high BP had been previously detected, of people already diagnosed with HTN < 30% were on treatment and < 20% of them had BP within the normal range (40).

Concerns have been raised regarding a possible increased risk of CVD (HTN included) as part of the metabolic complications related to the use of HAART in HIV infected individuals (19, 41). But even before the introduction of HAART, , in the early epidemic, the components of metabolic syndrome have been recognized in patients living with HIV infection; such as low high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and elevations in triglycerides, more often were seen in those with advanced disease but also were seen in asymptomatic patients (42).

However, previous studies examining the effect of HAART on BP have reported conflicting results. A study in Kenya reported a lower prevalence of 7.4%–11.2%, compared with a 12.3%–19.0% from Nigeria. This may be related to a lower prevalence of hypertension in Kenya (12.3%) compared with Nigeria (14.5% and 20%–25%) (43). A large cross-sectional study has shown that non- nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitors (PI) use were associated with HTN, but the association did not persist after adjusting for baseline characteristics such as age (44). Other studies suggested a lower risk of HTN among HIV infected patients receiving PIs compared with HIV uninfected individuals (45, 46). In studies that compared the prevalence of HTN among HIV positive patients receiving HAART to matched controls HIV positive not on HAART have shown increased prevalence of HTN and metabolic syndromes in patients on HAART (47-49).

The increase in life expectancy and alteration of lipid metabolism due to receipt of HAART are suspected to increase the prevalence of HTN and diabetes. On the other hand, direct effects of HIV associated nephropathy and thrombotic micro-angiopathy seem to play a major role in the development of this process (50). Drugs used for the treatment of the HIV infection that are associated with nephrotoxicity include aminoglycosides, amphotericin, foscarnet, trimetoprim-sulfamethoxazole, tenofovir, indinavir and acyclovir. Data on HTN in HIV infected patients on HAART in SSA are scarce, and few studies have assessed the occurrence of CVDs or HTN in these populations (51, 52). Metabolic complications and abnormal fat distribution have been frequently observed after a few years of HAART, and as the array of anti-retroviral drugs became broader, long term metabolic alterations are becoming far more common worldwide (11).

Given the extensive HAART roll-out, and reports from other studies of an association between HAART use and increasing blood pressure levels in HIV-infected patients (53), the incidence of HTN in the RWISA cohort from 2005-2010 was investigated by the researcher in order to assist the improvement of long-term management of patients with HIV infection, to prevent unfavourable cardiovascular outcomes. Lazar et al (28), in a cross-sectional study of the Rwanda Women Inter-association study and assessment (RWISA) cohort, assessed differences in arterial wave reflection, a marker of atherosclerosis, and noted no association of HIV infection with arterial stiffness. However, RWISA participants had had little exposure to HAART at the time of assessment (28).

Risk factors considered in this analysis are age, sex, marital status, education level and income or employment. Anthropometric factors that were looked at are SBP, DBP, BMI, CD_4 cell count for HIV positive groups, HDL, LDL, triglycerides and other factors such as depression, oral contraceptive pill (OCP) use.

Rwanda, like other SSA countries, has severe financial constraints, among others the costs of treating CVD and related disabilities, and access to health care. Therefore early diagnosis and adequate treatment of HTN will improve patients' outcomes and prevent serious complications such as stroke, myocardial infarction, renal failure and heart failure.

CHAPTER TWO

RESEARCH OBJECTIVES AND METHODOLOGY

2.1. STUDY OBJECTIVE

The aim of this research was to determine the incidence of HTN in HIV-infected and HIV-uninfected participants, and to assess risk factors associated with systolic and diastolic blood pressure changes over a 5 year period in a cohort of Rwandan women.

Research questions are:

(i) *Was the incidence of HTN higher in HIV-infected participants compared to the incidence among HIV-uninfected participants,*

(ii) *Is the incidence of HTN higher in HAART-treated than HAART-naïve participants?*

(iii) *Are the same risk factors of HTN across the three groups?*

2.2. SPECIFIC STUDY OBJECTIVES:

- To describe demographic, anthropometric and laboratory risk factors for hypertension in the HIV+ and HIV- participants at baseline in 2005.
- To illustrate the blood pressure trends in HIV-uninfected, HIV-infected HAART-treated, and HAART-naïve participants.
- To estimate the incidence rates and determine risk factors for HTN in HIV-infected and uninfected participants.

2.3. RESEARCH METHODOLOGY

2.3.1. Study design

This research is a secondary data analysis of data from the Rwanda Women's Inter-association Study and Assessment (RWISA), an observational cohort designed to assess the effectiveness and toxicity of antiretroviral therapy in HIV infected Rwandan women.

2.3.2. Data collection

The research was conducted in Kigali, Rwanda between May 2005 and February 2011. Amid May 2005 and November 2005, 710 HIV infected and 226 HIV uninfected women, older than 15 years of age with no prior history of receiving HAART, and who gave informed consent, were enrolled in the RWISA cohort (54). The baseline study visit consisted of an interview, physical and gynaecological exam and collection of blood, urine and gynaecological specimens. The interviews were conducted in Kinyarwanda by trained interviewers with a background in nursing or counselling or both. Follow-up visits were scheduled every six months (55). At study enrolment, demographic characteristics were collected. A physical examination was conducted by trained staff following HIV guideline protocol of that time. Foe follow-up visits, anthropometric measurements such as CD_4 count, weight and blood pressure were recorded at every visit attended. More details can be found in papers by JC Dusingize at al., and JM Lazar et al. (54, 56).

Data were entered directly into an ACCESS database through a user-friendly interface. Relevant data were extracted from the RWISA dataset to enable the researcher to answer the research question mentioned above. This secondary analysis included all study participants except those who at baseline had HTN (the outcome of interest) or were pregnant, and thus comprised 864 of the 936 participants who were enrolled.

2.3.2. Study procedures

2.3.3. Definitions of variables

Exposure

HAART: eligible participants were initiated on different HAART regimens according to national guidelines during the follow-up study period.

Outcome variable

Hypertension was defined as systolic BP≥140 or diastolic BP≥90 mmHg and/or use of anti-hypertensive medication. In particular, isolated SBP was defined as having SBP≥140 mmHg and DBP<90 mmHg. Isolated DBP was defined as having SBP<140 mmHg and DBP≥90 mmHg as defined by WHO. Two blood pressure readings were collected at each visit, in a sitting position, and the average of the two readings was computed and used for this analysis. An individual was considered hypertensive if she had at least 2 raised BP during the study period. This may have occurred at two consecutive visits or at different visits i.e first and third visit, or patients seen outside the 6 months scheduled visits initially.

Explanatory variables

Demographic variables were: age, marital status (single, married and widowed), level of education (no education, primary and secondary or more), employment and income. Anthropometric and laboratory variables included: blood pressure measures, weight and height translated into body mass index (BMI), CD4+ cell counts, plasma total cholesterol levels, high density lipoprotein cholesterol (HDL) levels, low density lipoprotein cholesterol (LDL) levels, and plasma triglyceride levels. Total cholesterol, triglycerides and high-density lipoprotein levels were measured in fasting blood samples. Low-density lipoprotein (LDL) was calculated from Friedewald equation if triglycerides < 400 and measured directly if triglycerides ≥ 400 mg/dl (57). Other cardiovascular risk factors included depression, measured as a continuous variable as per the Center of Epidemiologic Studies Depression

Scale (CES-D) (55), later assessed as an ordinal scale ranging from 0 to 2; 0 being normal, 1 mild to moderate depression and 2 major depression; and use of the oral contraceptive pill (OCP).

2.4. STATISTICAL ANALYSIS

After extraction from the original dataset, data were transferred into STATA 12 (StataCorp, College station, Texas, USA) for data cleaning and further statistical analysis. Baseline demographic and clinical characteristics were described using mean ± standard deviation (SD) or median (inter-quartile range) for continuous variables, and frequencies with percentages for categorical variables. Associations between variables were assessed using the chi-squared test or Fisher's exact test for categorical variables and Student's t-test for normally distributed variables or the Wilcoxon ranksum test when the normality assumption did not hold for continuous variables. For illustration of blood pressure changes over time in all the three groups, mean systolic and diastolic BP were computed for different visits: at baseline, at visit 3 (first year of follow-up), at visit 5 (second year of follow-up) and at visit 8 (fifth year of follow-up). All anthropometric measurements (BP included) recorded from baseline or at enrolment and at each follow-up study visit were included in this analysis.

The line graphs were used to depict the mean systolic and mean diastolic BP trends at baseline, at one year, two years and five years of follow-up for the 3 groups respectively: HIV negative, HIV positive not initiated on treatment (HAART-naïve), and HIV positive on HAART, according to age categories. Analysis of variance (ANOVA) was performed to assess the information given by the graphical displays.

Survival analysis was used to compute the incidence rate (IR) of HTN, for the HIV positive on HAART group of participants was calculated by dividing the total number of cases of HTN by the total time spent in the study from the time of HAART initiation till when

participants developed HTN and were censored. The IRs of HTN for HIV negative and positive HAART-naïve participants were computed by dividing the total number of cases of HTN for each of the two groups by the total number of person-years of follow-up spent from the time of enrolment in the study till the development of HTN, the outcome of interest.

Univariable and multivariable analyses were conducted to investigate the risk factors associated with systolic and diastolic BP changes in HIV infected women on HAART from the cohort using generalized estimating equations (GEE) models, with identity link as the link function, a Gaussian family and an unstructured working correlation structure. Further details on the GEE procedures are described in appendix A. All risk factors with $p < 0.20$ in the univariable models were included in the multivariable analyses. In the models, only subjects with non-missing values in all variables were considered and statistically significant associations were defined as those with $p < 0.05$. Further, sequential analysis was performed to look for other risk factors that might not have been found significant in earlier analysis, yet were shown to be significantly associated with HTN development in the literature review using the Bonferroni post hoc test. Parameters of all individuals that were present at each visit were included in the analysis.

2.5. ETHICAL CONSIDERATIONS

Informed consent was obtained from all participants included in the primary study, according to the protocols approved by the Rwandan National Ethics Committee and the Institutional Review Board of Montefiero Medical Center, Bronx, NY, USA. All participants in the present study were identified by a unique identifier in the dataset, and all personal identifiers were removed from the dataset before the secondary data analysis took place to maintain confidentiality.

Ethical clearance for the secondary data analysis was issued by the Human Research Ethics Committee, University of Witwatersrand (Appendix B) and the Rwandan National Ethics Committee, with permission to use the RWISA dataset by the Supervisor of the Project.

CHAPTER THREE

RESULTS OF THE RESEARCH

3.1. INTRODUCTION

This chapter presents the research findings. Section 3.1. reports on the analysis of baseline characteristics of all study participants stratified by HIV status, bearing in mind that all participants were either HIV negative or HIV positive and no one was on HAART yet. Section 3.2. presents and analyses the BP trends within different HIV groups according to their age categories and compares the age categories of different HIV groups. IRs are stratified by age and BMI categories according to HIV status in section 3.3., and predictors of mean SBP and mean DBP changes during the course of the study are presented according to HIV status and treatment group in section 3.4.

3.1.1. BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS

Demographic characteristics

Demographic characteristics of the study participants are shown in Table 1. There were 936 women aged 20 years and above who participated in the RWISA study. Of these, 52 were hypertensive and 20 women were pregnant at baseline. These 72 women were, therefore, excluded from the secondary analysis. The cohort for the current analysis consisted of 864 women. Of these, 202 (23%) were HIV negative, and 662 (77%) were HIV positive participants who were HAART-naïve at study enrolment. Of the 662 HIV positive study participants, 497 (75%) were initiated on HAART by the end of the study. HIV negative participants were significantly older (median 43 years) than HIV positive participants (median 35 years) ($p < 0.001$).

Table 1: Baseline characteristics of RWISA participants in 2005 by HIV sero-status**.**

characteristics:	HIV-uninfected (n=202)	HIV-infected (n=662)	p-value
Age (years), median(IQR)	42.7 (33.8-49.4)	34.6 (30.6-39.5)	<0.001
Marital status, n (%)			0.003
Married	40 (20)	82 (12)	
Single	34 (17)	173 (26)	
Widowed	111 (55)	381 (58)	
Missing information	17 (8)	26 (4)	
Education level, n (%)			0.023
None	58 (29)	151 (23)	
Primary	107 (53)	443 (67)	
Secondary	23 (11)	60 (9)	
Missing information	14 (7)	8 (1)	
Employment status, n (%)			0.729
Yes	139 (67)	477 (72)	
Missing information	20 (10)	27 (4)	
Monthly income, n (%)			0.010
< 10 000 RWFs (18USD$)	86 (43)	239 (36)	
10 000 – 35 000 (18 - 60)	68 (34)	324 (49)	
>35 000 (>60)	28 (14)	85 (13)	
Missing information	20 (10)	14 (2)	
Anthropometric and lab variables:			
Blood pressure (mmHg), mean±SD			
SBP	118.5±14.6	116.2±10.3	0.012
DBP	73.3±10.4	71.2±7.5	0.001
BMI (kg/m^2), median(IQR)	20.7 (18.5-23.3)	21.1 (19.1-23.4)	<0.001
Serum cholesterol (mg/dL),			
Total cholesterol, mean±SD	142±37	130±34	<0.001
Missing information	5	67	
HDL, median(IQR)	51 (43.7-63.4)	41.4 (33.3-51.8)	<0.001
Missing information	4	33	
LDL, median(IQR)	68.1 (49.3-93.6)	66.9 (50.7-86.6)	0.401
Missing information	82	296	
Triglycerides (mg/dL), median (IQR)	79 (58-104)	87 (66-119)	0.006
Missing information	74	226	
Depression score, mean±SD)	33±11.9	37±9.5	<0.001
Levels of CD4+, n (%)			
<200 CD4+ cells/µL	NA	231 (35)	
200-350 CD4+ cells/µL	NA	248 (37)	NA
>350 CD4+ cells/µL	NA	183 (28)	
OCP use, n (%)			0.758
Yes	24 (12)	76 (12)	
Missing information	9 (4)	8 (1)	

For all categorical variables, n (%) are reported. For continous variviables, data are expressed as mean±SD and medians with IQR. SBP: systolic blood pressure, DBP: diastolic blood pressure, Body Mass Index (BMI) was calculated by dividing the weight in Kilograms by the square of the height in meters (kg/m^2). HDL: high density lipoprotein, LDL: low density lipoprotein cholesterol. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. NA: not applicable. NB: p-values were computed without missing values.

More than half of the participants in both groups were widowed 55% vs 58% ($p < 0.003$). Although the percentage of widows is quite similar in both HIV status groups, there is a significant association between HIV status and marital status ($p = 0.003$). Specifically, the percentage of married women is higher in the HIV- group: 20% HIV- women are married while only 12% HIV+ women are married. This pattern is reversed in the group of single women where only 17% HIV- women are single and 26% HIV+ women are single. The HIV+ group had a lower percentage of individuals with no formal education level (23% vs. 29%). There was no significant difference in employment status between HIV- and HIV+ participants ($p = 0.729$). Of those who worked, 43% of HIV- participants earned less than 18 US$ per month, compared to 36% of the HIV+ participants.

Baseline anthropometric and laboratory variables

The results for baseline anthropometric and laboratory variables are presented in Table 1. There were statistically significant differences between HIV negative and HIV positive participants in mean SBP (119±15 vs. 116±10 mmHg, $p = 0.012$) and in mean DBP (73.3±10.4 vs. 71.2±7.5 mmHg, $p = 0.0013$) respectively. HIV negative and HIV positive participants differed in median BMI (20.7vs. 21.1 kg/m^2, $p < 0.001$), in mean total cholesterol level (142±37 vs. 130±34 mg/dl, $p<0.001$), in median HDL level ($p < 0.001$), in median triglyceride level ($p = 0.006$), and in mean depression score ($p < 0.001$).

Figure 1 shows the numbers of participants who attended each visit. The numbers decreased with time from 864 (202 HIV negative and 662 HIV positive) participants at the first visit to 583 (148 HIV negative and 435 HIV positive) participants at the eighth visit, with the sixth visit being the least attended because of budget issues at that time. Therefore, the sixth visit was excluded from the analysis. On average, participants were seen four times. Taken together, all individuals contributed 5339 readings of systolic and diastolic BP. The median

time of follow-up for the cohort was 5.10 years (IQR 3.12-5.32) for the whole cohort, and the median time on HAART was 3.37 years (IQR 2.07-4.90).

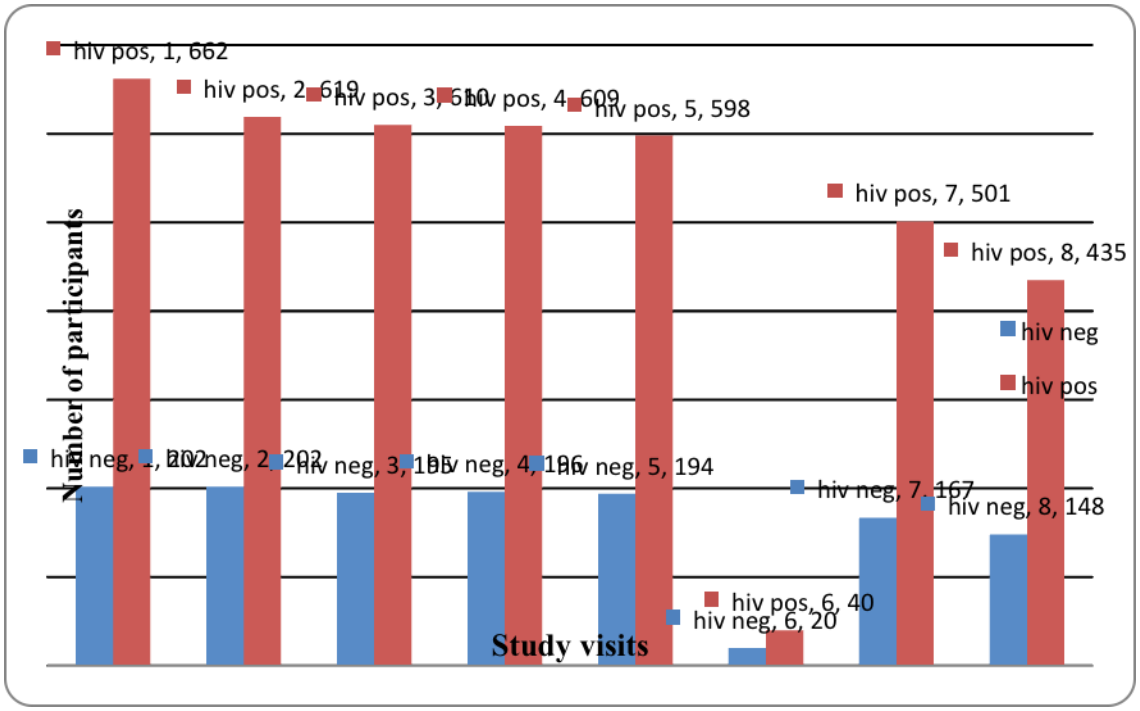


Figure 1: Number of participants per each study visit by HIV status over the study period.

3.2. BLOOD PRESSURE TRENDS OF THE THREE GROUPS OVER TIME

To conduct an analysis of SBP and DBP trends over time, the time points were chosen at one year intervals. However, because of lack of funds after the second year, there was a gap for year three and four. Hence, visit seven and eight were done in year five. Only four visits were considered for this analysis: visit one (baseline), visit three (year one), visit five (year two), and visit eight (year five).

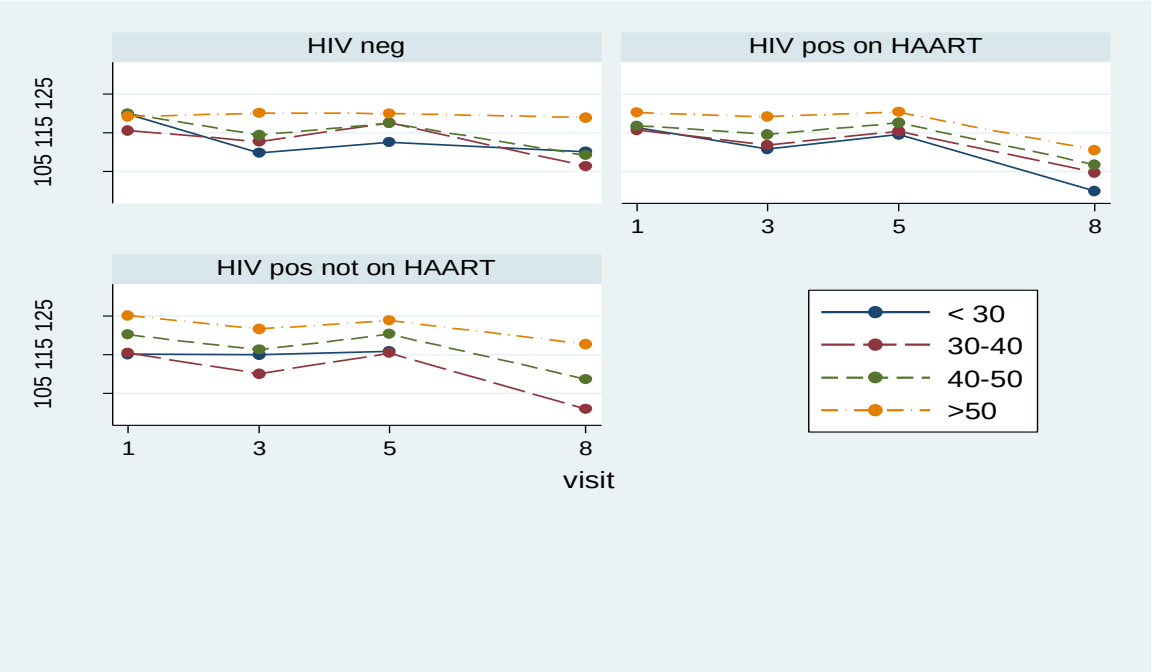


Figure 2: SBP trends for the HIV negative, HIV positive on HAART and HIV positive HAART naïve groups and per age categories throughout the study period.

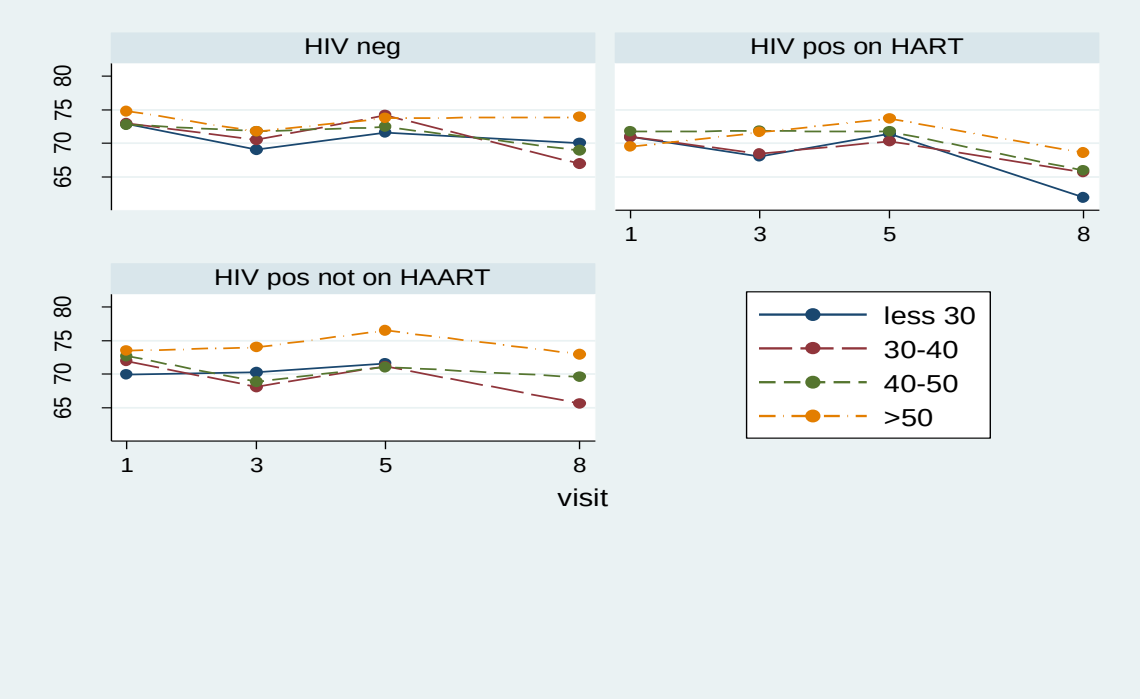


Figure 3: DBP trends for the HIV negative, HIV positive on HAART and HIV positive HAART naïve groups and per age categories throughout the study period.

Figure 2 and 3 show systolic and diastolic BP trends per age categories for HIV-, HIV+ on HAART, and HIV+ HAART- naïve study groups. Overall, both SBP and DBP increased with age in all three studied groups throughout the four visits. The 50 years and above age category had higher mean SBP and DBP in all the three studied groups. SBP and DBP followed similar trends over time visits.

In general, the figures show that similar SBP and DBP trends are observed over the visits for the three HIV groups. The mean BP decreased from the baseline visit to the first year and from the second year to the fifth year and increased from the first year to the second year of follow-up. Participants over 50 years of age had higher mean SBP and DBP measurements compared to the other age categories.

The patterns of the graphs were similar in the three HIV study groups, mainly for mean SBP and to some extent for mean DBP. A three-way analysis of variance (ANOVA) was performed to test the information given by the graphical displays, where the response variable was either the mean SBP or the mean DBP and the explanatory variables were age groups, HIV groups, and visits. For mean SBP, the ANOVA showed no significant differences between HIV study groups ($p = 0.085$), whereas significant differences between age categories ($p < 0.0001$) and between visits ($p < 0.0001$) were noted. The assessment of age categories with significantly different mean SBPs was conducted using the Bonferroni multiple comparison test. The test showed that participants aged 50 years and above had a mean SBP higher than the other three age categories ($p < 0.0001$). The result confirmed what was obtained from the exploration of the graphs in Figure 2. In addition, participants aged 40-50 years had higher mean SBP than those aged 30-40 years ($p = 0.023$). Similarly, the Bonferroni test showed that the mean SBP at visit eight was significantly lower than the mean SBP for the other three visits ($p < 0.0001$), and the mean SBP at visit three was significantly lower than the mean SBP at visit one and five ($p < 0.0001$).

For mean DBP, a significant difference between age categories, visits, and HIV study groups was also observed. The Bonferroni test showed that participants aged 50 years and above had a higher mean DBP than participants aged less than 30 years ($p = 0.004$), 30- 40 years ($p < 0.0001$) and 40- 50 years ($p = 0.002$). The mean DBP at visit eight was significantly lower than the mean DBP at the other three visits ($p < 0.0001$). In addition, the mean DBP was significantly lower at visit three than at visits one and five ($p < 0.0001$). The Bonferroni test also showed that the mean DBP was higher for HIV- patients than the mean DBP for HIV+ patients on HAART and HIV+ HAART-naïve patients ($p < 0.0001$).

Figures 4 and 5 compare the same age categories for different HIV groups (HIV-, HIV+ on HAART, and HIV+ HAART-naïve). For both SBP and DBP a decrease from the fifth visit (second year) to the eighth visit (fifth year) was noted. Thus, ANOVA was performed to assess whether the information displayed by the graphs was due to visits or HIV status groups. The results showed no significant differences between HIV study groups ($p = 0.275$), but showed significant differences between visits ($p < 0.0001$). To assess which visits were significantly different, the Bonferroni test showed that visit eight was significantly different from other visits with respective p-values of < 0.0001, 0.005 and < 0.0001. For DBP, similar analyses were performed, showing a significant difference between visits ($p = 0.0001$) and between the studied groups ($p = 0.013$). A three-way ANOVA showed significant differences between visits one and eight ($p = 0.001$) and between visits five and eight ($p < 0.0001$).

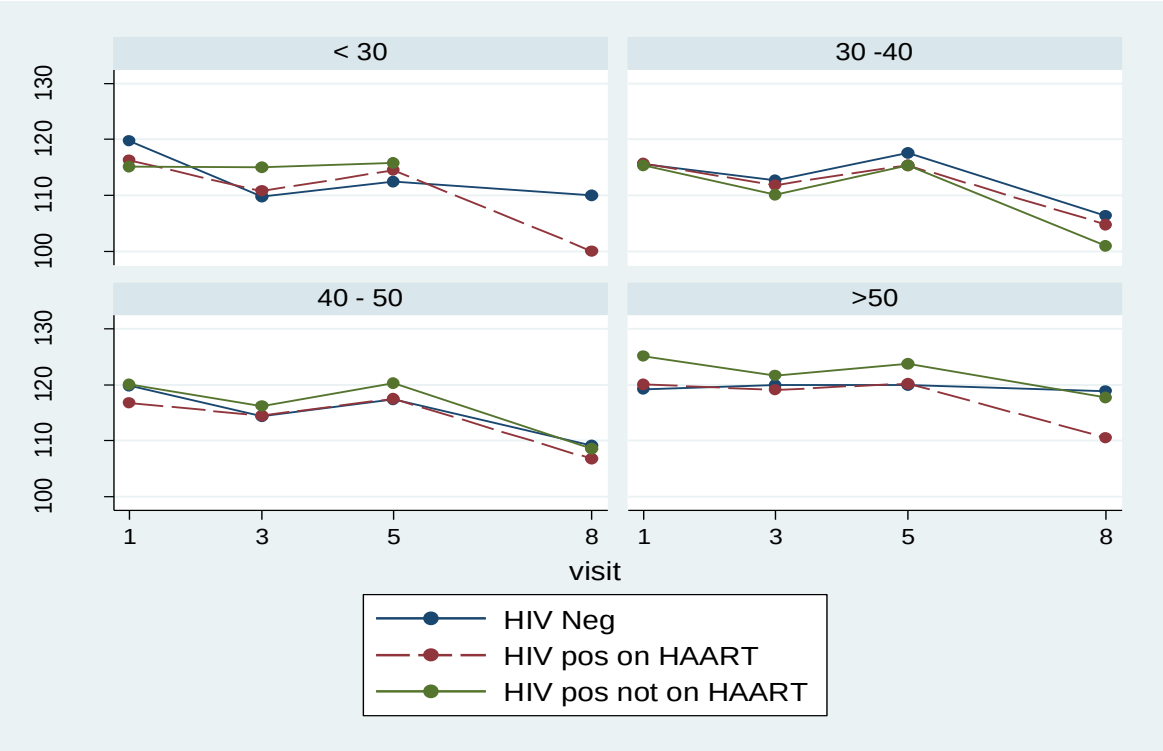


Figure 4: SBP trends per age categories and per study groups throughout the study period.

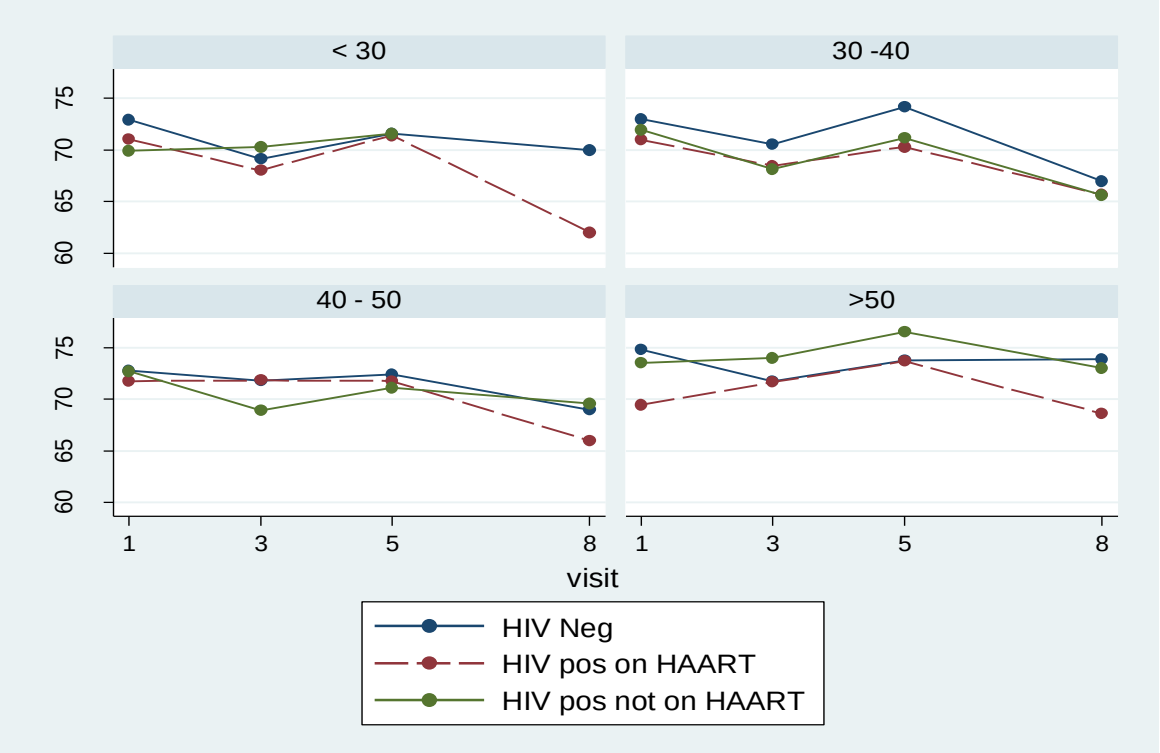


Figure 5: DBP trends per age categories and per study groups throughout the study period.

3.3. INCIDENCE RATES OF HYPERTENSION IN THE THREE STUDIED GROUPS FROM THE COHORT

There were in total 39 HTN cases. Of these, 17 incident cases were observed among the 592 HIV+ participants initiated on HAART, one from the 113 HIV+ HAART-naïve participants and 21 from the 225 HIV- participants. The incidence rates (IRs) for HTN were found to be seven cases (95% CI 4.22; 10.91), three cases (95% CI 0.41; 23.72), and 23 cases (95% CI 15.34; 36.08) per 1000 person-years at risk in HIV+ on HAART, HIV+ HAART-naïve and HIV- participants respectively.

HIV- participants were on average considerably older at study recruitment (Table 1). Hence, it was assessed whether incidence rates between the HIV- and HIV+ on HAART groups differed because of the different age distribution for HIV positive and negative participants (Table 2). BMI effects on incidence rates of the two groups were also assessed. HIV+ HAART-naïve patients were not considered as they had a very low HTN incidence rate.

Table 2: Incidence of hypertension by age and BMI categories

Incidence rates	**HIV neg n=202**	**HIV pos on HAART n=475**
Per age category		
<30 years	0	0
30-39 years	5 (0.7; 34.5)	5 (2.5; 10.9)
40-49 years	23 (10.9; 47.8)	8 (3.6; 17.7)
≥50 years	41 (23.8; 70.6)	20 (7.5; 53.9)
Per BMI category		
Underweight	18 (4.4; 70.3)	4.7 (0.7; 33.2)
Normal weight	20 (9.7; 42.9)	5.6 (2.5; 12.5)
Overweight	24 (6.1; 97.7)	10.9 (3.5; 33.7)
Obese	61 (15.3; 244.0)	17.9 (2.5; 126.8)

IRs are presented as number of cases per 1000 person-years with their 95% CIs. BMI or Body Mass Index was computed as the weight in Kilograms divided by the square of the height in meters (kg/m^2).

The results in Table 2 show that IRs of HTN increased with age for both HIV- participants and HIV+ participants on HAART. However, IRs of HTN for the 40-50 and ≥ 50 year age categories were considerably higher in the HIV- group compared to the HIV+ on HAART group. Assessment of the influence of BMI on HTN indicated increased risk of HTN with overweight and obesity (Table 2).

3.4. SYSTOLIC BP CHANGES WITHIN THE THREE HIV STUDY GROUPS

Univariable and multivariable analyses of the association between SBP changes and demographic, anthropometric and laboratory HTN risk factors are summarized in Tables 3 to 5. All the risk factors with associations at $p < 0.2$ in the univariable analysis were added in the multivariable analysis.

3.4.1. SBP CHANGES FOR HIV+ PARTICIPANTS ON HAART

Table 3 shows the risk factors for SBP changes for the HIV+ participants on HAART over the study period. In the unadjusted analysis of demographic characteristics, for every one year increase in age, SBP increased by 0.1 mmHg (95% CI 0.04; 0.17) ($p = 0.001$). Having a primary level of education was associated with an increase of 2.1 mmHg (95% CI 0.05; 4.15) ($p = 0.04$) in SBP compared to no education level, while having a secondary level of education was associated with an increase of 3.5 mmHg (95% CI 0.18; 6.86) ($p = 0.04$) in SBP compared to no education level. For every unit increase in monthly income, SBP increased by 0.7 mmHg (95% CI 0.28; 1.09) ($p = 0.001$). In the unadjusted analysis of clinical and laboratory variables, being underweight was associated with a decrease of 2.2 mmHg (95% CI -3.29; -1.02) ($p < 0.001$) in SBP compared to having a normal weight, and being overweight was associated with an increase of 1.2 mmHg (95 % CI 0.09; 2.23) ($p < 0.001$) in SBP, compared to having a normal weight. Being obese was found to be associated with an increase of 4.4 mmHg (95% CI 2.1; 6.6) ($p < 0.001$) in SBP compared to having a

normal weight. For every unit increase in depression score, SBP increased by 0.05 mmHg (95% CI 0.03; 0.06) ($p < 0.001$).

Table 3: Risk factors for SBP changes in HIV+ on HAART participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n = 475					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.1	0.04; 0.17	0.001	0.08	-0.06; 0.20	0.268
Marital status:						
Married	Ref	-	-			
Single	-0.9	-3.89; 1.93	0.50			
Widowed	-0.5	-3.17; 2.11	0.69			
Level of education:						
None	Ref	-	-			
Primary	2.1	0.05; 4.15	0.04	1.50	-0.72; 3.73	0.187
Secondary	3.5	0.18; 6.86	0.04	2.87	-0.76; 6.50	0.122
Employment status:						
No	Ref	-	-			
Yes	-0.8	-1.79; 0.21	0.12	-1.46	-3.64; 0.73	0.191
Monthly income	0.7	0.28; 1.09	0.001	0.21	-0.80; 1.24	0.677
Anthropometric and laboratory variables:						
CD4+	0.002	-0.001; -0.004	0.133	0.004	-0.002; 0.011	0.155
BMI categories:						
Normal weight (BMI≥18.5 & BMI<25)	Ref	-	-			
Underweight (BMI<18.5)	-2.2	-3.29; -1.02	<0.001	-3.086	-5.48; -0.68	0.012
Overweight (BMI≥25 & BMI<30)	1.2	0.09; 2.23	0.033	0.65	-2.17; 3.46	0.652
Obese (≥30)	4.4	2.10; 6.64	<0.001	4.53	-1.28; 10.34	0.127
Serum cholesterol (mg/dL):						
Total cholesterol	0.02	-0.01; 0.05	0.17	-0.78	-4.19; 2.62	0.65
HDL	0.03	-0.01; 0.08	0.14	0.02	-0.036; 0.07	0.546
LDL	0.002	-0.04; 0.04	0.92			
Plasma triglycerides (mg/dL)	0.00005	-0.003; 0.003	0.97			
Plasma glucose (mg/dL)	0.016	-0.002; 0.033	0.086	0.016	-0.003; 0.035	0.1
OCP use:						
Yes	Ref	-	-			
No	-0.225	-2.87; 2.42	0.867			
Depression score	0.05	0.03; 0.06	<0.001	0.005	-0.107; 0.098	0.931

Coef = coefficient, P = p-value, Ref = reference group. HDL: High density lipoprotein, LDL: Low density lipoprotein cholesterol. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. OCP: oral contraceptive pill.

The multivariable analysis showed that being underweight was associated with a 3.1 mmHg decrease in mean SBP compared to being of normal weight (95% CI -5.48; -0.68) (p =0.012).

All the other predictor variables were found not statistically significant for SBP after adjustment, as all associations had p-values > 0.05. However, by eliminating non-significant variables sequentially, starting with variables with the highest p-values, it was found that as age increased, mean SBP increased by 0.19 mmHg (95% CI 0.13; 0.25) ($p < 0.0001$) per year. With normal weight as the referent, being underweight was associated with a decrease of 2.53 mmHg (95% CI -3.66; -1.41) ($p < 0.001$), while being overweight was associated with an increase of 1.11 mmHg (95% CI 0.06; 2.17) ($p < 0.038$), and being obese was associated with an increase of 4.05 mmHg (95% CI 1.82; 6.63) ($p < 0.001$) in SBP.

3.4.2. SBP CHANGES FOR HIV HAART-NAÏVE PARTICIPANTS

Table 4 shows the univariable and multivariable analysis for demographic, anthropometric and laboratory risk factors associated with SBP changes for HIV+ participants not on HAART. In the unadjusted analysis for demographic characteristics, being employed was associated with 3.8 mmHg increase in SBP (95% CI 1.7; 5.9) ($p < 0.001$) compared to not being employed. In the unadjusted analysis for clinical and laboratory variables, being obese increased SBP by 3.75 mmHg (95% CI 0.03; 7.48) ($p = 0.048$) compared to having a normal weight. For every unit increase in serum HDL, SBP increased by 0.2 mmHg (95% CI 0.04; 0.29) ($p = 0.008$). For every unit increase in depression score, SBP increased by 0.08 mmHg (95% CI 0.06; 0.12) ($p < 0.001$).

Table 4: Risk factors for SBP changes for HIV+ HAART-naïve participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n=187					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.1	-0.026; 0.270	0.107	0.28	-0.028; 0.59	0.074
Marital status:						
Married	Ref	-	-			
Single	-2.3	-9.14; 4.56	0.513			
Widowed	-5.5	-11.84; 0.75	0.084			
Education level:						
No education	Ref	-	-			
Primary	1.32	-3.63; 6.28	0.6			
Secondary	- 2.08	-9.89; 5.72	0.6			
Employment status	3.79	1.68; 5.90	<0.001	0.76	-4.83; 6.36	0.789
Monthly income	0.75	-0.23; 1.72	0.133	2.34	0.08; 4.75	0.058
Anthropometric and laboratory variables:						
CD4+	0.0009	-0.004; 0.005	0.709			
BMI categories:						
Normal weight	Ref	-	-			
Underweight	-0.28	-2.88; 2.32	0.833	-4.18	-10.95; 2.59	0.226
Overweight	-0.18	-3.05; 2.69	0.901	-2.24	-10.07; 5.59	0.575
Obese	3.75	0.03; 7.48	0.048	-1.06	-11.49; 9.37	0.842
Serum plasma:						
Total cholesterol	0.04	-0.02; 0.10	0.178	0.02	-0.054; 0.095	0.590
HDL	0.2	0.04; 0.29	0.008	0.08	-0.068; 0.234	0.234
LDL	-0.06	-0.2; 0.03	0.217	-0.13	-0.56; 0.29	0.550
Plasma triglycerides	0.0003	-0.013; 0.013	0.971			
Glucose	0.006	-0.02; 0.03	0.639			
OCP use	0.78	-5.74; 7.31	0.814			
Depression score	0.08	0.06; 0.12	<0.001	-0.12	-0.38; 0.14	0.374

Coef=coefficient, P=p-value, Ref=reference group. BMI or Body Mass Index was calculated by dividing the weight in Kilograms by the square of the height in meters (kg/m^2). To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. CD4+ cell count, HDL: high density lipoprotein, LDL: low density lipoprotein cholesterol, OCP: oral contraceptive pill.

The multivariable analysis showed that of seven risk factors with associations at $p < 0.2$ in the bivariate analysis, only the monthly income was found to be a marginally significant predictor of SBP. For every unit increase in monthly income, the SBP for HIV+ participants not on HAART increased by 2.34 mmHg (95 % CI 0.08; 4.75) ($p = 0.058$).

By eliminating non-significant variables sequentially, starting with variables with the highest p-values, it was found that HDL increased SBP by 0.158 mmHg (95% CI 0.032; 0.283) (p = 0.014).

3.4.3. SBP CHANGES FOR HIV NEGATIVE PARTICIPANTS

Table 5 shows the univariable and multivariable analyses of demographic, anthropometric and laboratory risk factors associated with SBP changes for HIV negative participants. The unadjusted analysis for systolic BP and demographic characteristics showed that for every year increase in age, SBP increased by 0.2 mmHg (95% CI 0.11; 0.28) (p < 0.001). Having a monthly income was associated with 1.1 mmHg increase in SBP (95% CI 0.442; 1.773) (p = 0.001).

In the unadjusted analysis of clinical and laboratory variables, being obese increased SBP by 5.6 mmHg (95% CI 1.67; 9.47) (p = 0.005) compared to having a normal weight. The multivariable analysis showed that no predictor variable was statistically significant in explaining SBP changes of HIV- participants since all p-values were > 0.05. However, by sequentially eliminating non-significant variables, starting with those having the highest p–values, it was found that as age increased, mean SBP increased by 0.29 mmHg (95% CI 0.19; 0.40) (p < 0.0001), and for every unit increase in income, SBP increased by 1.40mmHg (95% CI 0.52; 2.29) (p < 0.0001).

Table 5: Risk factors for SBP changes for HIV- participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n = 202					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.2	0.11; 0.28	<0.001	0.2	-0.048; 0.409	0.122
Marital status:						
Married	Ref	-	-			
Single	-3.5	-10.22; 3.32	0.319			
Widowed	1.8	-3.53; 7.22	0.502			
Education level:						
None	Ref	-	-			
Primary	-1.6	-6.357; 3.116	0.503			
Secondary	1.7	-5.404; 8.843	0.636			
Employment status						
Yes	-1.6	-3.432; 0.31	0.102	5.2	-1.159; 0.172	0.362
Monthly income	1.1	0.442; 1.773	0.001	0.000	-0.077; 0.077	0.998
Anthropometric and laboratory variables:						
CD4+	0.002	-0.0008; 0.005	0.163			
BMI categories:						
Normal weight	Ref	-	-			
Underweight	-0.6	-2.512; 1.233	0.503	-5.3	-10.69; 0.107	0.055
Overweight	2.1	-0.175; 4.383	0.070	-4.4	-12.279; 3.429	0.27
Obese	5.6	1.673; 9.47	0.005	-5.2	-22.682; 0.345	0.563
Serum cholesterol:						
Total cholesterol	0.02	-0.038; 0.073	0.536			
HDL	0.07	-0.049; 0.189	0.252			
LDL	-0.01	-0.085; 0.063	0.768			
Plasma triglycerides	0.006	-0.027; 0.039	0.723			
Plasma glucose	-0.02	-0.05; 0.005	0.119	-0.02	-0.049; 0.01	0.197
OCP use:						
Yes	-5.02	-11.28; 1.23	0.115	3.07	-4.089;10.237	0.400
Depression score	0.004	-0.029; 0.038	0.801			

Coef=coefficient, P=p-value, Ref=reference group. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. CD4+ cell count, HDL: High density lipoprotein, LDL: Low density lipoprotein cholesterol, OCP: oral contraceptive pill.

3.5. DIASTOLIC BP CHANGES WITHIN THE THREE HIV STUDY GROUPS

Univariable and multivariable analyses for factors in DBP changes for HIV + on HAART, HIV+ HAART-naïve and HIV- participants are presented in Tables 6 to 8. All risk factors associated with DBP at $p < 0.2$ in the univariable analysis were added in the multivariable analysis.

3.5.1. DBP CHANGES FOR HIV+ PARTICIPANTS ON HAART

Table 6 shows the univariable and multivariable analysis of demographic, anthropometric and laboratory risk factors associated with DBP changes for HIV+ patients on HAART.

In the bivariate analysis for diastolic BP and demographic characteristics, for every year increase in age, DBP increased by 0.06 mmHg (95% CI 0.02; 0.09) ($p = 0.007$). Having a secondary level of education was associated with an increase of 2.3 mmHg in DBP (95% CI 0.07; 4.7) ($p = 0.06$) compared to having no education. For every unit increase in monthly income, DBP increased by 0.5 mmHg (95% CI 0.2; 0.8) ($p = 0.001$). The unadjusted analysis of clinical and laboratory variables showed that being underweight was associated with a decrease of 1.49 mmHg (95% CI -2.23; - 0.75) ($p < 0.001$) in DBP, while being obese was associated with an increase of 2.92 mmHg (95% CI 1.44; 4.38) ($p < 0.001$) in DBP, both comparisons with reference to having a normal weight. For every unit increase in depression score, DBP increased by 0.04 mmHg (95% CI 0.02; 0.05) ($p = 0.001$).

Table 6: Risk factors for DBP changes for HIV+ on HAART participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n = 475					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.06	0.02; 0.09	0.007	-0.006	-0.101; 0.09	0.894
Marital status:						
Married	Ref	-	-			
Single	2.37	0.31;4.45	0.024			
Widowed	0.96	-0.91; 2.83	0.315			
Level of education:						
None	Ref	-	-			
Primary	1.14	-0.32; 2.61	0.13	0.95	-0.62; 2.53	0.233
Secondary	2.32	0.07; 4.71	0.06	1.83	-0.79; 4.47	0.171
Employment status:						
No	Ref	-	-			
Yes	-0.19	-0.87; 0.49	0.59			
Monthly income	0.48	0.20; 0.75	0.001	0.29	-0.74; 1.33	0.575
Clinical and other related variables:						
CD4+	0.0001	-0.002; 0.002	0.885			
BMI levels:						
Normal weight	Ref	-	-			
Underweight	-1.49	-2.23; -0.75	<0.001	-1.27	-2.97; 0.44	0.145
Overweight	0.48	-0.21; 1.18	0.171	1.42	-0.57; 3.40	0.163
Obese	2.92	1.44; 4.38	<0.001	1.67	-2.49; 5.84	0.432
Serum cholesterol:						
Total	0.02	-0.01; 0.04	0.06			
HDL	0.012	-0.02; 0.05	0.48	0.01	-0.01; 0.03	0.299
LDL	0.002	-0.03; 0.04	0.92			
Plasma triglycerides	0.0004	-0.002; 0.003	0.72			
Plasma glucose	-0.005	-0.018; 0.008	0.49			
OCP use:						
No	Ref	-	-			
Yes	-1.88	-3.76; 0.002	0.05	-1.41	-3.39; 0.556	0.159
Depression score	0.04	0.02; 0.05	<0.001	0.011	-0.061; 0.84	0.762

Coef=Coefficient, P=p-value, Ref=reference group. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. HDL: high density lipoprotein, LDL: Low density lipoprotein cholesterol, OCP: oral contraceptive pill.

The multivariable analysis found that no predictor variable was statistically significant in explaining DBP changes in HIV+ on HAART participants as all the p-values were > 0.05. However, by eliminating non-significant variables sequentially, starting with variables with

the highest p–values, it was found that being underweight decreased DBP by 1.59 mmHg (95% CI -3.17; -0.013) (p = 0.048).

3.5.2. DBP CHANGES FOR HIV HAART-NAÏVE PARTICIPANTS

Table 7 shows the univariable and multivariable analysis of demographic, anthropometric and laboratory risk factors associated with DBP changes for HIV+ HAART-naïve participants.

In the unadjusted analysis of demographic characteristics, being employed was associated with a 1.9 mmHg increase in DBP (95% CI 0.5; 3.3) (p = 0.009), compared to not being employed. In the unadjusted analysis of clinical and laboratory variables, no clinical or laboratory predictor variable was found to be statistically significant to explain DBP change since all the p -values were > 0.05.

The multivariable analysis showed that being employed was the only statistically significant explanatory variable for DBP change in HIV+ HAART-naïve patients. Being employed was associated with 5.1 mmHg decrease in DBP (95% CI -9.06; -1.14) (p = 0.012) compared to not being employed. Subsequent sequential elimination did not improve the predictive value of any other variable.

Table 7 Risk factors for DBP changes for HIV+ HAART-naïve participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n = 187					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.09	-0.003; 0.2	0.056	0.09	-0.176; 0.349	0.520
Marital status:						
Married	Ref	-	-			
Single	4.1	-0.8; 9.04	0.101			
Widowed	-0.7	-5.2; 3.9	0.771			
Education level:						
No education	Ref	-	-			
Primary	0.08	-3.5; 3.7	0.966			
Secondary	1.7	-3.9; 7.4	0.547			
Employment status:						
No	Ref	-	-			
Yes	1.9	0.5; 3.3	0.009	-5.08	-9.025; -1.136	0.012
Monthly income	-0.2	-0.73; 0.43	0.608			
Anthropometric and laboratory variables						
CD4+	0.00006	-0.003; 0.003	0.972			
BMI categories:						
Underweight	Ref	-	-			
Normal weight	-0.9	-0.796; 2.763	0.279			
Overweight	0.02	-1.916; 1.956	0.984			
Obese	1.9	-0.593; 4.381	0.136			
Serum plasma:						
Total cholesterol	0.04	-0.009; 0.079	0.121	-0.0009	-0.062; 0.06	0.976
HDL	0.06	-0.026; 0.155	0.166	0.1335	-0.049; 0.316	0.152
LDL	-0.06	-0.146; 0.033	0.217			
Plasma triglycerides	0.007	-0.002; 0.017	0.141	0.015	-0.031; 0.06	0.532
Glucose	0.0007	-0.017; 0.018	0.941			
OCP use	1.2	-3.564; 5.952	0.623			
Depression score	0.01	-0.026; 0.045	0.601			

Coef=coefficient, P=p-value, Ref=reference group. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. CD4+ cell count, HDL: high density lipoprotein, LDL: Low density lipoprptein, OCP: Oral contraceptive pill.

3.5.3. DBP CHANGES FOR HIV NEGATIVE PARTICIPANTS

Table 8 shows the univariable and multivariable analyses of demographic, anthropometric and laboratory parameters risk factors associated with DBP changes for HIV negative participants.

In the unadjusted analysis for DBP and demographic characteristics, for every year increase in age, DBP increased by 0.1 mmHg (95% CI 0.06; 0.16) ($p < 0.001$). Being employed was associated with a 2 mmHg decrease in DBP (95% CI -3.12; -0.54) ($p = 0.005$) compared to not being employed. Having a monthly income was associated with 1 mmHg increase in DBP (95 % CI 0.60; 1.5) ($p < 0.001$). In the unadjusted analysis of anthropometric and laboratory variables, being overweight was non-significantly associated with a 2.1 mmHg increase in mean DBP compared to having a normal weight (95% CI -0.175; 4.38) ($p = 0.07$). Being obese was associated with 5.6 mmHg increase in mean DBP compared to having a normal weight (95% CI 1.67; 9.47) ($p = 0.005$). The use of OCP decreased DBP by 4.9 mmHg (95% CI -9.2; -0.5) ($p = 0.029$) compared to no use.

In the multivariable analysis DBP was explained by age and depression score. With every year increase in age, DBP increased by 0.2 mmHg (95% CI 0.02; 0.33) ($p = 0.028$), and with every unit increase in depression score, DBP decreased by 0.02 mmHg (95% CI -0.35; -0.02) ($p = 0.025$). However, by eliminating non-significant variables sequentially starting with variables with the highest p-values, it was found that, in addition to age and depression score, for every unit increase in income, DBP increased by 1.21 mmHg (95% CI 0.77;1.66) ($p < 0.0001$).

Table 8: Risk factors for DBP changes for HIV- participants over the study period.

RISK FACTORS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	n = 202					
	Coef	95% CI	P	Coef	95% CI	P
Demographic characteristics:						
Age	0.1	0.057; 0.163	<0.001	0.2	0.018; 0.327	0.028
Marital status:						
Married	Ref	-	-			
Single	-0.9	-5.753; 3.84	0.697			
Widowed	-1.0	-4.817; 2.805	0.605			
Education level:						
None	Ref	-	-			
Primary	-2.3	-5.604; 1.058	0.181			
Secondary	0.3	-4.695; 5.325	0.902			
Employment status						
Yes	-1.8	-3.122; 0.539	0.005	2.4	-1.39; 6.25	0.21
Monthly income	1.05	0.607; 1.501	<0.001	1.2	-0.232; 2.692	0.099
Anthropometric and laboratory variables:						
CD_4	0.002	-0.005; 0.003	0.138	-0.002	-0.006; 0.003	0.504
BMI categories:						
Normal weight	Ref	-	-			
Underweight	-0.6	-2.51; 1.23	0.503	-2.1	-5.779; 1.479	0.246
Overweight	2.1	-0.17; 4.38	0.070	2.6	-2.678; 7.941	0.331
Obese	5.6	1.67; 9.47	0.005	3.5	-1.077; 8.075	0.263
Serum cholesterol:						
Total cholesterol	0.02	-0.014; 0.064	0.215			
HDL	0.03	-0.054; 0.115	0.485			
LDL	0.04	-0.025; 0.095	0.256			
Plasma triglycerides						
	-0.01	-0.038; 0.015	0.386			
Plasma glucose	-0.01	-0.033; 0.007	0.213			
OCP use:						
Yes	-4.9	-9.2; -0.5)	0.029	3.5	-1.077; 8.075	0.134
Depression score	-0.02	-0.046; 0.005	0.116	-0.2	-0.35; -0.02	0.025

Coef=coefficient, P=p-value, Ref=reference group. HDL: high density lipoprotein, LDL: low density lipoprotein cholesterol. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. CD_4 cell count, OCP: Oral contraceptive pill.

CHAPTER FOUR: DISCUSSION

4.1. INTRODUCTION

To date, most studies assessing the relationship between HIV infection and treatment with blood pressure and HTN conducted in Sub-Saharan African countries have focused on the prevalence of HTN rather than on the incidence. The findings from this analysis have broadened our understanding of the incidence of HTN in both HIV infected and uninfected Rwandan women indicating that the incidence of HTN is higher in older HIV- participants. In addition, the study investigated the predictors of systolic and diastolic BP changes over a period of five years in the three HIV study groups: HIV negative participants, HIV positive participants HAART naive, and HIV positive participants on HAART. Age, BMI, employment status and monthly income were risk factors found to influence systolic and diastolic BP changes.

4.2. SYSTOLIC AND DIASTOLIC BP TRENDS ACCORDING TO HIV GROUPS AND AGE GROUPS

Systolic and diastolic BP trends were stratified according to HIV and age groups. Similar systolic and diastolic BP trends were observed throughout the study period, after one year, after two years and after five years in the three subject groups. Regarding the differences between the visits, it was noted that after five years systolic and diastolic BP were significantly different from the rest of the visits for both systolic and diastolic BP values. Systolic and diastolic BP measurements over the follow-up period decreased from baseline visit to visit three, from visit five to visit eight whereas both systolic and diastolic BP showed an increase from visit three to visit five, suggesting probable systematic measurement errors during the course of the study or some improvement in living conditions or it may be due to the fact that HIV infection was shown to be associated with a lower BMI and, thus, a lower

prevalence of raised BP compared with HIV-negative subjects. This also aligns with the fact well established that HIV is associated with weight loss and wasting (58). Another probable factor would be that the Rwandan population is slender in general, thus both systolic and diastolic BPs were in the normal range from baseline.

4.3. INCIDENCE OF HYPERTENSION

The incidence rates for HTN were observed to be higher in HIV- women (23 cases per 1000 person-years) than in HIV+ patients on HAART (7 cases per 1000 person-years) and HIV+ patients not on HAART (3 cases per 1000 person-years). Similar results were found in a South African study that showed HIV negative women being more likely to be hypertensive than HIV positive women (59). In the same line with previous results from the Data collection on Adverse events of anti- HIV Drugs (D:A:D) study (60), the incidence rates for HTN increased with age in HIV- women and in HIV+ women on HAART. This can be supported as well by the Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure results that showed that individuals who are normotensive at an older age have a lifetime high risk (90%) for developing HTN.

The higher incidence of HTN in the HIV– participants might be explained partly by the older age of HIV- women. Another possible explanation could be the fact that HIV+ participants had much more counselling sessions and follow-up visits for the CD_4 and viral load check-ups, that could have raised their awareness on riskier behaviour related to HTN development and that might have rendered them much cautious about safer healthy measures like regular check-up, alcohol and smoking secession, and eating healthy foods, and early detection and treatment of pre-HTN cases.

Higher IRs of HTN were observed among overweight and obese HIV negative and HIV positive patients on HAART. There was no significant difference in the prevalence of obesity and mean BMI between HIV-positive HAART-naïve and HIV-positive on HAART participants. HTN is developed as a result of high blood pressure and it is strongly correlated with body mass index; overweight and obesity are determined from BMI and obesity was noted to be on its own a single best predictor of HTN incidence.

A Ugandan population based survey on burden of HTN in a cohort established initially for HIV care showed similar findings, age and BMI were factors associated with high prevalence of HTN (61). Similarly, a South African study on HTN and obesity in adults living in a high HIV prevalence rural area found that both hypertension and obesity were significantly associated with age, female sex, HIV and being on HAART (62).

The relationship between HTN and obesity has been described as multifaceted. Obesity was noted to be a single best predictor of HTN incidence and was regarded as a major controllable contributor to HTN (63). Overweight and obesity is conveniently determined from BMI.

Dramatic advances in understanding the mechanisms of obesity – related HTN have been accomplished recently. Obesity was shown to be associated with several central and peripheral abnormalities that can explain the development or maintenance of high arterial BP. Clinical and animal studies have highlighted the key role of increased sympathetic activity in obesity-HTN. Several factors may account for the increase of sympathetic outflow associated with obesity such as the role of leptin, an adipocyte derived hormone that acts in the hypothalamus to regulate appetite and energy expenditure. In addition to its effect on sympathetic nervous system to the kidney, leptin may act directly on the kidney to increase oxidative stress, as evidenced by increased plasma concentration and urinary excretion of isoprostanes, increased level of lipid peroxidation products in renal homogenates, and

reduced renal aconitase activity (64). Long-term sympatho- activation could raise arterial pressure by causing peripheral vasoconstriction and by increasing renal tubular sodium reabsorption (65).

Renal function abnormalities could be explained by several alterations in renal structure and function associated with obesity by the activation of the sympathetic nervous system and the Renin Angiotensin System (RAS) as well as increases in plasma aldosterone levels that can cause abnormal sodium retention and increase arterial pressure. Compression of the kidney by the surrounding fat and the renal structural changes associated with obesity may also play a role in the renal damage associated with obesity.

Reduced activity of arachidonic acid pathways in renal tubular sites could be another potential explanation. Given the importance of arachidonic acid metabolic in inhibition of ion transport along the nephron, the down regulation of arachidonic acid pathways in obesity may be involved in the increased sodium reabsorption thereby promoting blood pressure elevation (66).

The activation of the Renin- Angiotensin System (RAS) in obesity on its own plays a role in explaining obesity development. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. It was demonstrated that adipocyte derived angiotensin can act locally to affect adipocytes growth and differentiation and/or may be released in the bloodstream and the high circulating levels of angiotensinogen associated partly to increase fat mass (67).

T*he involvement of aldosterone* in obesity associated HTN is another contributing factor in this process. It was established by blockade of mineralocorticoid receptors with the specific antagonist eplerenone located in different tissues, including the kidney, vasculature and brain, which inhibit the development of high BP without affecting the weight gain thus raising BP.

Damage to the endothelium is another important risk factor for CVDs as it leads to structural changes, such as thickening of the intima and media of the vessel wall. A number of mechanisms linking obesity with endothelial dysfunction are not yet fully clarified, several factors may contribute to this abnormality such as increased vascular production of endothelin-1 in hypertensive patients with increased body mass has been suggested as a potential mechanism for endothelial dysfunction (68).

4.4. RISK FACTORS OF BP CHANGES IN THE COHORT

Findings from this study indicate that at the baseline visit, HIV negative participants were older than their HIV positive counterparts, which may explain in part the observed statistically significant differences between HIV negative and HIV positive participants in terms of mean SBP and DBP measurements. These results are consistent with findings from the Framingham Heart study that documented increasing age as a long term risk factor for CVD (69).

Our findings suggest that depression decreased the risk for HTN among HIV negative women. Similar findings were found in a Norwegian prospective study that looked at repeated assessment of depression levels. The authors found that symptoms of anxiety and depression were associated with a decrease in DBP, with an even stronger decrease in individuals with a high symptom level (70). Another study by Licht et al (71) that assessed whether depression was associated with decreased BP and the role of antidepressant use on the development of HTN showed that depressive disorders were associated with lower BP and less HTN. Unfortunately this study did not look at the association between the use of certain antidepressants and their effect on both high diastolic and systolic blood pressures and hypertension development. More possible explanations being, one a higher occurrence of

hypotensive episodes in individuals with depression and second, that depression alters the cicardian BP profile (72).

Monthly income and being employed were found to be significant predictors of HTN among HIV positive women specifically among HAART naïve patients. These findings may be regarded as proxy measures of socio-economic status, which is believed to play an important role in all aspects of life. The findings are in line with a study done on association between wages and the development of HTN which showed strong association between wages and HTN among women aged 25- 44 year (73). The literature has been inconsistent about this association. In 1940 and 1960s studies in the US and UK found that high social economic status groups were at greater risk (74).

This study found HDL levels to be associated with raised systolic blood pressure in HIV infected participants HAART naïve. In a study that looked at patterns of lipoprotein in the same cohort (57) found higher HDL levels to be associated with increased alcohol use but in general HDL levels in this group were low. This finding may also be explained by the small sample size of the group and the changes associated with HIV infection such as chronic inflammation, hypercoagulability and platelet activation that contribute to endothelial dysfunction and later lead to CVD via different pathophysiological pathways (75).

4. 5. STRENGTHS OF THE STUDY

A few studies have determined the prevalence of HTN in the Rwandan population before; this is the first study to determine the incidence of HTN. The major strengths of this study lie in its prospective study design, three different comparison groups, and a substantial number of available BP measurements.

4.6. LIMITATIONS OF THE STUDY

One of the limitations of this study was that it did not measure HAART use and duration on HAART and some of the well-known risk factors like smoking, alcohol consumption, physical exercise and salt intake. As the study was a secondary data analysis, there were missing data and unbalanced observations of the variables related to the research question being answered here, which made the statistical analysis difficult. The study included a cohort of women recruited from a women's association in a Rwandan urban setting, and may not be representative for all Rwandan women and its results may only apply to women. This can limit the external validity of the study. Another limitation is the small sample size of the groups.

CHAPTER FIVE:

CONCLUSION AND RECOMMENDATIONS

5.1. CONCLUSION

Incidence rates of HTN were higher in HIV- compared with HIV positive counterparts. The findings also show that socio-economic factors such as income and employment status and lifestyle factors, for instance BMI and depression, were also associated with blood pressure changes. Given the worldwide medical, public health importance, and the low public awareness of risks and treatment of HTN in SSA (76, 77), a call for lifestyle changes through education of the population is key along with proper interventions both curative and preventive are needed.

5.2. RECOMMENDATIONS

A general comprehensive risk factor assessment for major chronic diseases of importance (hypertension, diabetes and non AIDS cancers) is needed while providing care to the Rwandan people. To help prevent complications of hypertensive disease, health care providers should educate the Rwandan population about potential risks of HTN among HIV negative and HIV positive patients (78) .

Additional considerations should be given to potential drug interactions between antihypertensive agents and HAART to inform clinician selection of these therapies.

This study did not look at some of the risk factors for HTN such as alcohol consumption, smoking, and the role of regular physical activity and salt intake. (79). Hence, future studies including them are advised.

This study did not look at the relationship between specific antiretroviral therapy regimens and the development of HTN. A study with a larger sample size looking at this association is highly recommended. A similar study in male participants is also recommended as disparities between the two sexes are known.

REFERENCES

1. WHO U. UNAIDS. Global HIV/AIDS response—epidemic update and health sector progress towards universal access—progress report 2011. 2012.
2. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet. 2006;368(9534):505-10.
3. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. New England Journal of Medicine. 2011;365(6):493-505.
4. Granich R, Kahn JG, Bennett R, Holmes CB, Garg N, Serenata C, et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011-2050. PloS one. 2012;7(2):e30216.
5. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. Annals of internal medicine. 2011;155(4):209-16.
6. Hogg RS, Heath KV, Yip B, Craib KJ, O'Shaughnessy MV, Schechter MT, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. Jama. 1998;279(6):450-4.
7. Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Medicine. 2013;10(4):e1001418.
8. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? Aids. 2002;16(4):597-603.
9. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. New England Journal of Medicine. 1998;338(13):853-60.
10. Julius H, Basu D, Ricci E, Wing J, Kusari Basu J, Pocaterra D, et al. The Burden of Metabolic Diseases Amongst HIV Positive Patients on HAART Attending the Johannesburg Hospital. Current HIV research. 2011;9(4):247-52.
11. Paula AA, Falcão MC, Pacheco AG. Metabolic syndrome in HIV-infected individuals: underlying mechanisms and epidemiological aspects. cardiovascular diseases (CVD). 2013;4:5.
12. Feleke Y, Fekade D, Mezegebu Y. Prevalence of highly active antiretroviral therapy associated metabolic abnormalities and lipodystrophy in HIV infected patients. Ethiopian medical journal. 2012;50(3):221-30.
13. van Griensven J, De Naeyer L, Mushi T, Ubarijoro S, Gashumba D, Gazille C, et al. High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101(8):793-8.
14. Alberti K, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabetic Medicine. 2006;23(5):469-80.
15. Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C. Definition of metabolic syndrome report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on scientific issues related to definition. Circulation. 2004;109(3):433-8.
16. Nguyen K, Peer N, Mills E, Kengne A. Burden, Determinants, and Pharmacological Management of Hypertension in HIV-Positive Patients and Populations: A Systematic Narrative Review. AIDS reviews. 2014;17(2):83-95.

17. Bloomfield GS, Hogan JW, Keter A, Sang E, Carter EJ, Velazquez EJ, et al. Hypertension and Obesity as Cardiovascular Risk Factors among HIV Seropositive Patients in Western Kenya. PloS one. 2011;6(7):e22288.
18. Thiébaut R, El-Sadr WM, Friis-Moller N, Rickenbach M, Reiss P, Monforte A, et al. Predictors of hypertension and changes of blood pressure in HIV-infected patients. Antiviral therapy. 2005;10(7):811.
19. Palacios R, Santos J, García A, Castells E, Gonzalez M, Ruiz J, et al. Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naive patients. HIV medicine. 2006;7(1):10-5.
20. Ajayi5 BADPJMWGDNMaNA. <Effects of highly active antiretroviral therapy (HAART) on blood pressure changes & associated factors ...Nigeria.pdf>. Archives of Applied Science Research. 2012;4 (3):1447- 52.
21. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Archives of internal medicine. 2000;160(13):2050.
22. Mutimura E, Crowther NJ, Stewart A, Todd Cade W. The human immunodeficiency virus and the cardiometabolic syndrome in the developing world: an African perspective. Journal of the cardiometabolic syndrome. 2008;3(2):106-10.
23. Chow D, Souza S, Chen R, Richmond-Crum S, Grandinetti A, Shikuma C. Elevated blood pressure in HIV-infected individuals receiving highly active antiretroviral therapy. HIV clinical trials. 2003;4(6):411.
24. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. 2014;311(5):507-20.
25. Sawicka K, Szczyrek M, Jastrzębska I, Prasał M, Zwolak A, Daniluk J. Hypertension–The Silent Killer. Journal of Pre-Clinical and Clinical Research. 2011;5(1):16-9.
26. Nsanzimana S, Ruton H, Lowrance DW, Cishahayo S, Nyemazi JP, Muhayimpundu R, et al. Cell phone-based and internet-based monitoring and evaluation of the national antiretroviral treatment program during rapid scale-up in Rwanda: TRACnet, 2004–2010. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2012;59(2):e17-e23.
27. Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. Globalization and Health. 2009;5(1):9.
28. Venter W, Sanne I. The cardiovascular consequences of HIV and antiretroviral therapy. Cardiovascular journal of Southern Africa. 2003;14(5):225-9.
29. Prendergast B. HIV and cardiovascular medicine. Heart. 2003;89(7):793.
30. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. The Lancet. 2003;362(9377):22-9.
31. Sudano I, Spieker LE, Noll G, Corti R, Weber R, Lüscher TF. Cardiovascular disease in HIV infection. American Heart Journal. 2006;151(6):1147-55.
32. Organization WH. A global brief on Hypertension, Silent killer, global public health crisis. 2013. URL: http://apps who int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013 2_eng pdf [accessed 2013-07-17][WebCite Cache ID 6IBqAI2eN]. 2014.
33. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.
34. Twagirumukiza M, De Bacquer D, Kips JG, de Backer G, Vander Stichele R, Van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. Journal of hypertension. 2011;29(7):1243-52.

35. Kagashe GAB, Fazal SA. Knowledge of Hypertensive Patients With or Without HIV on Hypertension and Their Experience in Using Their Medicines in Dar es Salaam, Tanzania: The Role of the Pharmacist. Tropical Journal of Pharmaceutical Research. 2011;10(6):825-31.
36. Pickering T. The effects of environmental and lifestyle factors on blood pressure and the intermediary role of the sympathetic nervous system. Journal of human hypertension. 1997;11:S9-18.
37. Luft FC. Molecular genetics of human hypertension. Journal of hypertension. 1998;16(12):1871-8.
38. Carretero OA, Oparil S. Essential hypertension part I: definition and etiology. Circulation. 2000;101(3):329-35.
39. De Socio GV, Ricci E, Maggi P, Parruti G, Pucci G, Di Biagio A, et al. Prevalence, awareness, treatment, and control rate of hypertension in HIV-infected patients: the HIV-HY study. American journal of hypertension. 2014;27(2):222-8.
40. Addo J, Smeeth L, Leon DA. Hypertension In Sub-Saharan Africa A Systematic Review. Hypertension. 2007;50(6):1012-8.
41. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. New England Journal of Medicine. 2003;348(8):702-10.
42. Jacobson DL, Tang AM, Spiegelman D, Thomas AM, Skinner S, Gorbach SL, et al. Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006;43(4):458-66.
43. Ogunmola OJ, Oladosu OY, Olamoyegun AM. association of hypertension and obesity with HiV and antiretroviral therapy in a rural tertiary health center in nigeria: a cross-sectional cohort study. Vascular health and risk management. 2014;10:129.
44. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, Monforte AA, et al. Cardiovascular disease risk factors in HIV patients-association with antiretroviral therapy. Results from the DAD study. Aids. 2003;17(8):1179.
45. Savès M, Chêne G, Ducimetière P, Leport C, Le Moal G, Amouyel P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clinical infectious diseases. 2003;37(2):292-8.
46. Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. Aids. 2006;20(7):1019-26.
47. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, et al. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. Journal of hypertension. 2003;21(7):1377.
48. Muhammad S, Sani MU, Okeahialam BN. Cardiovascular disease risk factors among HIV-infected Nigerians receiving highly active antiretroviral therapy. Nigerian medical journal: journal of the Nigeria Medical Association. 2013;54(3):185.
49. Domingo P, Sambeat MA, Pérez A, Ordoñez J, Rodríguez J, Vázquez G. Fat distribution and metabolic abnormalities in HIV-infected patients on first combination antiretroviral therapy including stavudine or zidovudine: role of physical activity as a protective factor. Antiviral therapy. 2003;8(3):223-32.
50. Röling J, Schmid H, Fischereder M, Draenert R, Goebel F. HIV-Associated Renal Diseases and Highly Active Antiretroviral Therapy—Induced Nephropathy. Clinical infectious diseases. 2006;42(10):1488-95.
51. de Ramirez SS, Enquobahrie D, Nyadzi G, Mjungu D, Magombo F, Ramirez M, et al. Prevalence and correlates of hypertension: a cross-sectional study among rural populations in sub-Saharan Africa. Journal of human hypertension. 2010;24(12):786-95.

52. Manuthu EM, Joshi M, Lule G, Karari E. Prevalence of dyslipidemia and dysglycaemia in HIV infected patients. East African Medical Journal. 2008;85(1):10-7.
53. So G. The Association of Antiroroviral Therapy and Hypertension among HIV-positive individuals in Canada and Tanzania. DigitalCommons@McMaster. 2011.
54. Lazar JM, Wu X, Shi Q, Kagame A, Cohen M, Binagwaho A, et al. Arterial wave reflection in HIV-infected and HIV-uninfected Rwandan women. AIDS Research And Human Retroviruses. 2009;25(9):877-82.
55. Cohen MH, Fabri M, Cai X, Shi Q, Hoover DR, Binagwaho A, et al. Prevalence and predictors of posttraumatic stress disorder and depression in HIV-infected and at-risk Rwandan women. Journal of women's health. 2009;18(11):1783-91.
56. Dusingize JC, Hoover DR, Shi Q, Mutimura E, Rudakemwa E, Ndacyayisenga V, et al. Association of Abnormal Liver Function Parameters with HIV Serostatus and CD4 Count in Antiretroviral-Naive Rwandan Women. AIDS Research And Human Retroviruses. 2015.
57. Anastos K, Ndamage F, Lu D, Cohen MH, Shi Q, Lazar J, et al. Lipoprotein levels and cardiovascular risk in HIV-infected and uninfected Rwandan women. AIDS research and therapy. 2010;7:34. Epub 2010/08/28.
58. Wanke C, Silva M, Knox T, Forrester J, Speigelman D, Gorbach S. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clinical infectious diseases. 2000;31(3):803-5.
59. Malaza A, Mossong J, Bärnighausen T, Newell M-L. Hypertension and obesity in adults living in a high HIV prevalence rural area in South Africa. PloS one. 2012;7(10):e47761.
60. Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. Circulation. 2005;112(23):3562-8.
61. Maher D, Waswa L, Baisley K, Karabarinde A, Unwin N. Epidemiology of hypertension in low-income countries: a cross-sectional population-based survey in rural Uganda. Journal of hypertension. 2011;29(6):1061-8.
62. Malaza A, Mossong J, Bärnighausen T, Newell M-L. Hypertension and obesity in adults living in a high HIV prevalence rural area in South Africa. 2012.
63. Kurukulasuriya LR, Stas S, Lastra G, Manrique C, Sowers JR. Hypertension in obesity. Medical Clinics of North America. 2011;95(5):903-17.
64. Bełtowski J, Wójcicka G, Marciniak A, Jamroz A. Oxidative stress, nitric oxide production, and renal sodium handling in leptin-induced hypertension. Life sciences. 2004;74(24):2987-3000.
65. Kang YS. Obesity associated hypertension: new insights into mechanism. Electrolytes & Blood Pressure. 2013;11(2):46-52.
66. Wang M-H, Smith A, Zhou Y, Chang H-H, Lin S, Zhao X, et al. Downregulation of renal CYP-derived eicosanoid synthesis in rats with diet-induced hypertension. Hypertension. 2003;42(4):594-9.
67. Boustany CM, Bharadwaj K, Daugherty A, Brown DR, Randall DC, Cassis LA. Activation of the systemic and adipose renin-angiotensin system in rats with diet-induced obesity and hypertension. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2004;287(4):R943-R9.
68. Cardillo C, Campia U, Iantorno M, Panza JA. Enhanced vascular activity of endogenous endothelin-1 in obese hypertensive patients. Hypertension. 2004;43(1):36-40.
69. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.
70. Hildrum B, Romild U, Holmen J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. BMC public health. 2011;11(1):601.
71. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension. 2009;53(4):631-8.

72. Scuteri A. Depression and cardiovascular risk: does blood pressure play a role? Journal of hypertension. 2008;26(9):1738-9.
73. Leigh JP, Du J. Are low wages risk factors for hypertension? The European Journal of Public Health. 2012;22(6):854-9.
74. Mendez MA, Cooper R, Wilks R, Luke A, Forrester T. Income, education, and blood pressure in adults in Jamaica, a middle-income developing country. International Journal of Epidemiology. 2003;32(3):400-8.
75. Dau B, Holodniy M. The relationship between HIV infection and cardiovascular disease. Current cardiology reviews. 2008;4(3):203.
76. Musinguzi G, Nuwaha F. Prevalence, Awareness and Control of Hypertension in Uganda. PloS one. 2013;8(4):e62236.
77. Agyemang C, Bruijnzeels MA, Owusu-Dabo E. Factors associated with hypertension awareness, treatment, and control in Ghana, West Africa. Journal of human hypertension. 2005;20(1):67-71.
78. Organization WH. The world health report 2003: shaping the future: World Health Organization; 2003.
79. Hu G, Barengo NC, Tuomilehto J, Lakka TA, Nissinen A, Jousilahti P. Relationship of physical activity and body mass index to the risk of hypertension: a prospective study in Finland. Hypertension. 2004;43(1):25-30.
80. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986:121-30.
81. Horton NJ, Lipsitz SR. Review of software to fit generalized estimating equation regression models. The American Statistician. 1999;53(2):160-9.
82. Dobson AJ. An introduction to generalized linear models: Chapman & Hall; 2002.
83. Kirkwood B, Sterne J. Essential medical statistics. 2nd. Massachusetts: Blackwell Science Ltd. 2003.
84. Twisk JW. Applied longitudinal data analysis for epidemiology: a practical guide: Cambridge University Press; 2003.

APPENDIX A

GENERALIZED ESTIMATING EQUATION (GEE) METHOD REVIEW

1. GENERALIZED ESTIMATION EQUATIONS MODELS

GEE were introduced by Liang and Zeger (1986) (80) as a means of analysing longitudinal data. GEE are extensions of generalized linear regression models (GLM) that (81) account for repeated or dependent observations and allow specifying the working correlation structure. The estimation and inference procedures for GLM models are, in principle, analogous to those for GEE models (82). GEE are used to characterise the marginal expectation of a set of outcomes as a function of a set of study variables. The marginal mean model can be written as follows:

$$g(\mathrm{E}[Y_{ij} \mid \chi_{ij}]) = \chi'_{ij}\beta$$

where χ_{ij} is a p times 1 vector of explanatory variables (covariates) for the *i*th subject at the *j*th outcome, β consists of the p regression parameters of interest, Y_{ij} denotes the*j*th outcome (for j = 1,⋯, J) for the *i*th subject (for i = 1,⋯,N) , and $g(\cdot)$ is a monotone, differentiable function called the link function.

Common choices for the link function are $g(a) = a$ for continuous data (identity link), $g(a) = \log(a)$ for count data (log link), or $g(a) = \log(a/1-a)$ for binary data (logit link). Other link functions exist (81).

In addition to the marginal mean model, the covariance structure of the correlated observations needs to be modelled on a given subject. Assuming no missing data, the J x J covariance matrix of $\mathbf{Y}_i = (Y_{i1}, Y_{i2}, \ldots, Y_J)$ is modelled as:

$$V_i = \phi A_i^{1/2} R(\alpha) A_i^{1/2}$$

where ϕ is a GLM dispersion parameter, A is a diagonal matrix of variance functions, and $R(\alpha)$ is the working correlation matrix of Y_i.

When fitting the model in GEE, the model for the mean and for the variance and the fact that data are missing completely at random are considered.

In GEE, model parameters and covariance structures are estimated as follows:

Quasi- likelihood estimation, where only the mean and variance are specified, rather than a full probability model of its distribution. The Quasi likelihood approach is generalized to allow a choice of structures for the correlation of outcomes within clusters; these are working correlation structures.

Robust standard errors are used to take account of the clustering, and the fact that the parameter estimates are not based on a full probability model. For normally distributed outcomes, parameter estimates from GEE are identical to those from the standard random-effects models. GEE adjust for both standard errors and parameter estimates to allow for clustering (83).

2. SPECIFICATION OF WORKING CORRELATION MATRIX

Because the repeated observations within one subject are not independent of each other, a correlation must be made for these within-subject observations. GEE takes into account the dependency of observations by specifying a priori a working correlation structure. There are

a variety of common structures (independent, exchangeable, autoregressive, stationary or m-dependent and fixed) (81, 84) that may be appropriate. In general, if the number of observations per cluster is small in a balanced and complete design, an unstructured matrix is recommended (81). For datasets with mistimed measurements, a model where M-dependent or autoregressive correlation is a function of the time between observations may be reasonable (81). For datasets with clustered observations, where there is no logical ordering for observations within a cluster, an exchangeable structure may be most appropriate (81).

1. *Independent*: with this structure the correlations between subsequent measurements are assumed to be zero therefore, the within- individual correlation matrix of the form:

Estimated within individuals' correlation matrix R:

	c1	*c2*	*c3*	*c4*	*c5*	*c6*
r1	*1*	*0*	*0*	*0*	*0*	*0*
r2	*0*	*1*	*0*	*0*	*0*	*0*
r3	*0*	*0*	*1*	*0*	*0*	*0*
r4	*0*	*0*	*0*	*1*	*0*	*0*
r5	*0*	*0*	*0*	*0*	*1*	*0*
r6	*0*	*0*	*0*	*0*	*0*	*1*

2. *Autoregressive* (1): the correlations one measurement apart are assumed to be ρ, two times measurement apart are assumed to be ρ^2, correlations at time *t* are assumed to be ρ^t. The term ρ is the intra-class correlation coefficient (ICC) and it is defined as the ratio of the between cluster variance to the total variance, which is the between and within cluster variances. Therefore, the within – individual correlation matrix *R* is of the form:

Estimated within individuals' correlation matrix R:

c1	*c2*	*c3*	*c4*	*c5*	*c6*

r1	*1*	ρ^1	ρ^2	ρ^3	ρ^4	ρ^5
r2	ρ^1	*1*	ρ^1	ρ^2	ρ^3	ρ^4
r3	ρ^2	ρ^1	*1*	ρ^1	ρ^2	ρ^3
r4	ρ^3	ρ^2	ρ^1	*1*	ρ^1	ρ^2
r5	ρ^4	ρ^3	ρ^2	ρ^1	*1*	ρ^1
r6	ρ^5	ρ^4	ρ^3	ρ^2	ρ^1	*1*

3. *Exchangeable (or compound symmetry)*: in this structure the correlations between subsequent measurements are assumed to be the same.

Estimated within-individuals correlation matrix R:

	c1	*c2*	*c3*	*c4*	*c5*	*c6*
r1	*1*	ρ	$\rho\rho$	$\rho\rho\rho$		
r2	ρ	*1*	ρ	$\rho\rho$	$\rho\rho\rho$	
r3	ρ	ρ	*1*	ρ	$\rho\rho$	
r4	ρ	$\rho\rho$	*1*	ρ	ρ	
r5	ρ	$\rho\rho\rho$	*1*	ρ		
r6	ρ	$\rho\rho\rho\rho$	*1*			

4. *Unstructured*: with this structure, all correlations are assumed to be different.

Estimated within-individuals correlation matrix R:

	c1	*c2*	*c3*	*c4*	*c5*	*c6*
r1	*1*	ρ_1	ρ_2	ρ_3	ρ_4	ρ_5
r2	ρ_1	*1*	ρ_6	ρ_7	ρ_8	ρ_9
r3	ρ_2	ρ_6	*1*	ρ_{10}	ρ_{11}	ρ_{12}
r4	ρ_3	ρ_7	ρ_{10}	*1*	ρ_{13}	ρ_{14}
r5	ρ_4	ρ_8	ρ_{11}	ρ_{13}	*1*	ρ_{15}
r6	ρ_5	ρ_9	ρ_{12}	ρ_{14}	ρ_{15}	*1*

5. *Stationary* or *m-dependent structure:* assumes that the correlations *t* measurements apart are equal, the correlations *t+1* measurements apart are assumed to be equal, and so on for *t=1* to *t=m*. Correlations more than m measurements apart are assumed to be 0.

Estimated within-individuals correlation matrix R:

	c1	*c2*	*c3*	*c4*	*c5*	*c6*
r1	*1*	ρ^1	ρ^2	*0*	*0*	*0*
r2	ρ^1	*1*	ρ^1	ρ^2	*0*	*0*
r3	ρ^2	ρ^1	*1*	ρ^1	ρ^2	*0*
r4	*0*	ρ^2	ρ^1	*1*	ρ^1	ρ^2
r5	*0*	*0*	ρ^2	ρ^1	*1*	ρ^1
r6	*0*	*0*	*0*	ρ^2	ρ^1	*1*

GEE analysis presents a pooled analysis of longitudinal and cross-sectional relationships; in other words, it combines a within-individuals relation with a between-individuals relationship, resulting in one single regression coefficient.

GEE models were used in this study due to analysing correlated longitudinal data as the interest was on the population averaged mean responses. The unstructured correlation was used due to missing values in some variables in the dataset. The exchangeable and autoregressive had failed to converge.

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Christine Mutaganzwa

CLEARANCE CERTIFICATE	**M121124**
PROJECT	The Incidence of Hypertension among HIV Infected Rwandan Women on Highly Active Antiretroviral Therapy from 2005 to 2008
INVESTIGATORS	Dr Christine Mutaganzwa.
DEPARTMENT	School of Public Health
DATE CONSIDERED	30/11/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/11/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof K Grobusch

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...