SCHOOL OF PUBLIC HEALTH
COLLEGE OF HEALTH SCIENCES
UNIVERSITY OF GHANA

HYPERTENSION AND ASSOCIATED FACTORS IN PATIENTS ATTENDING HIV CLINIC AT THE KORLE-BU TEACHING HOSPITAL IN ACCRA

BY

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THIS THESIS IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF PhD PUBLIC HEALTH DEGREE

JULY, 2017

DECLARATION

I, Edmund Tetteh Nartey, declare that except for other people's investigations which have been duly acknowledged, this work is the result of my own original research carried out under the supervision of Professor Richard Adanu, Dr Bismark Sarfo and Dr Francis Anto. and that this thesis, either in whole or in part has not been presented elsewhere for another degree.

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This thesis is dedicated to the memory of my late father,

Ex-Cpl John Kingsley Kwame Nartey (1924-2013)

ACKNOWLEDGEMENT

My foremost and profound gratitude goes to Jehovah God for his faithfulness to me in undertaking and completing this work.

I am deeply indebted to my supervisors, Prof. Richard Adanu, Dr. Bismark Sarfo and Dr Francis Anto, all of the School of Public Health, University of Ghana for their guidance, remarks and excellent suggestions throughout this successful academic journey. I am privileged to be mentored by these great academic advisors.

I wish to also acknowledge the Office of Research, Innovation and Development (ORID) of the University of Ghana for the financial support they offered me to undertake this work. To Prof. Andrew Adjei and his team, I say, a big thank you.

A special thank you also goes to my senior colleague and friend, Mr Raymond Tetteh of the Pharmacy Department of the Korle-Bu Teaching Hospital and to Prof. Margaret Lartey of SMD, UG for their continuous interest to see me complete this programme.

I am also grateful to my wife, Mrs Charlotte Naa Anowah Sackey-Nartey and my two children, Michael and Nathaniel for their support, understanding and sacrifices offered during the course of this work.

I am also grateful to the entire staff and patients of Fevers Unit, Korle-Bu Teaching Hospital for the assistance they gave me during the data collection period.

I also thank the staff of Centre for Tropical Clinical Pharmacology and Therapeutics (SMD, UG) for their support and words of encouragement throughout this work.

To all my colleague students (Cohort 1) of School of Public Health, University of Ghana, I say a big thank you for the words of encouragement throughout this episode of academic achievement.

ABSTRACT

Two decades into the highly active antiretroviral therapy (ART) era, there has been a lot of improvement in the management of HIV/AIDS. Persons Living with HIV (PLHIV) now have life expectancy near that of the general population. However, with increasing years of survival, patients will transit into age groups with greater prevalence of cardiovascular events including hypertension. PLHIV in sub-Saharan Africa are in addition faced with an epidemiological transition of an increasing burden of non-communicable diseases. With the debate still ongoing, on whether ART is associated with hypertension, this thesis aimed to determine the prevalence of hypertension and associated factors among patients attending the HIV clinic at the Korle-Bu Teaching Hospital (KBTH) and also estimates the average treatment effect on the treated (ATT) of ART on hypertension and blood pressure values.

The study design was cross sectional and 311 PLHIV were randomly selected into the study. The WHO STEPwise Approach to Chronic Disease Risk Factor Surveillance instrument was modified and used to collect data on socio-demographic, life-style factors, anthropometric, biochemical and HIV/ART-related parameters from study participants' clinical folders. The prevalence of hypertension was 36.7% (95% CI, 31.3-42.3). Study participants on ART had a significantly higher prevalence of hypertension (41.3% [95% CI, 35.2-47.3]) compared with their ART-naive counterparts (16.9%, [95% CI, 7.4-26.5]). Regression modelling indicated the factors associated with hypertension were, increasing age, positive family history of cardiovascular disease/hypertension, inadequate exercising, a BMI $\geq$25.0 kg/m^2, abdominal obesity, hypercholesterolemia and exposure to ART. Propensity score-matching analysis estimated an ATT of ART on systolic and diastolic blood pressure values of 12.0 mmHg

(95% CI, 5.7-18.3) and 6.1 mmHg (95% CI, 1.3-10.8) respectively and on hypertension of 26.2 % (95% CI, 13.3-39.1). Estimated risk of cardiovascular disease using the Data Collection on Adverse Events of anti-HIV Drugs (D:A:D) risk score indicated 52.4% of the study participants were of moderate to high risk of cardiovascular event.

This study showed that hypertension, as a cardiovascular risk factor is prevalent among patients on ART attending HIV clinic at the KBTH. It also established a plausible causal relation between ART and hypertension/blood pressure levels and estimated that most patients were of moderate to high risk of cardiovascular event.

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADRB1	Adrenergic receptor B1
AIDS	Acquired Immune-Deficiency Syndrome
aOR	Adjusted odds ratio
ARB	Angiotensin II receptor blockers
ARVs	Antiretrovirals
ART	Antiretroviral Therapy
ATP	Adenosine triphosphate
ATT	Average treatment on the treated (also ATET)
ATV	Atazanavir
AUC	Area under the curve
AZT	Zidovudine (also ZDV)
CBPM	Clinic blood pressure monitoring
CCB	Calcium channel blockers
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDC	Centres for Disease Control and Prevention
c.i	Conditional independence
CKD	Chronic kidney disease
CRF	Circulating recombinant forms
CVD	Cardiovascular disease

d4t	Stavudine
D:A:D	Data Collection on Adverse Events of anti-HIV Drugs
DALY	Disability adjusted life years
dBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
ENaC	Epithelial sodium channel
F VII	Factor VII
FI	Fusion inhibitor
FFA	Free fatty acids
FPG	Fasting plasma glucose
FRS	Framingham Risk Score
FTC	Emtricitabine
GDHS	Ghana Demographic and Health Survey
GWAS	Analysis of Genome-wide association studies
HDL-C	High-density lipoprotein cholesterol
HIC	High-income countries
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
HSS	HIV sentinel site survey
i.i.d	Independence and identically distributed sampling
IL6	Interleukin 6
INSTI	Integrase strand transfer inhibitor
ISH	International Society of Hypertension

IQR	Interquartile range
JNC 7	Joint National Committee on Prevention, Detection, Evaluation and Treatment of high blood pressure
KBTH	Korle-bu Teaching Hospital
LAV	Lymphadenopathy-associated virus
LDL-C	Low-density lipoprotein cholesterol
LMIC	Low- and middle- income countries
LPS	Lipopolysaccharide
MACS	Multicentre AIDS Cohort study
MDGs	Millennium Development Goals
MI	Myocardial infarction
mRNA	Messenger RNA
NACP	National AIDS Control Programme
NCDs	Non-communicable diseases
NICE	National Institute for Health and Care Excellence
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NO	Nitric oxide
NRTI	Nucleoside Reverse Transcriptase inhibitor
NtRTI	Nucleotide Reverse Transcriptase inhibitor
NVP	Nevirapine
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor type 1
PD-1	Programmed death 1
PI	Protease Inhibitor
PLHIV	Persons Living with HIV

PPARy	Peroxisome proliferator-activated receptors
PSM	Propensity score-matched
PURE	Prospective Urban Rural Epidemiology
RAS	Renin angiotensin aldosterone system/Renin angiotensin system
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristics
ROS	Reactive oxygen species
RPV	Rilpivirine
RTV	Ritonavir
SAGE	Study on Global Ageing and Health
SSA	sub-Saharan Africa
sBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
TDF	Tenofovir disoproxil fumarate
TG	Triglycerides
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-to-hip ratio
WIHS	Women's Interagency HIV Study

CHAPTER ONE

1.0 INTRODUCTION

1.1 Hypertension

Each time the heart beats, blood is pumped from the heart to parts of the body through the blood vessels (arteries). The force created by blood pushing against the walls of the blood vessels is termed blood pressure. Hypertension, defined as systolic blood pressure (sBP) ≥140 mm Hg and/or diastolic blood pressure (dBP) ≥90 mm Hg, is also known as high blood pressure and it is a condition in which the blood vessels have persistently elevated pressure (WHO, 2013a) . Hypertension occurs as a result of long periods of elevated pressure of the main arteries. Hypertension rarely causes symptoms (WHO, 2013a) and uncontrolled hypertension can lead to several outcomes affecting the heart and other vital organs in the body, hence the term "silent, invisible killer" (WHO, 2013a). Hypertension is a known risk factor for cardiovascular diseases (CVDs) and complications of the condition may result in rupture of blood vessels, renal impairment, retinal haemorrhage, visual impairment and cognitive impairment (WHO, 2013a; WHO, 2013b). According to a policy statement from "The World Hypertension League", hypertension is estimated to be accountable for at least 9.4 million deaths and 162 million years of life lost in 2010 and also the cause of 50% of heart disease, stroke, and heart failure, 18% of deaths overall and more than 40% of deaths in people with diabetes (Campbell et al., 2014). The World Health Organization (WHO) also reported that globally, hypertension is estimated to cause 7.5 million deaths which is about 12.8% of the total of all deaths, accounting for an estimated 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS (WHO, 2013b). The prevalence of hypertension is also increasing steadily in low and middle income countries (LMIC) and this has been attributed to population growth, ageing and other life-style factors like smoking, physical inactivity, unhealthy diet, harmful use of alcohol and obesity (Singh et al., 2000; Yusuf et al., 2001;

Seedat, 2004; WHO, 2013a). This makes hypertension and its associated factors a major public health issue especially in SSA but which can be prevented and managed appropriately with population targeted interventions and screening programmes.

1.2 Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS)

Human immunodeficiency virus (HIV) is the virus which causes the disease acquired immune deficiency syndrome (AIDS) in humans. The virus acts slowly and it may take several years for the observable clinical manifestation of the disease state. HIV is a lentivirus belonging to a group of viruses called retro viruses which use ribonucleic acid (RNA) instead of deoxyribonucleic acid (DNA) in replicating itself within living cells. The virus after entering into the body typically infects the human immune system attacking the cluster of differentiation 4 T-helper cells (CD4+ T-cells) and other cells and thereby leading to a decrease in CD4+ T-cells count. This decrease in CD4+ T-cells is through a number of mechanisms including direct killing of infected cells by the virus, killing of infected cells by cluster of differentiation 8 (CD8) cytotoxic lymphocytes and cell apoptosis of uninfected bystander cells (Garg et al., 2012). The decline in CD4+ T-cells (below a critical level) leads to a failure of the immune system. The functionality of the immune system depends on the presence of the T-cells; hence, any impairment in this function will lead to the occurrence of infections and the reduction of immune surveillance against several diseases. In addition to compromising the immune system, HIV may also attack organs like the kidneys, heart and brain resulting in metabolic pathologies like renal failure, cardiomyopathy, dementia and encephalopathy. The effect of the virus on both the immune system and direct attack on some organs if not controlled leads to AIDS characterised by the occurrence of opportunistic infections, cancers and other pathologies. Worth noting is that, in situations where a HIV-positive person does not access treatment, the estimated survival time after the infection is 11 years (UNAIDS, 2007).

The management of HIV/AIDS has gone through a series of changes. Three decades into the HIV epidemic (UNAIDS, 2013), a number of critical advances have been made in care and treatment of HIV positive patients. Anti-retroviral therapy now reaches nearly half of those eligible, resulting in dramatic reductions of illness and death (WHO, 2011b). Persons living with HIV (PLHIV) are living longer than ever before, and are able to establish families, work and lead normal lives. Treatment of HIV infection commonly requires a combination of 3 to 4 anti-retroviral drugs (ARVs), termed Highly Active Antiretroviral Therapy (ART) (Josephson, 2010). Presently in the ART era, five classes of ARVs are available for use but with specific combination groups for a patient depending on several factors including the type of HIV infection, the presence of resistance strains, availability of drug types per national guidelines, report of adverse events and history with previous ARVs. The different classes of ARVs act at different stages of the HIV replication cycle. These ARVs either impede the entry of HIV into host cells (fusion inhibitors-FIs), act as DNA chain terminators (nucleoside/nucleotide reverse transcriptase inhibitors-NRTIs/NtRTIs), hinder the catalytic activity of reverse transcriptase (non-nucleoside reverse transcriptase inhibitors-NNRTIs), inhibit the incorporation of HIV DNA into host cell DNA (integrase strand transfer inhibitors-INSTIs) or inhibit production of infectious viral particles (protease inhibitors-PIs) (Clavel and Hance, 2004). The chronic nature of HIV infection requires lifelong ART (Negredo et al., 2006) to continuously suppress HIV viral replication, thus reducing morbidity and mortality. However, ART is restricted by treatment barriers such as complex dosing, drug-drug interactions and toxicities. In addition, some HIV-positive patients still require concomitant treatment with drugs for opportunistic infections and medication to treat unrelated medical conditions and/or the metabolic complications of ARV therapy (Fichtenbaum and Gerber, 2002). These metabolic complications are also risk factors of other morbid conditions like hypertension, type II diabetes and dyslipidaemia (Busari et al., 2007; Busari and Busari, 2013). Therefore, the virtually limitless number of drug combinations that may be taken by patients undergoing treatment of HIV infection with co-morbidity markedly increases the risk of drug interactions, treatment failure, medication non-adherence, poor response rate of patients to ART and adverse drug reactions. The management of co-morbidities is therefore one of the major challenges associated with the multidrug regimens used for HIV therapy. Among the many co-morbid conditions, CVDs are of particular concern due to ARV induced metabolic changes. Available data suggests that even in SSA, chronic cardiovascular and pulmonary diseases are increasing in HIV-positive patients (Bloomfield et al., 2014a; Hyle et al., 2017). Hence, the risk of developing chronic cardiovascular and pulmonary diseases is increasingly being recognized as a major public health problem in PLHIV (Currier et al., 2003; Friis-Moller et al., 2007; Morris et al., 2012). Consequently, medical care for this population is focusing more intently on control and prevention of age- and metabolic-related co-morbidities (Aberg, 2009). Of the various risk factors associated with CVDs, the role played by hypertension as the major and leading risk factor for CVDs is unanimously agreed.

1.3 Hypertension and HIV/AIDS

Hypertension is an explanatory risk factor for myocardial infarction, stroke, heart failure, and kidney disease and has been established as a major risk factor that contributes to CVDs in adults with HIV-infection (Saves et al., 2003; Malvestutto and Aberg, 2010). The prevalence of hypertension in PLHIV ranges from 13% to 36% (Bergersen et al., 2003; Gazzaruso et al., 2003; Jerico et al., 2005; Baekken et al., 2008). Hypertension has also been related to mortality in HIV-positive patients in Kenya (Bloomfield et al., 2014a). It has also been suggested that the degree to which high blood pressure is related to mortality in HIV-positive patients in SSA has not been specifically addressed (Moore et al., 2011). Although a relationship between ART and other components of the metabolic syndrome, such as dyslipidaemia and hyperglycaemia, have been established, it is not clear whether HIV or specific ARVs are explanatory risk factors for hypertension. Studies have demonstrated that there is an association between HIV infection, ART and hypertension (Crane et al., 2006; Wilson et al., 2009; De Socio et al., 2010) but there is no conclusive evidence to this as other studies have indicated otherwise (Bergersen et al., 2003; Baekken et al., 2008).

1.4 Statement of the problem

The introduction of newer anti-retroviral drugs in the form of ART for the management of HIV has led to a better health care for PLHIV. As more people in SSA begun taking antiretroviral treatment, mortality rates have dropped (Mermin et al., 2008; Stover et al., 2008) and life expectancy of PLHIV has increased with studies indicating PLHIV on ART in SSA can achieve a normal life expectancy (Mills et al., 2011). As such, HIV infection is now considered a chronic disease. There is also evidence to indicate that both HIV infection and ART are risk factors for the development of non-communicable diseases (NCDs) in resource-limited settings including the likelihood of developing chronic pathologies like hypertension (Fedele et al., 2011; Post, 2011; Fabian et al., 2013; Kalra and Agrawal, 2013). In sub-Saharan Africa (SSA), there is ongoing demographic change with several populations showing an increase in life expectancy and an ageing population. In addition, there is epidemiologic transition in terms of disease burden from infectious diseases to non-communicable diseases and this has been attributed to various factors including rapid urbanization, improved healthcare and economic changes (CFR, 2014). This has resulted in several SSA populations increasingly demonstrating HIV as an infectious chronic disease with NCD co-morbidities like hypertension, diabetes and kidney disease (Remais et al., 2013).

In Ghana, the change in demographics indicate that the proportion of the population >15 years decreased from 45% in 1960 to 38% in 2010 while the proportion of the population ≥65 years increased from 3% to 5% over the same period (GSS et al., 2015). In addition, data from the

Ghana Demographic and Health surveys indicate that over the last five decades, life expectancy at birth has increased from 38 years to 60 years among males and from 43 years to 63 years among females (GSS et al., 2015). In view that the prevalence of NCDs, including hypertension is also increasing rapidly (Bosu, 2010), this brings with it an interaction between HIV, ARVs and hypertension in the HIV-infection population, which needs to be investigated especially in resource limited settings like Ghana. Anecdotal evidence from the KBTH indicates a prevalence of hypertension of 25% among patients attending HIV clinic which is higher than the 2014 Ghana Demographic and Health Survey report of hypertension prevalence of 13% in the general population of 15-49 years (GSS et al., 2015). Given that the patient population with HIV is increasingly getting older as a result of the success of ART in reducing HIV associated morbidity and mortality (supported by the fact that the 2016 Ghana HIV sentinel survey report indicate the 45-49 years group has the highest prevalence of HIV in Ghana of 5.7%, compared with the estimated national prevalence of 2.4% for all ages (NACP, 2017)) and age is known risk factor for both hypertension and several cardiovascular diseases, hypertension as a co-morbidity will increasingly be seen and importantly influence patient management and service delivery at HIV clinics.

Hypertension tends to cluster in families with strong genetic basis and resultant inherited biochemical abnormalities. It thus seems like several factors contribute to the pathogenesis of essential hypertension and these include hereditary, environmental, lifestyle and metabolic with the underlying factor being renal mechanisms (Guyton, 1991). As such hypertension is a result of an interaction between factors like sympathetic nervous system activity, overproduction of sodium-retaining hormones and vasoconstrictors, long-term high sodium intake, inadequate dietary potassium and calcium intake. Other factors implicated in the pathogenesis of hypertension include increased renin secretion with increased production of angiotensin II and aldosterone, reduction in the production of vasodilators like prostacycline, nitric oxide (NO) and the natriuretic peptides, changes in the kallikrein-kinin system affecting vascular tones and salt handling by the kidneys, diabetic mellitus, obesity, increased oxidative stress and endothelial dysfunction. Hypertension has been shown to be related to the risk of stroke and cardiovascular diseases and have become an important public health challenge and both hypertension and CVDs have been associated with mortality in PLHIV (Bloomfield et al., 2014b).

In the present ART era some studies have raised the possibility that ARVs may also induce hypertension (Chow et al., 2003; Gazzaruso et al., 2003; Palacios et al., 2006; Coloma Conde et al., 2008) through acceleration of atherogenesis and the subsequent hardening of the blood vessel walls (Dube et al., 2008). Additionally, results from two large prospective cohort studies (Mary-Krause et al., 2003; Friis-Moller et al., 2007) indicated that PLHIV are at an increased risk of CVDs in the long term. However, studies on the association between hypertension and ART and the role of different treatment regimens in hypertension genesis show conflicting results. Additionally, although a few of these studies have addressed this issue in SSA, these studies also show contradictory results in terms of the association between ARVs and hypertension. Whilst studies in Kenya (Kagaruki et al., 2014), Ghana (Ngala and Fianko, 2014) and South Africa (Oni et al., 2015) associated hypertension with ART, other studies in Kenya (Bloomfield et al., 2011), Senegal (Diouf et al., 2012) and South Africa (Edwards et al., 2015) found no association between ART and hypertension. However, in all these conflicting studies on the association between ART and hypertension, the study design and analysis has been through regression modelling. A systematic review and meta-analysis supports an association between ART and increased blood pressure and also increased risk of hypertension in PLHIV (Nduka et al., 2016a) but there is little evidence whether this association is causal in nature. In all the studies reviewed (Nduka et al., 2016a), the statistical methods employed in examining the association between ART and hypertension have been regression modelling which is seldom used for causal inferences. However, there is a growing appeal to use statistical methods in observational studies to infer or rule out causal effect especially in situations where controlled experiments are not feasible due to ethical reasons (Rosenbaum and Rubin, 1985; Austin, 2011a; Austin, 2011b). Inferences which draw on causal effect continue to evolve in modern-day epidemiology and causal effect has expanded beyond the "Hill's Criteria for Causation" (Hill, 1965; Lucas and McMichael, 2005; Mirtz et al., 2009). One of the statistical methods used in inferring causal effect in observational studies is propensity score-matching analysis. Unfortunately, a search of the literature indicates a dearth of studies in this analysis direction to link ART with increased blood pressure and increased risk of hypertension in PLHIV. A study by Nduka et al. (2016a) using propensity score-matching analysis reported of a plausible causal average treatment effect of ART on increased blood pressure in PLHIV (Nduka et al., 2016b). The present study determined the prevalence of hypertension and used propensity score-matching analysis to estimate the average treatment effect of ART on blood pressure and risk of hypertension in patients attending the HIV clinic at the Korle-Bu Teaching Hospital (KBTH) in Accra.

1.5 Conceptual framework

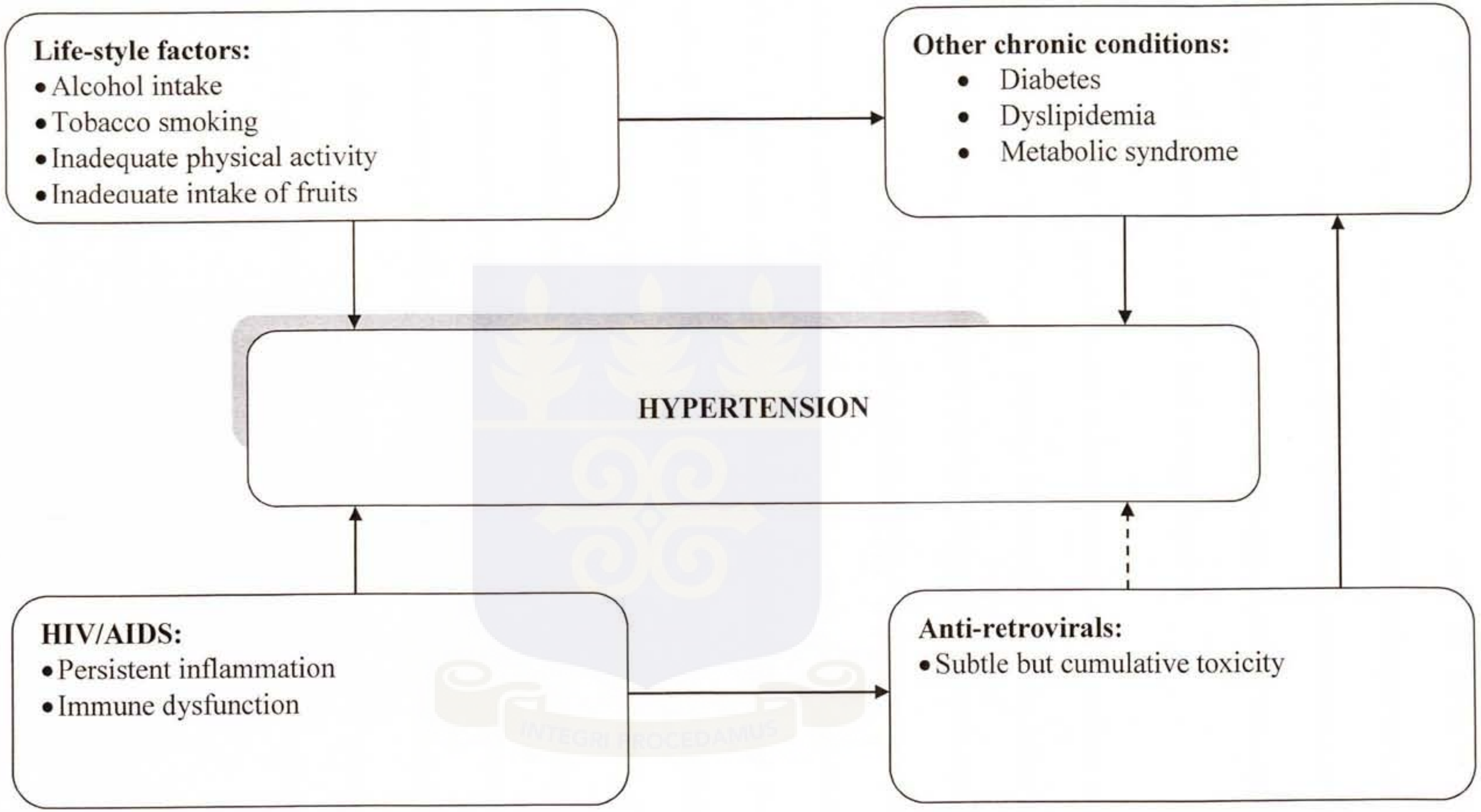

Figure 1. Conceptual framework of the interaction between socio-demographic, life-style, anthropometric, metabolic and HIV/ART-related factors in the pathogenesis of hypertension in persons living with HIV.

The proposed conceptual framework for this study, as shown in figure 1, assumes a complex interaction between the factors associated with hypertension in HIV infection. The pathways depicted shows that HIV infection can have both direct and indirect effect in the pathogenesis of hypertension. In the same context, life-style factors and other co-morbid conditions can also lead to hypertension.

HIV can directly damage the cells of blood vessels and contribute to atherosclerosis or hardening of the blood vessels. This has been attributed to the inflammation induced by the HIV infection or its associated proteins which may promote atherosclerosis and the formation of high-risk plaques (Hemkens and Bucher, 2014). Also attributed to the HIV infection is immune dysfunction which occurs due to the reduction in the levels of CD4+ T-cells and other immune function cells (Hemkens and Bucher, 2014). The indirect effect of HIV is the use of ARVs. ARVs have been attributed to cause subtle but cumulative toxicity by their effect on the lipid metabolism, and on mitochondrial function resulting in changes in body composition, with relative losses in subcutaneous fat and gains in abdominal adiposity. ARVs such as the PIs may also elevate the risk of hypertension by raising the level of cholesterol and triglycerides in the blood (Reyskens et al., 2014). Other metabolic abnormalities attributed to ARVs include dyslipidaemia, insulin resistance, diabetes and increased inflammatory indices (Hemkens and Bucher, 2014).

In addition to the HIV/ART-related factors, other risk factors like smoking, alcohol intake, inadequate physical activity, inadequate intake of fruits and vegetables are all known risk factors for hypertension. These factors in addition to a high body mass index (BMI) are associated with hypertension in the general population and thus are also present in PLHIV. In the context of the complexity in the array of causal effects or associated factors, it is highly possible that a combination of life-style factors, the effect of infection with the virus, the administration of ARVs and its associated metabolic as well as inflammatory effects would constitute a strong combination that could significantly determine the frequency and severity of hypertension in the HIV-infected population. Fortunately, all factors classified as HIV/ART-related, life-style related and anthropometric were likely to contribute to the overall burden of hypertension in the study population, as suggested above, were assessed and accounted for as covariates in both the propensity score-matching (PSM) analysis and in the regression model generation which yielded to the benefits of the study. The outcome of this, if proven, could undoubtedly place HIV/ART related factors as important factors associated with hypertension in PLHIV.

1.6 Justification

It is well known that some infections increase the risk of certain chronic diseases and vice versa. Numerous serious morbidities are more likely to occur among PLHIV than among the general population. Although there are increasing worldwide concerns of co-morbidity in PLHIV and there is considerable research into the commonly occurring non-communicable diseases and CVDs among PLHIV in resource-rich settings, less is known about the burden in resource-limited settings. With an increasing dual burden of HIV and CVDs in Sub-Saharan Africa, the associations between these diseases and our understanding of them will become of increased public health importance. In resource-limited settings, additional research is needed to better understand their risk and impact and identify optimal models of care to address this challenge in the areas where the majority of older PLHIV will be receiving care. It is important to understand the incidence rate of these CVDs among PLHIV, along with factors and outcomes associated with them, in order to guide clinical care and planning of health systems.

Given the importance and the urgency in adopting preventive measures for cardiovascular damage among PLHIV on ART, operational research on the factors associated with hypertension as a risk factor for CVDs in PLHIV would be significant in policy formulation, implementation and practice. Hence, determining the factors associated with hypertension, preventing the occurrence of hypertension and treating hypertension will be clinically relevant issues in PLHIV. In addition, the management of HIV and other co-morbidities in PLHIV is complicated with the issue with polypharmacy which can invariably lead to an increased rate of drug-drug interactions and facilitate drug toxicity and poor medication adherence (De Socio et al., 2014). This is supported by the fact that the European AIDS Clinical Society in its 2011 guidelines, warns of potentially significant interactions of PIs and NNRTIs with antihypertensive medications calcium-channel blockers and β-blockers (De Socio et al., 2014). It must however be said that even though the benefit of ART clearly outweighs the possible complications associated with it, the progressive aging of the HIV-infected population and the expected long-term use of ART will come with its own issues.

An evaluation of the factors associated with hypertension as a co-morbid condition in PLHIV and an estimation of CVD risk score in the Ghanaian population is very important. This will help define the scope of the problem, characterize the burden of CVDs among PLHIV and also understand the impact of modifiable risk factors, Outcomes from this study will help identify individuals with early signs of hypertension who could benefit from interventions to prevent or delay the onset of complications and thereby improve the overall quality of life of PLHIV. This thesis explored the nature of the relationship between HIV/ART and hypertension in patients attending HIV clinic at the KBTH using both a propensity score-matching analysis approach and regression modelling approach and also calculated the CVD risk score for each patient.

1.7 Objectives

1.7.1 General Objective

To identify factors associated with hypertension among patients attending the HIV clinic at the KBTH in Accra.

1.7.2 Specific Objectives

1. To determine the prevalence of hypertension among patients attending the HIV clinic at the KBTH.
2. To identify lifestyle, anthropometric, metabolic and HIV/ART-related factors associated with hypertension among HIV-positive patients.
3. To estimate average treatment effect of ART on hypertension among HIV-positive patients.
4. To estimate and classify cardiovascular disease risk score for HIV-positive patients.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Hypertension

Blood pressure refers to the force against the walls of the arteries as the heart pumps blood through the body. Hypertension is a long-term medical condition in which the arteries have persistently elevated blood pressure (Naish and Syndercombe Court, 2014). This elevated blood pressure makes the heart to work harder in pumping blood throughout the body and contributes to the hardening of the arteries (atherosclerosis) and to the development of several CVDs. Blood pressure is reported using two measurements; a systolic blood pressure (sBP) and a diastolic blood pressure (dBP). Hypertension is defined using standard definitions by the World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines: diastolic blood pressure (dBP) values of ≥90 mmHg or systolic blood pressure (sBP) values of ≥140 mmHg at 2 or more clinic visits (Whitworth, 2003). Hypertension has become an important public health challenge in both developed and developing countries (Kearney et al., 2004). Hypertension has now become an increasingly common health problem which is attributable to several risk factors including, race, family history, sedentary lifestyle, smoking, lack of physical activity, high levels of salt intake, high levels of alcohol consumption, tobacco use, being overweight or obese, stress and certain chronic medical conditions including kidney diseases (Yusuf et al., 2001). In the absence of broad and effective preventive measures in developing countries, the prevalence of hypertension is expected to increase (Chobanian et al., 2003).

2.1.1 Signs and symptoms of hypertension

Symptoms of hypertension are rarely seen although reports of headaches, light-headedness, vertigo, tinnitius and altered vision or fainting episodes are often reported (Fisher and Williams, 2005). Hypertension has also been associated with hypertension retinopathy, changes in the optic fundus of the eye of which the severity of the retinopathy can be used as an estimate of the duration and/or severity of the hypertensive state (Fisher and Williams, 2005).

2.1.2 Types of hypertension

There are two types of hypertension defined by the underlying cause of the elevated blood pressure. These are primary or essential hypertension and secondary hypertension.

2.1.2.1 Primary hypertension

Primary hypertension also referred to as "essential hypertension" is defined as high blood pressure without any clearly defined aetiology affecting the blood pressure regulating mechanism (Williams, 2015). It is the most common form of hypertension accounting for 97-98% of all hypertensive cases (Oparil et al., 2003) and practically its treatment results in lower blood pressure results and significant clinical benefits (Williams, 2015). Most people with essential hypertension show no symptoms, but symptoms like frequent headaches, tiredness, dizziness and nose bleeding has been reported in some cases. The cause of essential hypertension is unknown but factors like obesity, smoking, alcohol abuse, excess salt intake diet and heredity has been associated with the condition (Poulter et al., 2015).

2.1.2.2 Secondary hypertension

Secondary hypertension refers to a type of hypertension in which the underlying cause is specific and it usually involves the renal or endocrine system (Williams, 2015). Secondary hypertension accounts for 2-3% of patients with hypertension (Ilyas, 2009). Renal causes of secondary hypertension include glomerulonephritis, diabetic nephropathy, polycystic kidney disease and renal stenosis (Ilyas, 2009). Some diseases of the endocrine system like Cushing's syndrome, Conn's syndrome (hyperaldosteronism), phaecochromocytoma, thyroid dysfunction and over activity of the adrenal gland can lead to secondary hypertension (Ilyas, 2009; Rodriguez et al., 2010). Other factors attributed to secondary hypertension include sleep apnoea, pregnancy associated hypertension, alcohol abuse, some herbal medicines and the use of illicit drugs (Ilyas, 2009; Rodriguez et al., 2010; Grossman and Messerli, 2012). Arsenic contaminated drinking water has also been linked to secondary hypertension (Abhyankar et al., 2012; Farzan et al., 2015; Jiang et al., 2015).

2.1.3 Pathogenesis and pathophysiology of essential hypertension

Essential hypertension tends to cluster in families with strong genetic basis and resultant inherited biochemical abnormalities. It thus seems like several factors contribute to the pathogenesis of essential hypertension and these include hereditary, environmental, lifestyle and metabolic with the underlying factor being renal mechanisms (Guyton, 1991). As such, essential hypertension is a result of an interaction between genetic factors and environmental factors. In an appraisal of the various implicated or suggested mechanisms of the pathogenesis of essential hypertension, Oparil et al. (2003) noted several mechanisms including increased sympathetic nervous system activity, overproduction of sodium-retaining hormones and vasoconstrictors, long-term high sodium intake, inadequate dietary potassium and calcium intake, and increased renin secretion with increased production of angiotensin II and aldosterone (Oparil et al., 2003). Other mechanisms implicated are diabetic mellitus, insulin resistance, obesity, increase in the activity of vascular growth factors, changes in the adrenergic receptors affecting heart rate and vascular tone, increased oxidative stress, endothelial dysfunction and vascular remodelling (Oparil et al., 2003).

2.1.4 Measurement of blood pressure in adults

Measurement of blood pressure is in millimetres of mercury (mm Hg) recorded as systolic blood pressure and diastolic blood pressure. These two numbers are usually written one above the other with the upper number being the systolic blood pressure reading and the lower number being the diastolic blood pressure reading. Systolic blood pressure is the highest pressure in blood vessels when the heart contracts whilst diastolic blood pressure is the lowest pressure in blood vessels in between heart beats when the heart relaxes (WHO, 2013a). The WHO defines normal blood pressure in an adult as a systolic blood pressure of 120 mm Hg and a diastolic blood pressure of 80 mm Hg but with the recognition that the cardiovascular benefits of normal blood pressure extends to systolic blood pressure of 105 mm Hg and diastolic blood pressure of 60 mm Hg (WHO, 2013a). The WHO defines hypertension as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg (WHO, 2013a).

There are basically three different devices that can be used to measure blood pressure; electronic, mercury and aneroid devices (WHO, 2003; WHO, 2013a). The World Health Organisation recommends the use of affordable and reliable electronic devices that have the option to select manual readings (WHO, 2003; Parati et al., 2010; WHO, 2013a).

According to the National Institute for Health and Care Excellence (NICE) in its 2011 guidelines, hypertension should be diagnosed based on readings of blood pressure done on three separate occasions with at least one monthly intervals (NICE, 2011). First published in 2004 and subsequently reviewed in 2006, 2008, 2009 and 2011, the NICE guidelines distinguishes three types of blood pressure measurements available for the diagnosis of hypertension as follows;

- Clinic blood pressure monitoring (CBPM)
- Ambulatory blood pressure monitoring (ABPM) and
- Home blood pressure monitoring (HBPM)

In the measurement of blood pressure, health workers must ensure that all devices used are properly validated, maintained and regularly recalibrated to meet manufacturer's instructions (NICE, 2011). This is in addition to ensuring that the environment for the measurements should be standardised, relaxing and the person should be quiet, seated, arm outstretched and supported (NICE, 2011).

Both CBPM and ABPM are used in the diagnosis of hypertension but with ABPM identified as the most accurate and cost-effective means of confirming the diagnosis (NICE, 2011; McCormack et al., 2012; Siu, 2015). For CBPM, two measurements are recommended and if the second is substantially different from the first, a third measurement is done and the lower of the last two measurements used as the blood pressure readings (NICE, 2011; McCormack et al., 2012). In ABPM, the recommended protocol involves taking blood pressure measurements at least twice hourly during the persons wake hours (e.g. between 8.00 am and 10.00 pm) in a day (NICE, 2011; McCormack et al., 2012). Thereafter, the diagnosis of hypertension is made based on the average of 14 readings taken during the period.

In situations where ABPM is unsuitable or intolerable, then HBPM is used. This involves taking blood pressure readings twice daily (in the morning and evening) for 4-7 days and calculating the average but making sure to ignore the first day's readings in the calculations (NICE, 2011; McCormack et al., 2012)

2.1.5 Diagnosis and stages of hypertension in adults

According to the NICE guidelines, diagnosis of hypertension is divided into 3 stages depending on the type of measurements done (NICE, 2011);

- Stage I hypertension: CBPM systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg and subsequent ABPM or HBPM values of systolic blood pressure ≥135 mmHg and/or diastolic blood pressure ≥85 mmHg.
- Stage II hypertension: CBPM systolic blood pressure ≥160 mmHg and/or diastolic ≥100 mmHg and subsequent ABPM or HBPM values of systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥95 mmHg.
- Stage III hypertension (Severe hypertension): CBPM systolic blood pressure ≥180 mmHg and/or diastolic ≥110 mmHg.

Guidelines of the American Heart Association recommend a minimum of three blood pressure measurements done on at least two separate hospital visits (Aronow et al., 2011). The 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of high blood pressure (JNC 7) classifies blood pressure readings as follows (Chobanian et al., 2003);

- Normal: Systolic blood pressure readings of 90-119 mmHg and/or diastolic blood pressure readings of 60-79 mmHg
- Pre-hypertension: Systolic blood pressure readings of 120-139 mmHg and/or diastolic blood pressure readings of 80-89 mmHg

- Stage I hypertension: Systolic blood pressure readings of 140-159 mmHg and/or diastolic blood pressure readings of 90-99 mmHg.
- Stage II hypertension: Systolic blood pressure readings of 160-179 mmHg and/or diastolic blood pressure readings of 100-109 mmHg.
- Isolated systolic hypertension: Systolic blood pressure readings of $\geq$140 mmHg and diastolic blood pressure readings <90 mmHg.

2.1.6 Prevention of hypertension

Strategies adapted to prevent hypertension are usually population based, as this will invariably reduce the intake of antihypertensive medications. In general, most programs to reduce the incidence of hypertension involve lifestyle modifications. Behavioural factors play an essential role in the incidence of hypertension. A policy statement from the World Hypertension League in 2014 indicated the following facts (Campbell et al., 2014);

- Unhealthy diet is major factor estimated to contribute to about half of all hypertensive cases
- An estimated 30% of hypertensive cases are related to increase in salt intake
- About 20% of hypertensive cases are related to insufficient intake of dietary potassium
- Lack of effective exercise is related to about 20% of hypertensive cases
- Obesity accounts for about 30% of hypertensive cases and
- Excessive consumption of alcohol is also associated with hypertension

The British Hypertensive Society and the U.S. National Education Programme all focuses on lifestyle modification as these modifications may lower blood pressure as much as will individual antihypertensive medications (Whelton et al., 2002; Williams et al., 2004). Their programmes are focused on the following indices;

1. Reduction and subsequent maintenance of body mass index (BMI) to be between 20 and 25 kg/m^2
2. Reduction of dietary salt intake (<6g of salt/day)
3. Participation in regular aerobic physical activity or exercising (≥30 minutes/day)
4. Limit to alcohol intake (not more than 3 units/day for men and 2 units/day for women)
5. Ensuring fruit and vegetable become part of the daily dietary intake (at least 5 portions/day)

The WHO in consonant with advocating bodies recommends population-wide policy interventions to reduce the incidence of hypertension. These interventions should include policies addressed to reduce the harmful use of alcohol, increase activity through exercises, reduction in overweight and obesity, reduce the intake of dietary salt, stopping tobacco use and exposure and managing stress (UNAIDS, 2015).

2.1.7 Management of hypertension

The management of hypertension involves lifestyle modifications (as in the prevention of hypertension) and the use of antihypertensive medications. Different guidelines indicate target blood pressure readings for the general population and patients with co-morbidities like diabetes and kidney disease in the management of hypertension. Other guidelines suggest different target blood pressure readings for patients aged over 60 years and those aged over 80 years. In most guidelines the recommended target for the general population is between 140 and 160 mmHg for systolic blood pressure and 90-

100 mmHg for diastolic blood pressure (Arguedas et al., 2009; NICE, 2011; Mancia et al., 2013; James et al., 2014; Daskalopoulou et al., 2015).

Several classes of antihypertensive medication are available for the management of hypertension and these include diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), adrenergic receptor antagonists, vasodilators, benzodiazepines, renin inhibitors, aldosterone receptor antagonists, α-2 adrenergic receptor agonists and endothelin receptor blockers. First line antihypertensive medications include thiazide-type diuretics, calcium-channel blockers, ACE inhibitors and angiotensin II receptor blockers (ARBs) (James et al., 2014). The diuretics increase the secretion of excess salt and water by the kidneys from the body whilst the CCBs block the entry of calcium into muscle cells of the artery walls. The ACE inhibitors inhibit the activity of angiotensin converting enzyme and the ARBs work by antagonising the activation of angiotensin receptors. Drugs from the various classes are used alone or in combination but with a majority of cases needing more than one medication in the management of hypertension (Go et al., 2014).

2.1.8 Epidemiology of hypertension worldwide

In the year 2000, about 25% (estimated to be 972 million) of the world's adult population were estimated to be have hypertension defined as either a blood pressure reading of ≥140/90 mmHg or in the use of antihypertensive medication (Williams, 2015). The WHO estimates this proportion will hit 29% (representing about 1.6 billion) i.e. a prevalence of 60%, by the year 2025 (Williams, 2015). This dramatic increase in the worldwide prevalence of hypertension is expected to come primarily from the economically developing countries contributing to an estimated 75% of the world's hypertensive population by 2025 (Kearney et al., 2005; Williams, 2015). This is said will continue to maintain hypertension at its position as the World's single most important preventable cause of death prematurely over the next 2 decades with an estimate of 7.1 million deaths/year (Williams, 2015). The higher the blood pressure, the higher the risk of heart and blood vessel damage to the brain and kidneys. As such, hypertension causes about one-half of all deaths from stroke and heart diseases (WHO, 2008b; WHO, 2015).

In 2013, all the 194 states of the WHO agreed on measures to reduce avoidable non-communicable diseases with nine voluntary global targets. The 6th of these targets is to reduce by 25% the global prevalence of elevated blood pressure between 2013 and 2030 (WHO, 2013b). This intervention and declaration is important, as elevated blood pressure is rated as the leading risk factor for death and disability worldwide (Lim et al., 2012). A systematic review of disease burdens indicated that globally, elevated sBP >110-115 mmHg is the leading risk factor for both mortality (9.4 million deaths) and morbidity (7% of daily-adjusted life years) (Lim et al., 2012). In addition, a joint policy statement from the World Hypertension League and the International Society of Hypertension released in 2014 also emphatically implicated hypertension as causing an estimated 9.4 million deaths and 162 million years of life lost in 2010 (Campbell et al., 2014). The statement also implicated hypertension as disproportionately impacting on low and middle-income countries (LMIC) with two-thirds of cases being in economically developing countries and the fact that heart disease and stroke is more common in economically-developing countries than the developed countries (WHO, 2013b; Campbell et al., 2014).

Although figures indicate that the global age-standardised blood pressure has decreased within the past 30 years (1980-2008), the population of persons with hypertension has increased from 605 million to 978 million which has been attributed to both population growth and ageing of most populations (Danaei et al., 2011).

Studies have indicated an association between elevated blood pressure and socioeconomic status. A cohort study involving 27,000 women showed a lower socioeconomic status, lower education and lower income were associated with the development of hypertension (Conen et al., 2009). Two major studies in this area are the WHO Study on Global Ageing and Health (SAGE) and the Prospective Urban Rural Epidemiology (PURE) study. Interestingly figures from SAGE indicate comparably age-standardised hypertension (defined as sBP ≥140 mmHg and/or dBP ≥90mmHg) among people aged >50 years in low and middle-income countries and high-income countries (Lloyd-Sherlock et al., 2014). The PURE study showed that in LIC, 30% of urban hypertension patients receive anti-hypertension medication but only 20% of the rural patients receive anti-hypertensive medication (Chow et al., 2013). The PURE study also indicated difference between LMIC and HIC such that in HIC, men have significantly higher rates of hypertension than women do, but in LMIC, the reverse is true (Teo et al., 2009). The PURE study also showed that the worldwide rate of hypertension awareness among hypertension patients was 47% with 13% being able to control their blood pressure levels to <140/90 mmHg (Chow et al., 2013). The PURE study results that, whilst 32% of hypertension patients in LIC were treated for the condition with 13% been able to achieve blood pressure levels of <140/90 mmHg is comparable to the SAGE study which showed rates of blood pressure control in LIC is low ranging from 4% in Ghana to 14% in India (Chow et al., 2013; Lloyd-Sherlock et al., 2014).

In SSA, hypertension and other cardiovascular diseases continue to be rated as the leading causes of mortality and disability (Lawes et al., 2006; WHO, 2013b). An African Union report in 2006 stated that hypertension is next to HIV/AIDS in posing the greatest challenge to the healthcare systems in most Africa countries (WHO and AU, 2006). Africa is also reported to have a higher burden of hypertension compared with other world regions but the extent of this burden in most countries is still unknown (Addo et al., 2007; WHO, 2013b). In the year 2000, the WHO reported a hypertension prevalence of 46% in the African region which was highest globally (WHO, 2011a). Although this prevalence is higher than what has been projected and reported by most studies it is generally accepted that the prevalence of hypertension in SSA is rising. This increase is being seen more in young and active Africans and this has been attributed to several factors including the ageing of most African population, increasing populations, rapid urbanization and increasing rural-urban migration (Opie and Seedat, 2005; de-Graft Aikins et al., 2010). A systematic review involving 92 selected studies on hypertension in Africa indicated an overall pooled crude prevalence of hypertension of 19.7% in 1990, 27.4% in 2000 and 30.8% in 2010 and a pooled awareness rate of 16.9% in 1990, 29.2% in 2000 and 33.3% in 2010 (Adeloye and Basquill, 2014). With the exception of 1990, in all the other years, the rates were comparatively higher in females than males. Using modelling estimates the study further reported of an estimate of 54.6 million hypertensive cases in 1990 (age-adjusted prevalence of 19.1%), 92.3 million cases in 2000 (age-adjusted prevalence of 24.3%), 130.2 million cases in 2010 (age-adjusted prevalence of 25.9%) and a projection of 216.8 million cases by 2030 (age-adjusted prevalence of 25.3%) (Adeloye and Basquill, 2014).

These results indicate global differences between HIC and LMIC with major shortfalls in the awareness of hypertension, uptake of anti-hypertensive medication and the subsequent control of the elevated blood pressure (Rahimi et al., 2015).

2.1.9 Epidemiology of hypertension in Ghana

In 1979, hypertension was described as an epidemic in Ghana (Pobee et al., 1979). Several studies including two systematic reviews by Bosu (2010) and Addo et al. (2012) have been conducted in the epidemiology of hypertension in Ghana. Since then, hypertension has been rated as the third most common cause of mortality in Ghana (Owusu-Sekyere et al., 2013). A review of the literature indicates several population studies have been conducted on the prevalence of hypertension in different sub-populations in Ghana. Most of these studies were conducted in the Greater Accra Region and Ashanti Region of Ghana (the two most populous regions in Ghana), with a few in the Volta Region and Upper East Region. These studies were conducted in urban or rural communities. With the exception of the studies by Pobee et al. (1977 and 1979), Ikeme et al. (1978) and Chukwuemeka et al. (1983) which used a criteria of hypertension of sBP $\geq$160 and/or dBP $\geq$95, the rest of the studies used a criteria of hypertension of sBP $\geq$140 and/or dBP $\geq$90.

A study conducted in 1972 by Pobee et al. (1979) involving 6900 study participants (public servants-urban dwellers) in the Greater Accra Region indicate a hypertension prevalence of 8.9%. Studies conducted in 1975 by Ikeme et al. (1978) and in 1981 by Chukwuemeka et al. (1983) indicate a hypertension prevalence of 13.1% and 13.0% respectively in an urban community in the Greater Accra Region. Other studies conducted in 1998 by Amoah et al. (2003) (study participants of 4733), in 2000 by Escalona et al. (2004) (study participants of 598) and in 2005 by Addo et al. (2008)

(study participants of 1015) indicated a hypertension prevalence of 28.3%, 26.8% and 30.2% respectively in urban communities in the Greater Accra Region. Studies conducted in other urban communities in other regions in Ghana have shown similar results; Agyeman et al. (2006) indicated a hypertension prevalence of 29.4% (1431 study participants) in a study conducted in 2004 in Kumasi Metropolis (urban community) plus four rural communities.

Population studies on hypertension prevalence have also been conducted in rural communities in the Greater Accra Region. Studies conducted in 1973 by Pobee et al. (1977) in 20 rural communities in the Greater Accra Region (study participants of 1670) indicated hypertension prevalence of 4.5% (criteria of hypertension of sBP ≥160 and/or dBP ≥95). Another study conducted in 2001 by Addo et al. (2006) in four rural communities in the Greater Accra Region (study participants of 362) indicated hypertension prevalence 25.4% (criteria of hypertension of sBP ≥140 and/or dBP ≥90). Other studies conducted in rural communities in other parts of Ghana indicate comparable hypertension prevalence. A study conducted in the Volta region in 2002 by Burket et al., (2006) indicated a hypertension prevalence of 32.8% (287 study participants). Other studies conducted by Cappucio et al. (2004) in 2001 in the Ashanti region and Kunutsor & Powles (2009) in 2007 in the Upper East region indicate hypertension prevalence of 28.7% (1013 study participants) and 19.2% (574 study participants) respectively.

In 2008, the Ghana Health Service reported that the incidence of hypertension increased from 49,087 persons in 1988 to 505,180 persons in 2007 (a span of two decades) and also the proportion of hypertension in outpatients relative to other reported diseases increased from 1.7% to 4.0% (GHS, 2008). In Ghana, the Ministry of Health and the

Ghana Health Service have reported that hypertension ranked second as the most common medical condition and cause of outpatient morbidity and attributed it to poor unhealthy lifestyle of most urban dwellers (MOH, 2005; GHS, 2012). Figures from the 2011 annual report of the Ministry of Health indicate a prevalence of hypertension between 30% and 40% and that, at the Korle-Bu Teaching Hospital (the premier tertiary hospital in Ghana), hypertension and related condition is responsible for about 70% of all cases of death and constitutes more than 50% of cases on admission (MOH, 2011).

A systematic review of 17 epidemiological studies in Ghana reported in 2010 indicated that most studies reported crude hypertension prevalence between 25% and 48% with a higher prevalence in males compared with females (Bosu, 2010). The study indicated an epidemic of hypertension in Ghana and reported that the prevalence of hypertension increased from about 25%-28% in the period 1976-1998 to about 37%-45% between 2002 and 2006 (Bosu, 2010). In addition, the study reported of higher prevalence of hypertension among urban dwellers compared with rural dwellers and an association between hypertension and age, BMI, alcohol consumption and educational level (Bosu, 2010). The review also reported that between 22% and 54% of hypertension patients had knowledge of their condition and 7%-31% were on medication (Bosu, 2010). Another systematic review by Addo et al. (2012), involving 11 population studies on hypertension conducted between 1973 and 2007 indicated that the mean sBP was 122.0-139.4 mmHg in women and 123.8-132.9 mmHg in men. The review also reported that the mean dBP was 68.8-86.4 mmHg in women and 69.2-78.4 mmHg in men. The prevalence of hypertension from the review was between 19.3% and 54.6% using a criteria of hypertension of blood pressure readings of >140/90 mmHg (Addo et al., 2012). The review also reported a consistent difference in the prevalence of hypertension between urban populations and rural populations. Addo et al. (2012), also indicated that hypertension was associated with increasing age, BMI, waist circumference and pulse rate. Other factors associated with hypertension from the review were excessive alcohol and salt consumption and a family history of the condition (Addo et al., 2012). However, factors like physical activity and socio-economic status were either not determined or the results inconclusive (Addo et al., 2012). In terms of treatment and control, the review indicated low rates of detection, treatment and control of hypertension and further reported of differences in these indicators between urban populations and rural populations (Addo et al., 2012).

Although several hypertension prevalence studies have been conducted in Ghana, the 2014 Ghana Demographic and Health Survey (GDHS) was the first national survey to include measurements of blood pressure among adults aged 15-49 year. The national survey indicated a hypertension prevalence of 13.0% (GSS, 2015). The survey also reported of a higher prevalence of hypertension in urban areas (16.0%) compared with rural areas (9.0%) (GSS, 2015). In addition, the survey also reported an association between hypertension and both increasing age and increasing wealth (GSS, 2015). Interestingly, although the survey instrument indicated that a high proportion of study participants with hypertension were unaware of their blood pressure condition (63% in women and 86% in men).

Conclusively, these studies point to an epidemic of hypertension in Ghana with increasing prevalence but low levels of control and management.

2.2 Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS)

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). Upon infection with the virus, an infected person is said to sero-convert with an activation of the immune system to produce antibodies to the virus and this is followed by a latent or asymptomatic stage. If undetected and/or unmanaged, there is progressive immunosuppression and the latent stage gradually leads to a symptomatic stage with the occurrence of opportunistic infections and malignancies. In the last stages of the infection, the infected individual is said to have AIDS or HIV disease. Although currently there is no vaccine against HIV, available therapeutic management involves the use of ART which can delay an infected individual's suppression of the immune system and also control the occurrence of opportunistic infections. With the implementation of ART, HIV-positive patients can now boast of a considerable survival pattern and may now have a near-normal life expectancy (UNAIDS, 2012; CDC, 2015). The HIV infection which was formerly seen as a fatal disease when it emerged is now more of a chronic disease when managed appropriately and timely (Braitstein et al., 2006; Hall et al., 2006).

2.2.1 Background to the HIV/AIDS pandemic

HIV/AIDS is deemed to have originated during the mid-20th century from sub-Saharan Africa (Gao et al., 1999) and is considered as a global pandemic- a disease, which is widespread in geographical distribution and actively spreading (Cohen et al., 2008; Kallings, 2008). The recognition of AIDS as a new disease was reported by Centres for Disease Control and Prevention (CDC) in 1981 when a rare form of pneumonia caused by *Pnemocystis jiroveci* (previously called *Pneumocystis carinii*) and other opportunistic infections and rare malignancies were reported in young homosexual men (CDC, 1981). This was followed by a series of reports of similar immune deficiency syndromes in several diverse populations (CDC, 1982; Masur et al., 1982; CDC, 1983; Clumeck et al., 1983). In 1983, a group of scientists working at Pasteur Institute in France led by Luc Montagnier described the causative organism of AIDS as lymphadenopathy-associated virus (LAV) (Barre-Sinoussi et al., 1983). This was later confirmed by another group of scientists working in the United States led by Robert Gallo, then working with the National Cancer Institute (part of National Institute of Health, U.S.A) who described it as Human T lymphotropic virus type III (HTLV-III) (Gallo et al., 1984). Thereafter after much consultations and discussions, the virus was renamed human immunodeficiency virus (HIV) (Coffin et al., 1986a; Coffin et al., 1986b).

2.2.2 Global HIV/AIDS epidemiology

Since the HIV/AIDS pandemic broke out in the early 1980's, it has increased the disease burden of countries and has been one of the leading causes of both mortality and morbidity such that in sub-Saharan Africa, life expectancy has been reduced by more than 20 years, economic growth slowed, and household poverty deepened (UNAIDS/WHO, 2008).

Estimates indicate that globally, HIV is the leading cause of DALYS among people age 30-44 years (Ortblad et al., 2013). With an increasing burden of the disease in most countries, HIV/AIDS is considered a major global public health issue and the "single greatest reversal in human development" in modern history (UNDP, 2005; Maartens et al., 2014). From the year 2000 to 2014, it was estimated that 38.1 million people were infected with HIV and 25.3 million people died from AIDS-related illnesses (UNAIDS, 2015). However, the incidence of new infections has decreased by 35% from 3.1 million in 2000 to 2.0 million by the end of 2014 and an estimated prevalence of 36.9 million people as at the end of 2014 (UNAIDS, 2015). In addition, the decrease in the incidence of HIV between 2000 and 2014 was accompanied by a decrease of 24% globally in AIDS-related deaths from a peak of 2.0 million deaths in 2004/2005 to 1.2

million deaths in 2014 (UNAIDS, 2015). This has been attributed to a concerted effort of all countries in achieving the Millennium Development Goals (MDGs) on HIV/AIDS and the introduction of ART (UNAIDS, 2015).

Although with an estimated population of 10% of the world's population, sub-Saharan African (SSA) carries the heaviest burden of the HIV/AIDS pandemic (Aryee, 2009). In most countries in SSA where the disease has a high prevalence, the socio-economic impact of HIV/AIDS includes a decrease in life expectancy, a reduction in economic growth and an increase in household poverty levels (UNAIDS and WHO, 2008; Aryee, 2009). Estimates as at the end of 2014 indicate 25.8 million people with HIV/AIDS live in SSA with 57% being women (UNAIDS, 2015). In addition, an estimated 1.4 million new infections were accountable to SSA (UNAIDS, 2015) but this is a decrease of about 41% between 2000 and 2014 (UNAIDS, 2015). Despite this progress, SSA still leads in the global proportion of total new infection (UNAIDS, 2015). AIDS-related deaths in SSA in 2014 were estimated to be 790,000 people representing 34.2% of the global estimate but this is seen as a decrease by 48% between 2004 and 2014 (UNAIDS, 2015).

Generally, the number of patients with access to ART has increased over the years; 6.1 million people in 2009 to 14.9 million people in 2014 (UNAIDS, 2015). Globally, as at June 2015, 15.8 million PLHIV were assessing ART (UNAIDS, 2015). Within the SSA sub-region, 10.7 million PLHIV were receiving ART in 2014, which accounts for 41.0% of all HIV patients in the sub-region (UNAIDS, 2015). This proportion is made up of 47% of women and 36% of men. Although the access to anti-retroviral in the SSA is still below the expected proportion, it is a vast improvement over the fewer than a 100,000 people assessing ART in 2002 (UNAIDS, 2015).

2.2.3 HIV classification and sub-types

HIV, the virus that causes AIDS is characterised into two main types; HIV-Type 1 (HIV-1) and HIV-Type 2 (HIV-2). HIV-1 is assumed to have been transmitted from apes whilst HIV-2 is from sooty mangabey monkeys (Sharp and Hahn, 2011; Maartens et al., 2014). Four different groups of HIV-1 have been isolated namely group M, N, O and P (Maartens et al., 2014). Whilst groups N, O and P are restricted to the West Africa sub-region, group M is widespread and is the cause of the global HIV pandemic (Maartens et al., 2014). HIV-1 group M is further characterised into nine (9) subtypes; A, B, C, D, F, G, H, J and K of which sub-type C is the dominant type found in Africa and India and accounting for an estimated 48% of all HIV-1 infections worldwide in 2007 (Sharp and Hahn, 2011). Apart from these nine sub-types of HIV-1, studies indicate circulating recombinant forms (CRFs) of sub-type M are becoming common (Maartens et al., 2014).

HIV-2 is predominantly confined to the West-Africa sub-region. It is made up of seven (7) groups (A, B, C, D, E, F and G) with Groups A and B being the prominent groups found in most individuals with HIV-2 infection (Clavel et al., 1986a; Trevino et al., 2011). Although both HIV-1 and HIV-2 immunodeficiency illness progresses to AIDS if unmanaged, the rate of progression for HIV-2 is slower compared with HIV-1 and less transmissible as an infection (Sharp and Hahn, 2011). The underlying basis for these differences in their disease progression remains unclear but it has been suggested it has to do with the virus itself and the host of the infection (Clavel et al., 1986b; Schim van der Loeff and Aaby, 1999).

2.2.4 HIV transmission and risk factors

HIV is transmitted mainly through three (3) different routes; unprotected sex (including anal sex), contaminated blood transfusions and hypodermic needles and mother-to-child transmission during pregnancy, delivery or through breastfeeding (Markowitz, 2007).

2.2.4.1 Transmission of HIV through sexual intercourse

Unprotected sexual contact is the most frequent mode of HIV transmission with the majority been through heterosexual intercourse (Markowitz, 2007). In both heterosexual and homosexual contacts, the risk of infection through anal intercourse is high, estimated at 1.4-1.7% per act (Boily et al., 2009; Beyrer et al., 2012). In low-income countries, the risk of transmission in heterosexual contacts is estimated at 0.34% per act, which is far higher than the estimated 0.06% per act in high-income countries (Boily et al., 2009). Although, only a few cases of oral sex transmission have been reported, the risk of infection through oral sex is still considered a possibility (Pattman, 2010; Yu and Vajdy, 2010).

Factors associated with increased risk of sexual transmission of HIV include the viral load (2.4 fold-increased risk per 1 $\log_{10}$ increase in viral load), presence of other sexually transmitted infections and genital ulcers, pregnancy and anal intercourse (Maartens et al., 2014). Other factors are number of sexual partners and concurrent sexual partnerships (Maartens et al., 2014).

2.2.4.2 Transmission of HIV through contaminated blood/blood products

Transmission of HIV through contaminated blood and blood products including blood transfusion and its products, sharing of hypodermic needles during intravenous drug usage is the second most frequent mode of HIV transmission (Markowitz, 2007). In low-income countries, it is estimated that transmission through this route accounts for 15% of all new infections which is estimated to be 5-10% of all global infections (Markowitz, 2007).

2.2.4.3 Mother-to-child transmission of HIV

Mother-to child transmission, also termed vertical transmission can be during pregnancy, childbirth or breastfeeding. It is the third most frequent route of HIV transmission globally (Markowitz, 2007). In the absence of ART, the risk of transmission of HIV from an infected mother to a child during pregnancy or childbirth is estimated to be 20% whilst transmission through breastfeeding is estimated at a 35% risk (Coutsoudis et al., 2010). Policies targeted at ensuring every pregnant woman is screened during antenatal care have greatly reduced the rate of HIV infection through this route.

2.2.5 HIV life-cycle and pathogenesis

HIV, the causative organism of AIDS is a retrovirus belonging to the family Retroviradae and the genus Lentivirus (ICTV, 2002). Lentiviruses characteristically do have long incubation periods with accompanying long disease duration (Levy, 1993). They are transmitted as single-strand positive-sense enveloped viral RNA, which upon entry into the host cell is transcribed into a double-stranded DNA, enters into the nucleus and is integrated with the hosts cellular DNA. Figure 2 shows a schematic diagram of HIV showing the HIV envelope with the protein spikes and the capsid containing the HIV nucleic acid and enzymes (AIDSinfo, 2016). There are seven stages of the HIV life cycle namely: 1. binding, 2. fusion, 3. reverse transcription, 4. integration, 5. replication, 6. assembly, and 7. budding (AIDSinfo, 2016). Figure 3 shows the various stages of the HIV life cycle. Upon entry into the human body, the single-stranded RNA-HIV (founder virus) docks and infiltrates into the target cell. The main target cells are the CD4+ T lymphocytes and other cells with the beta-chemokine receptor (CCR5) or the alpha-chemokine receptor (CXCR4) (Coakley et al., 2005) and these include resting CD4+ T-cells, monocytes and macrophages and dendritic cells (Maartens et al., 2014). The binding of the virus to the target cells is an interaction between the virion envelope glycoprotein (gp 120) with the chemokine co-receptors. The infiltrated viral RNA is then reverse-transcribed into a double-stranded DNA by a virally encoded reverse transcriptase, which was also transported into the host cell during the infiltration process. Although the virally encoded reverse transcriptase has multi-functional activity including RNA-dependent DNA polymerase activity, DNA-dependent DNA polymerase activity and RNase-H activity, it has no proof-reading activity lead, hence is prone to transcription errors (Hu and Hughes, 2012). The viral double-stranded DNA then enters the host's cell nucleus and integrates into the host's cellular DNA by viral encoded integrase and other host's co-factors (Smith and Daniel, 2006). Once integrated into the host's DNA, the virion takes over the cells cellular machinery and dictates its replication activity. At this stage, two pathways are possible for the virus;

a. The virus becomes latent and this allows it to avoid detection together with its host cell from the host's immune system.

b. Alternatively, the virus may become active and is transcribed via messenger RNA (mRNA) encoding for viral proteins and the assembling of the Gag and Gag-Pol multi-protein complexes and translated into infectious viral RNA which bud off the cell membrane surface into the extracellular fluid or the blood stream to infect other cells (Pier, 2004; Reyskens et al., 2014). HIV spreads between CD4+ T-cells by a hybrid spreading mechanism by either cell-free spread or cell-to-cell spread (Zhang et al., 2015). This hybrid spreading mechanism of HIV is considered to a source of the virion's continual replication and resistance to ARVs (Sigal et al., 2011; Zhang et al., 2015).

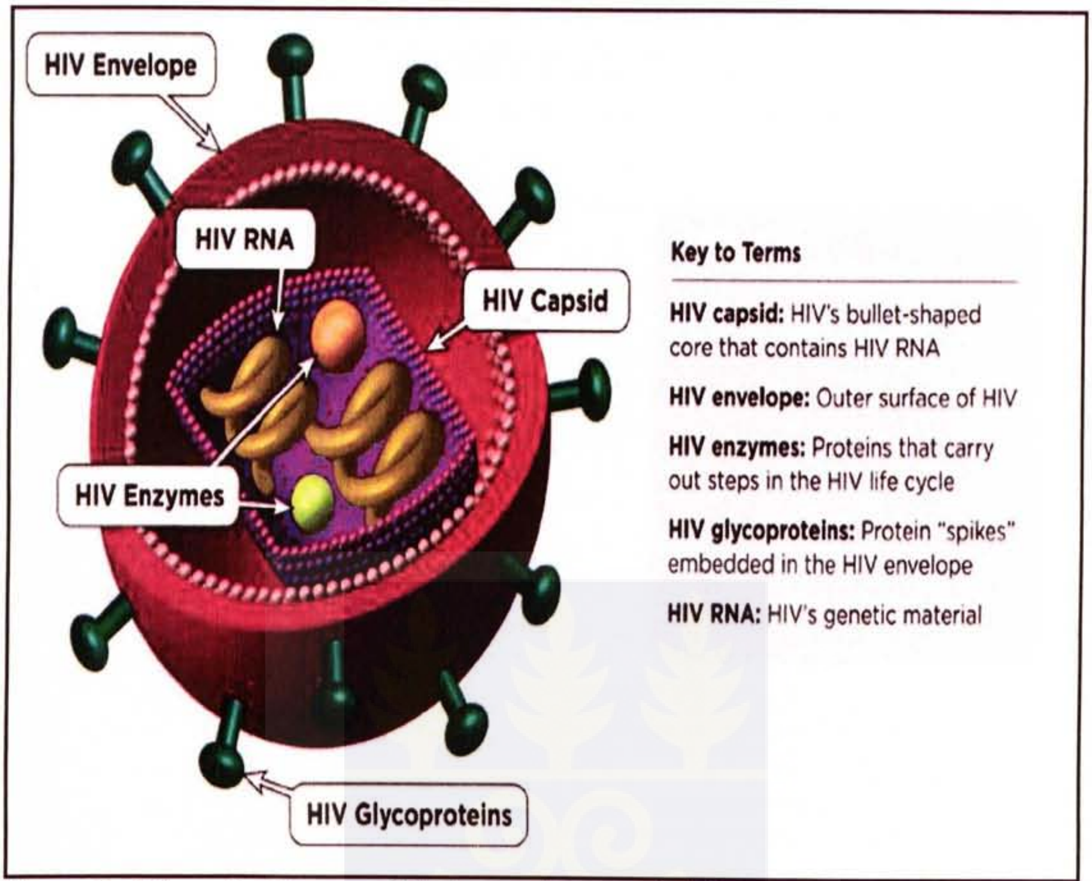

Figure 2. Schematic diagram of the human immunodeficiency virus (HIV). Source (AIDSinfo, 2016)

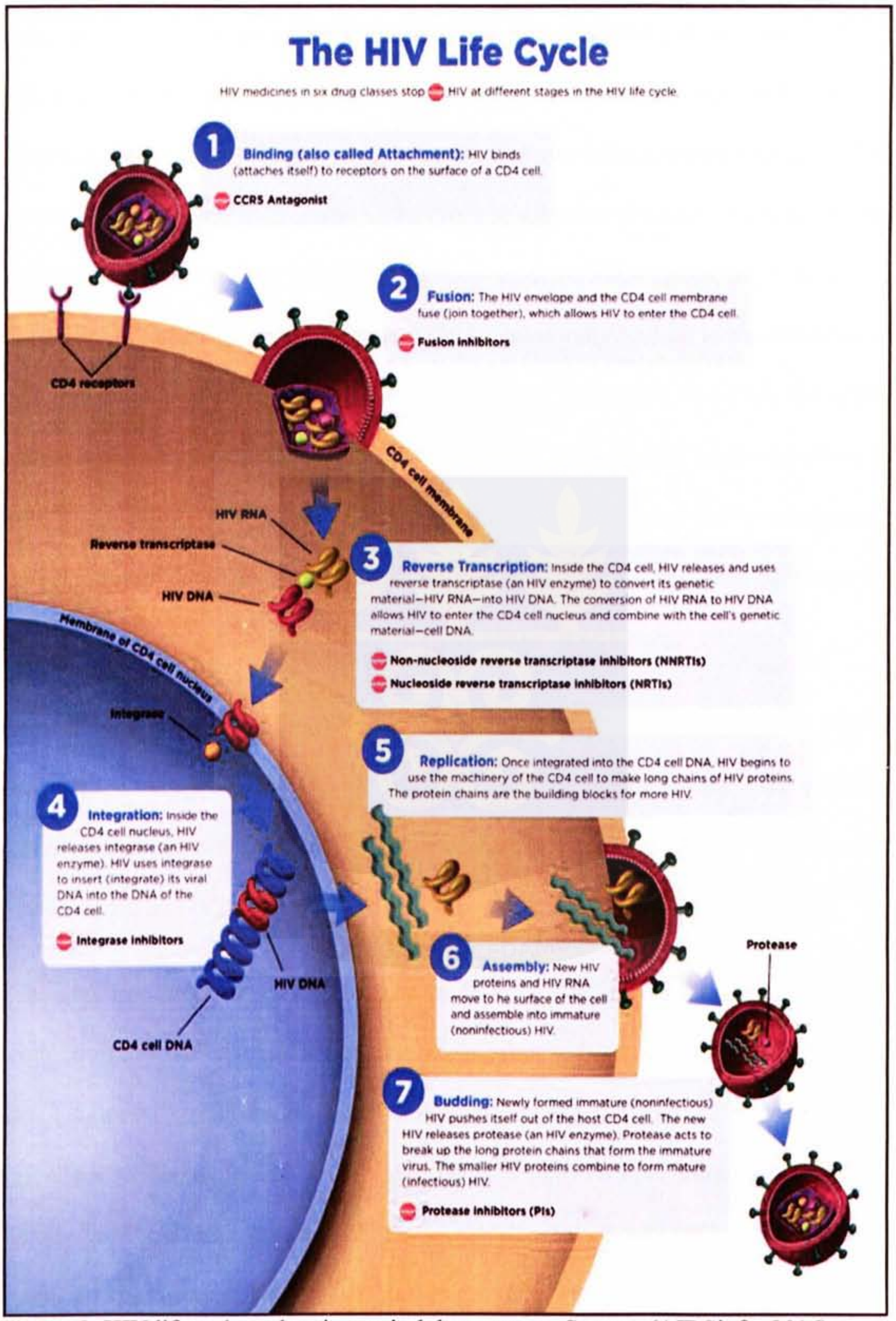

Figure 3. HIV lifecycle and antiretroviral drug targets. Source: (AIDSinfo, 2016).

Soon after infection, there is an intense viral replication and infection of lymphoid tissue to establish the grounds for the virus (Moir et al., 2011). During this early stage after infection, there is an intense production of inflammatory cytokine and chemokines (Maartens et al., 2014). Revealing is that, this intense inflammatory processes during the first stage is in sharp contrast to the more modest and delayed response as seen in the activity of other viral infections (Stacey et al., 2009). In response to the acute infection, HIV-specific CD8+ cells then kill infected cells leading to a decrease in viral load but invariably selecting for the emergence of mutations to escape the immune system response (Goonetilleke et al., 2009). Thus, in most individuals the acute state leads to a profound exhaustion of HIV-specific T-cells programmed by the expression of programmed death 1 (PD-1) leading to a loss of effector function (Trautmann et al., 2006).

About three months after the infection, neutralising antibodies appear which select for viral escape mutants. This innate immune response to control the viral population mediated through the killer cells however leads to the evolution of mutant cells to counter the effect of these natural killer cells (Alter et al., 2011).

The most important characteristic feature of HIV infection is the combined reduced production of CD4+ T-cells and their continual destruction together with their subtypes like T-helper-17 cells and mucosal associated invariant T-cells needed for bacterial defence (Prendergast et al., 2010; Cosgrove et al., 2013). This combined effect on the T-cells leads to a total depletion of their population (Prendergast et al., 2010; Cosgrove et al., 2013; Maartens et al., 2014).

2.2.6 Stages of HIV infection

After introduction of HIV into a host, three different stages of the infection is characterised; an acute stage, a chronic stage and an advanced stage. The acute stage of HIV disease is immediate after the infection of the virus and most infected individuals experience non-specific flu-like symptoms like fever, sore throat, headache, nausea, gastrointestinal disturbances and /or genital or mouth ulcers (Kahn and Walker, 1998; DHHS, 2010).

The second stage of the infection is termed the clinical latency stage, asymptomatic HIV or chronic HIV. Although most infected individuals experience fewer or no symptoms at the early part of this stage, symptoms like weight loss, myalgia, fever and persistent generalised lymphadenopathy may appear during the latter parts of this second stage (DHHS, 2010). In the absence of ART, the second stage can last between 3 and 20 years.

The last stage of HIV disease is AIDS which is define by specific parameters of CD4+ count of <200 cells/μL and other symptomatic features like pneumocystis pneumonia, cachexia and respiratory tract infections (DHHS, 2010). Cancers like Kaposi's sarcoma and cervical cancer may occur in addition to the symptoms experienced during the first stage of the infection.

2.2.7 HIV infection classification

Due to the chronic and progressive nature of HIV infection, HIV and HIV-related diseases are clinically classified for appropriate management. There are basically two different but related classification systems; the WHO HIV staging system which is more appropriate for resource-limited setting and the CDC classification which on the other hand is idle for developed countries.

The WHO HIV staging classifies the course of the infection into five different stages as follows:

- Primary HIV infection: An infected individual may be either symptomatic or will exhibit acute retroviral syndrome.
- Stage I: An infected individual may be asymptomatic but with a CD4+ T-cell count of <500 cells/μL
- Stage II: An infected individual may show minor mococutaneous manifestation and recurrent upper respiratory tract infection with a CD4+ T-cell count of <500 cells/μL
- Stage III: An infected individual may show advanced symptoms like chronic diarrhoea, tuberculosis of the lungs and a CD4+ T-cell count of <350 cells/μL
- Stage IV: An infected individual in WHO stage IV is said to have AIDS. Symptoms include toxoplasmosis of the brain, candidiasis of the oesophagus and other organs and a CD4+ T-cell count of <200 cells/μL of blood.

The CDC system classifies HIV infection into 5 stages as follows:

- Stage 0: This stage refers to the period immediate to < 180 days before an infected person tests positive to the HIV test.
- Stage 1: The infected individual shows no AIDS defining illness and a CD4+ T-cell count of ≥500 cells/μL.
- Stage 2: The infected individual shows AIDS defining illness and a CD4+ T-cell count of between 200 cells/μL and 500 cells/μL.
- Stage 3: The infected individual shows AIDS defining illness and a CD4+ T-cell count of ≤ 200 cells/μL.

- Unknown: This stage refers to a known infected individual but without sufficient clinical information to be classified to any of the above stages.

2.2.8 Therapeutic management of HIV infection

The development of ART in the mid 1990's has turned HIV infection into a chronic infectious disease which when well managed can lead to a sustained life. Currently more than 25 licensed drugs (approved by the U.S FDA) are available in managing HIV infection (Maartens et al., 2014). These drugs effect their antiretroviral activity at different stages of the HIV replication life-cycle (Figure 3). ARVs are generally classified into 5 classes depending on the stage of the HIV life cycle that they interfere with (Arts and Hazuda, 2012) as follows;

1. **Fusion inhibitors/Entry inhibitors**: This class of ARVs interfere with the fusion and entry of the HIV virus into the target host cell. The fusion inhibitors prevent the formation of the "hairpin" structure required for the fusion of the virion to the host cell's cell membrane by attaching to the HIV envelope glycoprotein gp41. The entry inhibitors are CCR5 co-receptor antagonists and they block proteins on the CD4+ T-cells that are needed for the virus to enter the target cell.
2. **Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)**: ARVs that belong to this class targets the virion's reverse transcriptase, the enzyme employed by the virus during the reverse transcription of viral RNA genome into genomic RNA. NRTIs/NtRTIs thus act as DNA-chain terminators during the virion's reverse transcription process.
3. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**: This class of ARVs also inhibit the virion's reverse transcriptase enzyme by binding

to a spot close to the enzyme's active site (allosteric site) and thereby causing a conformational change in the active site (non-competitive inhibition) (Tantillo et al., 1994; Spence et al., 1995).

4. **Integrase strand transfer inhibitors (INSTIs)**: Integrase inhibitors block the integration of the viral double-stranded DNA into the host's DNA by inhibiting the viral enzyme integrase (Arts and Hazuda, 2012).

5. **Protease inhibitors (PIs)**: Protease inhibitors interfere with the activity of HIV replication by inhibiting viral protease needed for the assembling of the inner core (Gag and Gag-Pol multiprotein complexes) of viral proteins before they bud off the cell surface to be matured virus (Hartman and Buckheit, 2012).

Table 1 shows the various ARVs approved by U.S Food and Drugs Administration and their therapeutic classes (AIDSinfo, 2016).

Table 1. Anti-retrovirals and their therapeutic classes

Therapeutic Class	Generic Name
Fusion Inhibitors	Enfuvirtide
Entry Inhibitors	Maraviroc
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)	Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir disoproxil fumarate Zidovudine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Delavirdine Efavirenz Etravirine Nevirapine Rilpivirine
Integrase Inhibitors	Dolutegravir Elvitegravir Raltegravir
Protease inhibitors (PIs)	Atazanavir Darunavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir

Source: (AIDSinfo, 2016)

In addition to these classes of ARVs, a pharmacokinetic enhancer, cobicistat which increases the effectiveness of ARVs have also been approved by the U.S FDA (AIDSinfo, 2016). Also available are combination HIV medicines, which contain two or more ARVs, from one or more drug classes (Table 2).

Table 2. Combination anti-retroviral medicines

Generic Name
Abacavir and lamivudine
Abacavir, lamivudine, and zidovudine
Atazanavir and cobicistat
Darunavir and cobicistat
Efavirenz, emtricitabine, and tenofovir disoproxil fumarate
Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate
Elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate
Emtricitabine, rilpivirine, and tenofovir alafenamide
Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
Emtricitabine and tenofovir alafenamide
Emtricitabine and tenofovir disoproxil fumarate
Lamivudine and zidovudine
Lopinavir and ritonavir
Abacavir, lamivudine, and zidovudine

Source: (AIDSinfo, 2016)

The management of HIV involves the continuous monitoring of immunological, virological and clinical indices in PLHIV. ART requires the use of ARVs to change the natural history of HIV infection by preventing clinical progression. The development of effective combination ART in the mid-1990s led to the rapid, widespread clinical use in developed countries. This resulted in reducing the death of PLHIV by two-thirds from 1995 to 1997 (Mouton et al., 1997; Palella et al., 1998). Since then ART regimens have become easier to take, less toxic, and more potent (Gallant et al., 2008; Mills et al., 2009; Molina et al., 2010). In addition, the average life expectancy after HIV diagnosis of a HIV-positive patient who is treated appropriately with ART increased from 10.5 years in 1996 to 22.5 years in 2005 (Harrison et al., 2010) and now is estimated to approach that of the general population (Bhaskaran et al., 2008). The use of ART in managing HIV infection leads to a suppression of viral replication, an improvement in CD4+ T-cells count and an improvement in the function of the general immune system.

In the developing countries the use of ART expanded markedly after year 2000 with demonstrated clinical benefits similar to those seen in developed countries. It is currently estimated that 5 million PLHIV in the developing countries are on ART (WHO, 2013c). Despite these marked improvements, challenges of access, adherence, toxicity, drug–drug interactions, and drug resistance remain, particularly in disadvantaged populations (Gulick, 2010). The current WHO recommendations indicates that as a priority, ART should be initiated in all HIV-positive individuals (adults and adolescents) with CD4 count between 350 cells/μL and 500 cells/μL regardless of WHO clinical stage (strong recommendation, moderate-quality evidence) (WHO, 2013c).

Current therapy involves the combination of drugs from three different classes; NRTI/NtRTI, NNRTI and boosted-PI. The WHO Guidelines currently recommend as a first line therapy for HIV infection, dual NRTI/NtRTI combinations of either tenofovir (TDF) and lamivudine (TC) (or emtricitabine-FTC), in combination with a single NNRTI, efavirenz (EFV) as a single pill, given once daily (strong recommendation, moderate-quality evidence) (WHO, 2013c). However, in situations where TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended (strong recommendation, moderate-quality evidence) (WHO, 2013c).

- Zidovudine (AZT) + Lamivudine (3TC) + Efavirenz (EFV)
- Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)
- Tenofovir (TDF) + Lamivudine (3TC) (or Emtricitabine-FTC) + Nevirapine (NVP)

2.2.9 HIV/AIDS epidemiology in Ghana

HIV was first identified in Ghana in March 1986 and since then the epidemic has spread slowly. In 1987, the National AIDS/STI Control Programme (NACP) was established under the Ministry of Health to implement and coordinate the country's HIV/AIDS programme through various strategies. These strategies include maintaining a safe blood supply, ensuring safe use of needles, and disseminating information through public campaigns to change social attitudes and behaviour to contain and limit the spread of the infection. In 2000, the Ghana AIDS Commission (GAC) was established for effective resource mobilization, management, and co-ordination of HIV/AIDS activities being conducted by various organisations. Since then the NACP and the GAC have concerted their efforts to reduce the spread of HIV in Ghana in addition to formulating policies on HIV-care in our various hospitals.

The HIV epidemic in Ghana is described as a generalised epidemic with a consistent prevalence of more than 1% in the general population (GHS and NACP, 2012; GSS et al., 2015). Prevalence estimates of HIV in Ghana has mainly been derived from HIV sentinel surveillance (HSS) that focuses on HIV testing of pregnant women who attend antenatal clinics. This data (generated yearly since 1992) is generated from results of conducting HIV test for pregnant women seeking antenatal care for the first time and patients newly diagnosed with sexually transmitted infections attending STI clinics in the sentinel sites. The data is collected using an anonymous, unlinked method, and the results reported yearly by the NACP. Using the annual HSS the HIV epidemic in Ghana appears to be in a downward trend between 2003 and 2013, from 3.6% in 2003 through to 2.2% in 2008 and to 2.0% in 2011 (NACP, 2008; NACP, 2009; NACP, 2010). Data from the 2012 and 2013 HIV sentinel survey indicate HIV prevalence of 1.37% and 1.30% respectively (NACP, 2014). This shows a downward trend in the prevalence of the disease between 2003 and 2013. However, data from the 2014, 2015 and 2016 sentinel reports suggest an upsurge of HIV prevalence. The prevalence of HIV in 2014 was 1.6% (up from 1.3% in 2013) and further surged to 1.8% in 2015 and in 2016 a third consecutive upsurge of the prevalence to 2.4% (NACP, 2015; NACP, 2016; NACP, 2017).

Although data from pregnant women in HSS has been shown to be a reasonable proxy for HIV prevalence estimation (WHO and UNAIDS, 2000) some limitations are present when using sentinel surveillance estimates derived exclusively from pregnant women attending select antenatal clinics for estimating the HIV rate in the general adult population. These limitations include the fact that the HSS does not capture information on HIV prevalence in men, sexually inactive women, women who protect themselves from HIV and pregnancy using condoms, non-pregnant women, nor in women who either do not attend a clinic for pregnancy care or receive antenatal care at facilities not represented in the surveillance system. Despite these limitations, HSS data is very useful for monitoring trends in HIV levels. In 2003, the Ghana Demographic and Health Survey (GDHS) introduced an instrument to measure the sero-prevalence of HIV in the country. The GDHS data which is a population-based data is intended to improve the calibration of annual HSS data, so that trends in HIV infection can be more accurately measured in the intervals between general population surveys (WHO and UNAIDS, 2000). Two of such population-based HIV sero-prevalence is currently available in the 2003 and 2014 GDHS. The 2003 GDHS indicated HIV prevalence (in 15-49 years old) of 2.2% with the 35-39 years' age group having the highest prevalence of 3.5%. In addition, the Eastern region recorded the highest HIV prevalence of 3.7% and Greater Accra recorded a prevalence of 2.2% (95% CI, 1.8-2.5) (GSS et al., 2004). Data from the 2014 GDHS showed a slightly lower but insignificant decrease in HIV prevalence (in 15-49 years old) to 2.0% (95% CI, 1.6-2.4) and the 40-49 years' age group having the highest prevalence of 3.8% (GSS et al., 2004). The Greater Accra prevalence increased to 3.8%, whilst the highest prevalence of 4.5% was recorded in Eastern Region (GSS et al., 2004).

Although the HSS data indicate a rather gently but continual upsurge in prevalence of HIV in Ghana between 2014 and 2016, the availability of population-based sero-prevalence data from the 2003 and 2014 GDHS obviously enhances the body of information available on the HIV/AIDS epidemic in Ghana.

2.2.10 Anti-retroviral therapy and HIV management in Ghana

Ghana, in order to sustain the progress been made in the area of care for PLHIV and to strive for the best impact of reducing morbidity among PLHIV whilst ensuring a reduction in the incidence of new infection has adopted the 2013 WHO guidelines resulting in the necessity of reviewing its guidelines for ART. The current 5th edition guidelines recommends two (2) NRTIs/NtRTI + one (1) NNRTI or two (2) NRTIs + one (1) boosted PI (NACP et al., 2014). In Ghana, the current drugs used are shown in Table 3 (NACP et al., 2014).

Table 3. Drug regimens used in managing HIV infection in Ghana

Therapeutic Class	Drug	Abbreviation
NRTI	Zidovudine	AZT/ZDV
	Lamivudine	3TC
	Emtricitabine	FTC
NtRTI	Tenofovir	TDF
NNRTI	Nevirapine	NVP
	Efavirenz	EFV
Boosted PI	Ritonavir boosted Atazanavir	ATV/r
	Ritonavir boosted Lopinavir	LPV/r

NRTI=Nucleoside reverse transcriptase inhibitor; NtRI=Nucleotide reverse transcriptase inhibitor; NNRTI=Non-nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor

The first line drugs are

- TDF + 3TC (or FTC) + EFV- Preferred Regimen or
- TDF + 3TC (or FTC) + NVP–Alternative regimen or
- AZT + 3TC + NVP- Alternative regimen or
- AZT + 3TC + EFV- Alternative regimen

The second line drugs are

- AZT + 3TC (or FTC) + LPV/r (or ATV/r)- 1st Alternative Regimen or
- TDF + 3TC (or FTC) + LPV/r (or ATV/r)- 2nd Alternative Regimen

These guidelines are based on several factors including efficacy, convenience, toxicity, drug resistance and especially for resource-limited settings, accessibility, availability and cost. In consideration of these guidelines, ART must still be individualised to the patient, which requires a careful assessment of each patient's conditions and ART readiness.

2.3 Cardiovascular diseases, hypertension, HIV/AIDS and ART

Non-communicable diseases (NCDs), which are among the known chronic diseases, are of long duration and generally slow progression. They share common risk factors mainly tobacco use, unhealthy diets (high in fat, salt, and refined sugars), physical inactivity and harmful use of alcohol. Worldwide, NCDs are the leading causes of death accounting for 63% of the 57 million deaths yearly, with 80% of these deaths occurring in developing countries and one-third occurring in people below 60 years (WHO, 2011a). The four major non-communicable diseases namely cardiovascular diseases (CVDs), cancers, chronic respiratory diseases and diabetes account for about 80% of the total NCD deaths (Nigatu et al., 2012). NCDs are among the co-morbidities that exit with HIV/AIDS (Hirschhorn et al., 2012) and co-morbidities are becoming more important in the comprehensive management of HIV in PLHIV (Meguid El Nahas and Bello, 2005). NCD co-morbidity in PLHIV has gained attention due to the fast emergence of NCDs as a major public health disease importance in high HIV prevalent areas especially in low-and-middle income countries where the incidence of NCDs is on the rise (IDF et al., 2009). Co-morbidity refers to the occurrence of a disease(s) or disorder together with an index disease in an individual. The measurement of co-morbidity as a confounder, an effect modifier, an exposure or an outcome in epidemiological studies has recently received more attention due to the issue of comprehensive healthcare of patients.

2.3.1 Cardiovascular diseases in PLHIV

Cardiovascular diseases (CVDs), one of the major NCDs, is a term used commonly to refer to a group of disorders of the heart and blood vessels which include coronary heart disease (such as angina and myocardial infarction), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (WHO, 2016). CVDs are the number one cause of death globally with projections indicating mortality due to CVDs will reach 23.9 million by the year 2030 (Mathers and Loncar, 2006). CVDs in LMIC is reported to represents more than 80% of the global burden of CVDs (Yusuf et al., 2004).

With the introduction of ART in the mid-1990s, there has been a great reduction in morbidity and mortality attributed to HIV/AIDS in PLHIV. This has led to an improvement in the quality of life of HIV-positive patients and an increase in life expectancy (WHO, 2009a). However, this is being challenged by the occurrence of CVDs and metabolic syndrome in PLHIV (Bain et al., 2016; Benjamin et al., 2016). Studies from HIC with large sample sizes have implicated HIV and ART as likely mediators of this observed increase in the risk of CVDs in PLHIV and reports have cited CVDs as a significant cause of morbidity and mortality in PLHIV (Mary-Krause et al., 2003; Friis-Moller et al., 2007; Duprez et al., 2009). An analysis of 13 cohort studies in HIC implicated CVDs as the most common non-AIDS related cause of death among HIV-positive patients (Colloboration, 2010). A multi-centred, comparative, cross-sectional survey of HIV-infected individuals in 12 countries on 5 continents reported in 2014 indicated a prevalence of self-reported CVD risk factors in PLHIV of 28% and in PLHIV in SSA to be 12% (Sherer et al., 2014). Although HIV itself is a chronic inflammatory condition, the causes of these co-morbid abnormalities are complex as the association between HIV and CVDs is not fully understood. Nonetheless, it is established that it involves phenomena related to the virus, ARVs administered and to the host (Chastain et al., 2015).

Whilst some studies indicate that certain ARVs such as PIs may elevate the risk of CVDs by raising the level of cholesterol and triglycerides in the blood (Malvestutto and Aberg, 2010), other studies contradict this (Bavinger et al., 2013). The institution of ART may place HIV-infected individuals at a greater risk of cardiovascular diseases due to the effect some ARVs on lipid metabolism and mitochondrial function (Grunfeld et al., 2008). A study in the USA where HIV-positive patients were compared with HIV-negative patients indicated an association between HIV and CVD risk after taking into account Framingham risk factors, co-infections and substance abuse (HR = 1.48; 95% [CI, 1.27-1.72]) (Freiberg et al., 2013).

A systematic review and meta-analysis conducted by Islam et al. (2012), involving 23 studies indicated that, the relative risk of CVD in PLHIV on ART compared with HIV-uninfected people was 2.00 (95% CI, 1.70-2.37, p<0.001), whilst the relative risk of

CVD in PLHIV but ART-naive compared with HIV-uninfected people was 1.61(95% CI, 1.43-1.81, p<0.001). The review also reported an association between ART and risk of CVD (RR=1.52, [95% CI, 1.35-1.70], p=0.001) and also reported an association between PI-based therapy and CVD (Islam et al., 2012).

Another systematic review of the risk of cardiovascular disease in PLHIV on ART conducted by Bavinger et al. (2013) indicated that there is an association between cumulative and recent exposure to ART and the risk of myocardial infarction (MI), a CVD. The ARVs implicated in the review were recent exposure to abacavir and PIs and cumulative exposure to indinavir and lopinavir (Bavinger et al., 2013). This was at the background that some earlier studies have associated cardiovascular disease with ART in general and specific ARVs, abacavir and didanosine (Friis-Moller et al., 2003; Friis-Moller et al., 2007; Sabin et al., 2008; Worm et al., 2010) whilst others have reported contrasting evidence of no association (Brothers et al., 2009; Lang et al., 2010; Ribaudo et al., 2011; Ding et al., 2012).

These evidences thus suggest an increased risk of CVD among PLHIV with ARVs being implicated in this increased risk of CVDs in PLHIV.

2.3.2 Cardiovascular diseases in PLHIV in sub-Saharan Africa

In the midst of an epidemiological transition from infectious diseases to non-communicable diseases, the prevalence of CVDs have increased in most countries in SSA. However, mortality due to CVD is reported to have decreased in SSA over the past few decades (Stringhini et al., 2012; Roth and Murray, 2013) despite earlier projections of an increase in CVD attributable deaths to 2.4 million by 2030 (WHO, 2004). This can be attributed to much attention in the diagnosis, treatment, and prevention of CVDs (Joshi et al., 2008; Mayosi et al., 2009; Chin, 2012; Chow et al.,

2013) including appropriate and cost effective intervention methods (Lim et al., 2007; Ortegon et al., 2012) in the general population in SSA.

Most countries in SSA have also deployed the use of ART. According to a WHO report in 2011, 49% of all eligible HIV-positive patients in SSA were receiving ART as at 2010. This has greatly affected the life of PLHIV in Africa. However, coincidentally and parallel to the ART era in SSA, is the epidemiological transition of NCDs including CVDs been experienced by most SSA countries. Although relatively few studies are available in the co-morbid condition of CVDs and HIV/AIDS in PLHIV in SSA, there has been reviews of studies in the occurrence of cardio-metabolic traits and CVDs in PLHIV in SSA (Mutimura et al., 2008; Levitt et al., 2011; Dillon et al., 2013; Syed and Sani, 2013; Bloomfield et al., 2014a; Nguyen et al., 2016; Hyle et al., 2017; Mayne and George, 2017). A systematic review and meta-analysis of 49 published and 3 unpublished studies involving 29,755 individuals in SSA suggested differences in cardio-metabolic traits between HIV-infected and uninfected individuals in SSA with HIV infection being associated with TGs, HDL, BMI, sBP and dBP (Dillon et al., 2013). The review also reported of ART use associated with LDL, HDL and haemoglobin A1c (HbA1c) (Dillon et al., 2013). Another review of published literature in LMIC indicated that CVDs like heart failure, hypertension, coronary heart disease and stroke is common and more frequent in PLHIV compared with the general population (Bloomfield et al., 2014a).

Stroke is a known CVD of which prevalence is increasing in most countries in SSA and is associated with high rates of mortality, morbidity, and post-stroke disability (Kolapo and Vento, 2011; Chin, 2012; Norrving and Kissela, 2013). Similar to studies conducted in HIC which have associated stroke with HIV infection (Ovbiagele and

Nath, 2011; Rasmussen et al., 2011; Chow et al., 2012), data emerging from SSA also suggest a high prevalence of stroke among PLHIV. Whilst some studies in South Africa have indicated no significant overall increased rate of stroke in association with HIV infection, other studies indicated otherwise (Hoffmann et al., 2000; Mochan et al., 2003; Patel et al., 2005). However, the prevalence of cryptogenic stroke has been reported to be more common among HIV-infected persons compared with age- and sex-matched HIV-seronegative controls suggesting the presence of a co-existent pro-thrombotic state in HIV infection (Hoffmann et al., 2000). Other studies also found HIV-positive stroke patients to be of younger age and had fewer traditional CVD risk factors compared with HIV-uninfected stroke patients (Hoffmann et al., 2000; Kumwenda et al., 2005; Tipping et al., 2007; Heikinheimo et al., 2012) indicating a role of HIV infection and non-traditional risk factors in the aetiology of stroke in PLHIV including the role played by immunosuppression and opportunistic infections.

Although data from SSA on the implication of HIV-infection on heart failure in PLHIV were mostly generated in the era when ART was not widely available in SSA, the prevalence of heart failure in PLHIV was reported to be between 9% and 57% (Hakim et al., 1996; Longo-Mbenza et al., 1997; Longo-Mbenza et al., 1998; Niakara et al., 2002; Ntsekhe and Hakim, 2005). Studies have also implicated cardiomyopathy as a relevant form of HIV associated CVD with prevalence between 5% and 29% in PLHIV in SSA (Tantchou Tchoumi et al., 2011; Chillo et al., 2012; Sliwa et al., 2012; Syed and Sani, 2013) and often associated with low CD4 counts, higher viral load, and advanced HIV stage in young persons with HIV infection (Nzuobontane et al., 2002; Twagirumukiza et al., 2007). Although specific ART drug classes have been associated with a higher prevalence of cardiomyopathy in the post-ART era (Tanuma et al., 2003), the relationship between peripartum cardiomyopathy and HIV remains unclear in

PLHIV in SSA (Longenecker et al., 2011; Sliwa et al., 2011). Studies in PLHIV in SSA have also reported of the presence of large thrombus burden rather than having substantial atherosclerotic plaques in HIV-positive individuals suggesting a unique pathophysiology that may be related to thrombophilia (Becker et al., 2010; Becker et al., 2011)

Whilst some studies in SSA have reported of no evidence of increased atherosclerosis in PLHIV in SSA (Lazar et al., 2009; Fourie et al., 2015) most other studies have reported of early subclinical atherosclerosis in PLHIV in SSA when compared with HIV-uninfected study participants (Fourie et al., 2011; Ngatchou et al., 2013; Ssinabulya et al., 2014; Siedner et al., 2016; Feinstein et al., 2017). A study in Uganda by Ssinabulya et al. (2014), reported of a prevalence of 18% of sub-clinical atherosclerosis in PLHIV (Ssinabulya et al., 2014). Two studies in Uganda reported of subclinical atherosclerosis and arterial stiffness in HIV-positive patients attending clinic with an even higher risk among patient with older age, elevated BMI, elevated LDL-cholesterol and ART-exposure (Ssinabulya et al., 2014; Siedner et al., 2016). A study conducted among South Africans indicated a prevalence of 12% of subclinical atherosclerosis in PLHIV but indicated no association with HIV-related factors (Schoffelen et al., 2015). Another study in conducted among South Africans also indicated that among a cohort of 255 patients undergoing vascular surgery, 32% were HIV-positive with 23% being ART-exposed. However, no association was found between HIV-infection and myocardial infarction (Redman et al., 2014).

With the fact that hypertension is counted as an important risk factor for myocardial infarction (a CVD) among Africans (Steyn et al., 2005), it is important to determine the factors associated with hypertension among PLHIV especially in resource-constrained countries. Despite the high volume of studies on CVDs in PLHIV in HIC, it would be inappropriate to extend conclusions from studies in HIC to SSA as there are differences in terms of socio-demographic, economic and related characteristics (Edward et al., 2013). A study conducted in South Africa on PLHIV on ART indicated that using the D:A:D risk equation, 31.1% of participants had a moderate to high 5-year D:A:D cardiovascular risk but a 6.7% of a moderate to high 10-year Framingham risk of CVD (Mashinya et al., 2015).

2.3.3 Hypertension as a cardiovascular risk factor in PLHIV

Hypertension, one of the five risk factors for metabolic syndrome, is a major factor used in assessing the risk of CVDs. Blood pressure levels are continuous and consistent with the risk of CVD events and it is independent of other risk factors such that the higher the blood pressure levels, the greater the chances of heart attack, stroke, heart failure and renal disorder (Chobanian et al., 2003). This risk has been estimated to be such that for every 20 mmHg increment in systolic blood pressure or 10 mmHg increment in diastolic blood pressure (115/75 to 185/115 mmHg), the risk of CVD doubles (Lewington et al., 2002) and this also doubles the risk of mortality from ischemic heart disease and stroke (Chobanian et al., 2003). Worldwide, hypertension is reported to be the leading risk factor for cardiovascular and cerebrovascular mortality and the leading global risk for mortality (responsible for 13% of deaths globally) (WHO, 2009b).

A wide range of hypertension prevalence has been reported globally in PLHIV from different studies. However, in most of these studies, the conventional risk factors associated with this prevalence were the same as the general population such as age, male sex, overweight, and hyper-triglyceridemia (Arruda Junior et al., 2010). Two studies conducted in Brazil showed a prevalence of hypertension in PLHIV of 19.9%

(Silva et al., 2009) and 25.6% (Arruda Junior et al., 2010). A multi-centre study in South America indicated a prevalence of 31.5% using criteria of hypertension of sBP ≥130mmHg and/or dBP ≥85mmHg (Cahn et al., 2010). Studies conducted in Norway, Spain, Italy and the United States indicated a prevalence of hypertension between 20% and 40% among populations exposed to ARVs (Bergersen et al., 2003; Gazzaruso et al., 2003; Palacios et al., 2006; Baekken et al., 2008; Coloma Conde et al., 2008; Mothe et al., 2009). This therefore calls for the need to examine the association between HIV/AIDS, ART and CVDs and its risk factors including hypertension in order to be informed on this double burden of disease on both mortality and morbidity in PLHIV.

2.3.4 Prevalence of hypertension in PLHIV in sub-Saharan Africa

Most countries in SSA are experiencing an ageing of the population, which in addition to the epidemiological transition has resulted in an increase in the prevalence of hypertension. This rise in the prevalence of hypertension is expected to increase the burden of diseases in PLHIV in SSA. A review of the literature published on studies conducted in SSA indicates several prevalence of hypertension in PLHIV and specifically in those on ART (ART-exposed) compared with those not on ART (ART-naive). Among the general HIV-positive population, varying prevalence has been reported in different countries. Two studies in Cameroon both reported prevalence of hypertension of 28.5% in PLHIV (Dimodi et al., 2014; Dimala et al., 2016) and a third study reported a prevalence of 25.5% (Nsagha et al., 2015). Studies in South Africa reported a prevalence of 19.5% in PLHIV (Malaza et al., 2012); Uganda, 27.9% (Mateen et al., 2013), 8.0% (Sander et al., 2015) and 11.0% (Kwarisiima et al., 2016) in PLHIV.

A cross sectional study conducted in Tanzania reported a prevalence of hypertension of 26.2% in PLHIV and was significantly higher among those on ART compared with patients yet to be on ART (Kagaruki et al., 2014). However, a multi-centred cross-sectional study in Tanzania involving 12 HIV Care and Treatment Centres and a study population of 34,111 PLHIV reported a prevalence of 12.5% of hypertension in ART-naive patients (Njelekela et al., 2016).

A study conducted in Kenya indicated an 11.2% prevalence of hypertension among Kenyan HIV-positive men and 7.4% prevalence among Kenyan HIV-positive women (Bloomfield et al., 2011). Overweight/obesity was also prevalent among men (10.6%) but higher among women (22.6%). In Ghana, Ngala and Fianko (2014) reported a systolic hypertension prevalence of 15.2% and a diastolic hypertension prevalence of 23.8% in ART-exposed HIV-positive patients whilst a systolic hypertension prevalence of 3.5% and diastolic hypertension prevalence of 6.4% was reported in ART-naive HIV-positive patients.

A study in Nigeria reported of a prevalence of hypertension of 16.3% in ART-exposed patients and 9.0% in ART-naive patients (Nduka et al., 2016b). A study in Senegal indicted that the prevalence of hypertension among PLHIV was 28.1% (Diouf et al., 2012). Table 4 below shows a summary of the various studies conducted in SSA reporting on the prevalence of hypertension in PLHIV. These studies point to the fact that although most of them were conducted as cross-sectional studies, there is a wide variation in the prevalence reported between countries and even within some countries. This calls for a systematic review and meta-analysis of the prevalence of hypertension (and CVDs) in PLHIV in SSA.

Table 4. Studies assessing prevalence of hypertension in PLHIV in sub-Saharan Africa.

Country	Authors	Year	Study-design	Sample size	% female	Prevalence of hypertension in study participants (%)		
						Overall	ART-exposed	ART-naive
Botswana	Schwartz et al.	2011	Cross-sectional	179	57.5	14.0	NR	NR
	Shapiro et al.	2012	Cross-sectional	62	100	NR	65.0	28.0
Cameroon	Ekali et al.	2013	Cross-sectional	143	72.0	NR	27.8	10.7
	Dimodi et al.	2014	Cross-sectional	463	74.7	28.5	31.3	20.3
	Nsagha et al.	2015	Cross-sectional	215	74.9	25.6	29.4	14.5
	Dimala et al.	2016	Cross-sectional	200	70.0	28.5	38.0	19.0
Ghana	Ngala and Fianko	2014	Cross-sectional	305	68.2	25.6	SH: 15.2; DH: 23.8	SH: 3.5; DH: 6.4
Kenya	Nyabera et al.	2011	Cross-sectional	4629	33.0	32.0	NR	NR
	Bloomfield et al.	2011	Cohort	12,194	64.8	Men: 11.2; Women: 7.4	NR	NR
	Bloomfield et al.	2014	Cohort	49, 475	74.0	Men: 10.2; Women: 7.0	NR	NR
Nigeria	Denue et al.	2012	Cohort	268	48.9	NR	NR	26.4
	Edwards et al.	2013	Cross-sectional	265	67.5	NR	12.1	7.8
	Muhammad et al.	2013	Cross-sectional	200	53.0	NR	17.0	2.0
	Ogunmola et al.	2014	Cross-sectional	250	62.4	NR	12.3	19.0
	Nduka et al.	2016	Cross-sectional	406	68.5	NR	16.3	9.0
Senegal	Diouf et al.	2012	Cross-sectional	242	57.9	NR	28.1	NR
South Africa	Julius et al.	2011	Cross-sectional	304	78.0	NR	19.1	NR
	Malaza	2012	Cross-sectional	2513	71.4	19.5	NR	NR
	Mashinya et al.	2014	Cross-sectional	89	70.8	NR	NR	42.7
	Mashinya et al.	2015	Cross-sectional	214	79.9	NR	26.2	NR
	Oni et al.	2015	Cross-sectional	5511	73.3	NR	19.7	NR

SH=Systolic hypertension; DH=Diastolic hypertension; PLHIV=Persons living with HIV; NR=Not reported

Table 4 (cont.). Studies assessing prevalence of hypertension in PLHIV in sub-Saharan Africa.

Country	Authors	Year	Study-design	Sample size	% female	Prevalence of hypertension in study participants (%)		
						Overall	ART-exposed	ART-naive
Tanzania	Perk et al.	2014	Cross-sectional	301	67.8	NR	28.7	5.3
	Kagaruki et al.	2014	Cross-sectional	671	70.5	26.2	30.0	21.9
	Njelekela et al.	2016	Cross-sectional	34,111	67.2	NR	NR	12.5
Uganda	Scholten et al.	2011	Cross-sectional	189	55.0	NR	Men: 31.6; Women: 25.3	Men: 28.9; Women: 12.2
	Mateen et al.	2013	Cross-sectional	5,563	66.9	27.9	NR	NR
	Sander et al.	2015	Cross-sectional	426	71.0	8.0	8.2	7.8
	Kwarisiima et al.	2016	Cross-sectional	3,545	65.0	11.0	NR	NR
Zimbabwe	Mutede et al.	2015	Cross-sectional	393	56.7	NR	34.9	NR

SH=Systolic hypertension; DH=Diastolic hypertension; PLHIV=Persons living with HIV; NR=Not reported

2.3.5 Review of factors associated with hypertension in PLHIV

Most studies determining the prevalence of hypertension in PLHIV have also reported of the factors associated with it. In most of these studies, the reported associated factors included the risk factors of hypertension as pertains in the general population; age, elevated body mass index, diabetes, smoking, excessive alcohol use and hyperlipidaemia. However, PLHIV present HIV-related factors like CD4+ T-cell count, viral load and components of the ART (ARVs) which must also be investigated in order to determine their association with the increasing prevalence of hypertension in PLHIV in the ART era.

2.3.5.1 Socio-demographic and life-style factors

Several socio-demographic and life-style factors have been investigated to determine their association with hypertension in PLHIV. These include age, sex, marital status, education, employment status, alcohol use, smoking of tobacco, regular physical activity, fruit and vegetable consumption and family history of cardiovascular event.

2.3.5.1.1 Age

Increasing age is one of the known risk factors associated with hypertension in the general population. The risk of hypertension increases with increasing age such that over 50% of persons between 60 and 69 years and three-quarters of those aged 70 years are hypertensive (Burt et al., 1995). This increased risk of hypertension as age increases is present in all age groups $\geq$ 40 years and is associated with the age-related rise in systolic blood pressure (Chobanian et al., 2003). Most studies have also associated increasing age with the risk of hypertension in PLHIV (Crane et al., 2006; Palacios et al., 2006; Baekken et al., 2008; Medina-Torne et al., 2012; Manner et al., 2013b; De Socio et al., 2014). Two large cohort studies, the Data Collection on Adverse Events of

Anti-HIV Drugs (D:A:D) (Friis-Moller et al., 2003) and the Multicentre AIDS Cohort Study (MACS) (Seaberg et al., 2005) also indicated a positive association between age and hypertension. A study reported by Arruda Junior et al. (2010), indicated that the odds of hypertension in PLHIV above the age of 40 years was 3.06 (adjusted OR=3.06 [95% CI, 1.91-4.97], $p<0.001$) compared with those ≤40 years. Although most study results are in this direction, Hajazi et al. (2013), reported of a lack of association between PLHIV aged ≥40 years and hypertension in Malaysia (adjusted OR=0.83 [95% CI, 0.35-1.98], p=0.674) but an increased odds of hypertension for every additional age in years (adjusted OR=1.07, [95%, CI, 1.02-1.12], p=0.010).

Studies conducted in SSA have also reported of an association between age and hypertension. A large retrospective cohort study in Kenya reported of an association between increasing age and the risk of hypertension in both men (OR=2.21 [95% CI, 1.95-2.50]) and women (OR=1.61 [95% CI, 1.40-1.87]) (Bloomfield et al., 2011). Other studies have also reported an association between increasing age and hypertension in PLHIV in SSA (Diouf et al., 2012; Okello et al., 2015; Sander et al., 2015; Kwarisiima et al., 2016; Njelekela et al., 2016). Other studies have reported of an association between PLHIV aged >40 years and hypertension (adjusted OR=2.29 [95% CI, 1.49-.02], p=0.002) (Dimala et al., 2016). Such an association have also been reported in patients >50 years compared with ≤50 years (Mashinya et al., 2015), patients >45 years compared with ≤45 years (Mutede et al., 2015) and in patients aged >40 years (both ART-experienced and ART-naive) (Kagaruki et al., 2014).

2.3.5.1.2 Sex

Many studies have reported men being at a greater risk of CVDs and show higher blood pressure levels when compared with their age-matched pre-menopausal women in the general population (Kusuma et al., 2002; Jervase et al., 2008). Although most studies have determined the association between sex and hypertension in PLHIV, the results have been conflicting. The MACs study reported of a strong association with males having higher odds of hypertension compared with females (Friis-Moller et al., 2003; Thiebaut et al., 2005). A similar association was reported with males having higher odds of hypertension (adjusted OR=2.55 [95% CI, 1.23-5.29], p=0.012) (Manner et al., 2013b). Other studies have also reported similar increased odds of hypertension in men compared with women; (adjusted OR=1.85 [95% CI, 1.15-3.01], p=0.019) (Arruda Junior et al., 2010), (adjusted OR=3.03 [95% CI, 1.18-.79], p=0.022) (Hejazi et al., 2013) and (adjusted OR=1.63 [95% CI, 1.18-2.26]) (De Socio et al., 2014). However, other studies have reported no association between sex and hypertension in PLHIV (Jerico et al., 2005; Palacios et al., 2006; Medina-Torne et al., 2012; Ikeda et al., 2013).

Studies reported from SSA have also indicated conflicting results. Whilst some studies indicate a significantly higher prevalence of hypertension in men compared with women among PLHIV (Denue et al., 2012; Mashinya et al., 2015; Njelekela et al., 2016), other studies indicate of no such difference or no association between sex and hypertension in PLHIV (Edward et al., 2013). Dimala et al. (2016) and Mateen et al. (2013) both indicated that men are at higher odds of hypertension compared with women. Whilst a study by Mutede et al. (2015), reported of females of being at higher odds of hypertension (adjusted OR=2.38 [95% CI, 1.31-4.34]), other studies have reported of no association between sex and hypertension among PLHIV (Diouf et al., 2012; Ogunmola et al., 2014; Kwarisiima et al., 2016).

2.3.5.1.3 Marital status

Studies, which have determined the association between marital status and hypertension, have reported of married individuals having elevated blood pressure than the never married in the general population (Lipowicz et al., 2002; Ekezie et al., 2009). However, a review of the literature indicates no such determined relationship in PLHIV.

2.3.5.1.4 Education and employment status

Few studies have determined the association between education and hypertension in PLHIV. Whilst a study by Krauskopf et al. (2013), associated college education with lower odds of hypertension in PLHIV (adjusted OR=0.74 [95% CI, 0.57-0.98]), other studies have reported of no association between highest educational level attained and hypertension in PLHIV (Ikeda et al., 2013; Ogunmola et al., 2014; Kwarisiima et al., 2016).

In terms of employment, two studies both reported of lack of association between employment status and hypertension (Krauskopf et al., 2013; Hejazi et al., 2013), but a study reported by Mutede et al. (2015), indicated a lower odds of hypertension in PLHIV working in an informal sector (adjusted OR=0.49 [95% CI, 0.25-0.96]).

2.3.5.1.5 Alcohol use

Excessive alcohol use is associated with high blood pressure regardless of other risks factors (Beilin et al., 1996; Gravlee et al., 2005; Nunez-Cordoba et al., 2009; Fu et al., 2010) and alcoholic beverage reduction has been associated with lowering of both systolic and diastolic blood pressure, with a dose-response relationship (Xin et al., 2001) in the general population. On the other hand, results from the 20-year follow-up from the "Coronary Artery Risk Development in Young Adults Study" indicate no association between baseline alcohol consumption and incident hypertension

(Halanych et al., 2010). A systematic review and meta-analysis indicated an increased risk of hypertension in men with heavy alcohol consumption and a trend toward increased risk of hypertension with low and moderate alcohol consumption in the general population (Briasoulis et al., 2012).

Most studies involving PLHIV indicate either no significant difference in prevalence rate of alcohol consumption between hypertensives and non-hypertensives (Dimala et al., 2016) or no association between alcohol consumption and hypertension in PLHIV (Arruda Junior et al., 2010; Kagaruki et al., 2014; Mashinya et al., 2015; Mutede et al., 2015; Kwarisiima et al., 2016). A study by Ikeda et al. (2013), however reported of an increased odds of hypertension in PLHIV who consume alcohol compared with non-consumers of alcohol.

2.3.5.1.6 Smoking of tobacco

Tobacco smoking is a known major risk factor for the development of CVDs in the general population (Linneberg et al., 2015). However, whilst some observational studies have reported lower systolic and diastolic blood pressure levels and a lower risk of hypertension in current smokers compared with non-smokers (Brummett et al., 2011; Cheng et al., 2012; Linneberg et al., 2015), others have reported a decrease in blood pressure levels following smoking cessation (Ward et al., 1993; Hatsukami et al., 2005).

Studies on the effect of smoking on the risk of hypertension in PLHIV have reported conflicting results. A study by Denue et al. (2012) in PLHIV, reported of significant difference between hypertensives who smoke (11.1%) and non-hypertensives who smoke (2.5%). The MACs study also reported of smoking being associated with systolic hypertension but not diastolic hypertension (Seaberg et al., 2005). Results from a study by Mutede et al. (2015), indicate of an increased odds of hypertension in PLHIV who smoke compared with non-smokers (adjusted OR=5.06 [95% CI, 2.20-11.66]). A review of most studies however indicated of no association between smoking and hypertension in PLHIV (Bergersen et al., 2003; Jerico et al., 2005; Crane et al., 2006; Palacios et al., 2006; Arruda Junior et al., 2010; Ikeda et al., 2013; Manner et al., 2013b; Kagaruki et al., 2014; Antonello et al., 2015; Dimala et al., 2016).

2.3.5.1.7 Regular physical activity

Several epidemiological studies have demonstrated the association of regular physical activity with the reduction in risk of hypertension in the general population (Diaz and Shimbo, 2013). Diaz and Shimbo (2013), in a review proposed several mechanisms by which regular physical activity may reduce the incidence of hypertension. These include decrease in oxidative stress, decrease in the RAS, decrease in inflammation and decrease in body weight/body mass accompanied by increase in endothelial function, increase in renal function and increase in sodium handling and angiogenesis (Diaz and Shimbo, 2013). Regular physical activity is therefore one of the recommended cardinal points in the prevention and management of hypertension (Chobanian et al., 2003).

Studies on the association between regular physical activity and hypertension in PLHIV have reported of mixed results. Dimala et al. reported of lack of significant difference between hypertensive and non-hypertensives in terms of proportions of PLHIV who lack regular physical activity in both ART-naive and ART-experienced individuals (Dimala et al., 2016). Other studies have similarly reported of lack of association between regular physical activity and hypertension in PLHIV (Ikeda et al., 2013; Kagaruki et al., 2014; Mashinya et al., 2015). However, Mutede et al. (2015), reported of an increased odds of hypertension in PLHIV who are physically inactive compared with those physically active (pOR=3.16 [95% CI, 1.69-5.85]).

2.3.5.1.8 Fruit and vegetable consumption

One of the recommendations of the WHO to prevent the onset of hypertension is regular fruit and vegetable consumption. However, most of studies that determined the factors associated with hypertension in PLHIV did not report of fruit/vegetable consumption. Arruda Junior et al. (2010), however reported a decreased odds of regular vegetable consumption associated with hypertension (OR= 0.69 [95% CI, 0.49-0.98], p=0.039), but no association between regular fruit intake and hypertension.

2.3.5.1.9 Family history of cardiovascular disease

The risk of CVD has been known to run in families and longitudinal studies have shown that individuals with a parental history of hypertension are at an increased risk of developing hypertension in the general population. These individuals are classified as high-risk for target intervention in the prevention of hypertension (Whelton et al., 2002; Wang et al., 2008).

Studies on the association between family history of CVD and hypertension in PLHIV indicate that individuals with family history of CVD are at an increased odds of hypertension compared with individuals with no such family history (OR=1.68 [95% CI, 1.15-2.47], p=0.008) (Arruda Junior et al., 2010); (adjusted OR=1.58 (95% CI, 1.18-2.12) (De Socio et al., 2014). However, studies by Thiebaut et al. (2005) and Dimala et al. (2016) indicate no such association between family history of CVD and hypertension in PLHIV.

2.3.5.2 Anthropometric and biochemical/metabolic factors

Studies have determined the association between hypertension and anthropometric indices like body mass index, waist circumference and waist-to-hip ratio in PLHIV. Some biochemical/metabolic factors like fasting plasma glucose, lipid profile and creatinine clearance rate have also been investigated to determine their association with hypertension in PLHIV.

2.3.5.2.1 Body mass index (general obesity)

Body mass index (BMI) is obtained by dividing body weight (in kilogram) by height (in metres) squared i.e. BMI= body weight (in kg)/ (height in m)^2. BMI is used as an index/marker of general obesity in terms of being under weight (BMI < 18.5 kg/m^2), normal weight (BMI between 18.5 kg/m^2 and 24.9 kg/m^2), overweight (BMI between 25.0 kg/m2 and 29.9 kg/m^2) and general obese (BMI ≥ 30.0 kg/m^2) (WHO, 1995). Observational studies have established general obesity as a known risk factor for hypertension in the general population (Brown et al., 2000; Sakurai et al., 2006) and clinical trials have shown lowering in blood pressure after reduction in weight (Stevens et al., 2001).

Similarly, most studies conducted in PLHIV have indicated an association between BMI and hypertension. Studies from both MACS (Seaberg et al., 2005) and D:A:D (Friis-Moller et al., 2003; Thiebaut et al., 2005) have strongly associated BMI ≥25.00 kg/m^2 with increased odds of hypertension. Arruda Junior et al. (2010), and De Socio et al. (2014), also reported increased odds of hypertension for BMI ≥25.00 kg/m^2 (adjusted OR=5.51 [95% CI, 3.36-9.17], p<0.001; adjusted OR=2.52 [95% CI, 1.91-3.33] respectively). Other studies also indicated an increased odds of hypertension per each unit increase in BMI (adjusted OR=1.1, [95% CI, 1.1-1.2], p<0.001) (Medina-Torne et al., 2012). Similar trend of association has been reported by other studies (Jerico et al., 2005; Crane et al., 2006).

Studies conducted in SSA have also reported an association between BMI and hypertension in PLHIV. Bloomfield et al. (2011), reported of PLHIV with BMI ≥ 25.00

kg/m^2 having an increased odds of hypertension in both men (OR=2.42 [95% CI, 1.88-3.09]) and women (OR=1.80 [95% CI, 1.50-2.16]). Several other studies have also reported increased odds of hypertension in overweight/obese HIV-positive patients compared with underweight/normal HIV-positive patients (Mutede et al., 2015; Dimala et al., 2016; Kwarisiima et al., 2016; Njelekela et al., 2016). Other studies have also reported the association of overweight/obesity with hypertension in PI-experienced patients (Bloomfield et al., 2011) and in both ART-naive and ART-exposed patients (Kagaruki et al., 2014).

2.3.5.2.2 Waist-to-Hip ratio and waist circumference (abdominal obesity)

Waist-to-hip ratio (WHR) is used as an anthropometric marker of abdominal obesity. Abdominal obesity, also known as central obesity refers to the accumulation of excess abdominal fat around the stomach and abdomen, which is likely to have a detrimental effect on health status. Abdominal obesity is associated with increased risk of hypertension, dyslipidaemia, heart disease, insulin resistance, type 2 diabetes and an overall increase in risk of developing CVDs and death in the general population (Anjana et al., 2004; Cameron and Zimmet, 2008; Westphal, 2008). WHR is calculated as the ratio of the waist circumference to the hip circumference with ratios > 0.9 (men) and > 0.85 (women) considered as evidence of abdominal obesity (WHO, 2000; NCEP, 2002; Yusuf et al., 2004).

Studies on WHR as a risk factor of hypertension in PLHIV have been few but with conflicting results. Whilst Bergersen et al. (2003), and De socio et al. (2014) reported of increased odds of hypertension in abdominal obese PLHIV (OR=2.22 [95% CI, 1.18-4.17], p=0.001 and adjusted OR=1.42 [5% CI, 1.03-1.97] respectively), other studies reported of lack of association between WHR and hypertension in PLHIV (Hejazi et al., 2013 ; Mashinya et al., 2015; Dimala et al., 2016).

Waist circumference (WC) is also used in a measure of abdominal obesity. Absolute waist circumference of >102 cm (in men) and >88 cm (in women) is classified as abdominal obesity (WHO, 2000; Yusuf et al., 2004). Arruda Junior et al. (2010), reported of abdominal obesity associated with increased odds of hypertension in PLHIV (OR=3.96 [95% CI, 2.57-6.18], p< 0.0001). Using a cut-off point of male ≥94 cm and female >80 cm as measure of abdominal obesity, Kagaruki et al. (2014), also reported of abdominal obesity association with increased odds of hypertension in both ART-naive (OR=1.64 [95% CI, 1.03-2.62], p=0.023) and ART-exposed patients (OR=2.37 [95% CI, 1.13-5.00], p=0.023). However, a study by Hejazi et al. (2013), reported of no association between abdominal obesity and hypertension in PLHIV.

2.3.5.2.3 Diabetes

Diabetes and hypertension are both indices used in the classification of the metabolic syndrome. Metabolic syndrome is a cluster of interrelated cardio-metabolic abnormalities comprising hyperglycaemia, elevated blood pressure, dyslipidaemia (elevated triglycerides and reduced high-density lipoprotein cholesterol) and abdominal obesity with abdominal obesity being a key component of the syndrome (Nguyen et al., 2016). Metabolic syndrome is used as a predictor of CVDs, type 2 diabetes and hypertension (Cheung et al., 2007; Cheung et al., 2008b) and its presence is increasing been seen in PLHIV on ART.

Diabetes is directly linked to atherosclerosis, which can lead to hypertension and other CVDs. Studies have shown that in the general population, the incidence of diabetes in hypertensive patients is disproportionately higher and vice-versa (Gress et al., 2000;

Cheung et al., 2008a; Ferrannini and Cushman, 2012). The rate at which these two conditions occur together has led to several suggestions that they both share common aetiology being obesity, physical inactivity and the metabolic syndrome (Cheung, 2010; Cheung and Li, 2012).

In PLHIV, reports of the association between diabetes and hypertension have been mixed. This could be attributed to different studies reporting of different fasting plasma glucose (FPG) level used as criterion in the assessment of diabetes. Bergersen et al. (2003), used a classification of diabetes to be FPG of >5.1 mmol/L and/or the taking of anti-diabetic medication and reported of no association between diabetes and hypertension in PLHIV. Hejasi et al. (2013) used a classification of diabetes as FPG ≥6.1 mmol/L and/or the taking of anti-diabetic medication and reported of no association between diabetes and hypertension in HIV-positive patients. Other studies have also reported of lack of association between diabetes and hypertension in PLHIV (Baekken et al., 2008; Antonello et al., 2015).

On the other hand, several other reports have associated diabetes with hypertension in PLHIV. Arruda Junior et al. (2010), used a criterion of diabetes as FPG > 100mg/dL reported of diabetes been associated with increased odds of hypertension (OR=3.62 [95% CI, 1.93-7.00], p< 0.001). De Socio et al. (2014) used a criterion of FPG >126 mg/dL also reported of increased odds of hypertension in HIV-positive individuals who are diabetic (adjusted OR=2.66 [95% CI, 1.65-4.27]). Medina-Torne et al. (2012), and Krauskopf et al. (2013), both reported of increased odds of hypertension in HIV-positive individuals who are diabetic (adjusted OR=1.82 [95% CI, 1.28-2.57]; adjusted OR=1.82 [95% CI, 1.28-2.57] respectively).

2.3.5.2.4 Dyslipidaemia

Dyslipidaemia is an important risk factor for CVD (Halperin et al., 2006; Di Angelantonio et al., 2009) and it refers to a disorder of the lipoprotein metabolism, classified as either over-production of lipoprotein (hyperlipidaemia) or under-production of lipoproteins (hyperlipidaemia). Most dyslipidaemia is characterised by hyperlipidaemia marked by elevated serum concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides with a corresponding decrease in high-density lipoprotein cholesterol (HDL-C). Reduced concentration level of HDL-C is also regarded as an independent significant risk factor for CVD (Jerico et al., 2006).

Several studies have associated dyslipidaemia with hypertension in the general population. Elevated serum concentration of HDL-C shows an independent and inverse association with the incident of hypertension (Laaksonen et al., 2008). Elevated serum concentrations of total cholesterol, LDL-C and triglycerides have also been shown to increase the risk of hypertension in the general population (de Simone et al., 2006; Halperin et al., 2006; Laaksonen et al., 2008). Although the pathophysiology of dyslipidaemia in hypertension is not fully understood, key mechanisms postulated include atherosclerosis (Oparil et al., 2003), renal microvascular injuries (Schaeffner et al., 2003) and alterations in nitric oxide and endothelial functions (Nofer et al., 2002).

Review of several studies determining the association between components of the lipid profile and hypertension in PLHIV show contrasting results. Antonello et al. (2015) reported of no association between dyslipidaemia and hypertension in PLHIV. Whilst some studies have associated elevated levels of total cholesterol with hypertension (Bergersen et al., 2003; Thiebaut et al., 2005; Baekken et al., 2008; Diouf et al., 2012;

Kagaruki et al., 2014), others have reported of no such association (Palacios et al., 2006; Arruda Junior et al., 2010; Medina-Torne et al., 2012; Manner et al., 2013b), Similarly, whilst some studies associate elevated triglycerides with increased odds of hypertension (Bergersen et al., 2003; Palacios et al., 2006; Arruda Junior et al., 2010), others have reported no association between elevated triglycerides and hypertension (Thiebaut et al., 2005; Diouf et al., 2012; Medina-Torne et al., 2012; Hejazi et al., 2013) in PLHIV. Kagaruki et al. (2014), however reported that elevated triglycerides level is associated with hypertension in ART-naive PLHIV (OR=1.96 [95% CI, 1.22-3.16]), but not in ART-experienced PLHIV (OR=0.94 [95% CI, 0.49-1.83]). Kagaruki et al. (2014), also reported of no association in both ART-naive and ART-experienced PLHIV between levels of HDL-C and hypertension and this is similar to other reports (Bergersen et al., 2003; Palacios et al., 2006; Arruda Junior et al., 2010). Other studies have also reported of reported of no association between elevated levels of LDL-C and hypertension (Palacios et al., 2006; Arruda Junior et al., 2010). Despite the fact that different studies used different cut off-points in the classification of elevated lipid levels, it seems that there is no conformity in the association between serum lipid levels and hypertension in PLHIV.

2.3.5.2.5 Renal impairment

Hypertension and chronic kidney disease (CKD) are so related that hypertension is seen as both a cause and consequence of CKD (Singh, 2013). Renal dysfunction is associated with CVDs (Sarnak et al., 2003) and CKD is an important independent risk factor for cardiovascular diseases (Lasserson et al., 2016). The prevalence of hypertension in CKD patients is 80-85% (Whaley-Connell et al., 2008) and this prevalence increases as the CKD progresses (USRDS, 2010). The mechanisms through which renal dysfunction mediates in the pathogenesis of hypertension include sodium and volume homeostasis, RAS, oxidative stress and nitric oxide antagonism, endothelial dysfunction and sympathetic nervous system and renal dopaminergic system (Tedla et al., 2011; Monhart, 2013; Singh, 2013).

Although there is strong relationship between renal impairment and hypertension, only few studies have determined this association in PLHIV. In studies reviewed, estimated glomerular filtration rate (eGFR) or change in creatinine clearance was not associated with hypertension in PLHIV (Baekken et al., 2008; Denue et al., 2012; Manner et al., 2013b). Peck et al. (2014), in an observational study involving both HIV-positive and HIV-negative participants indicated a prevalence of renal impairment (defined as eGFR <60 mL/min) to be 10.7% in ART-exposed, 12.6% in ART-naive and 13.1% in HIV-negative individuals. The study also reported of an association between renal impairment and higher grades of hypertension in ART-exposed individuals but not in ART-naive individuals (Peck et al., 2014).

2.3.5.3 HIV/ART-related factors

With the onset of the ART era, studies that have determine factors associated with hypertension in PLHIV have included HIV/ART-related like HIV-positive status, viral load, CD4+ T cell count and the type of ARVs administered.

2.3.5.3.1 HIV, viral load and duration of infection

Although some studies have implicated HIV status been associated with hypertension, there is still the need to know the direction of this association. The mechanisms postulated to mediate the higher prevalence of hypertension in PLHIV include atherosclerosis, coagulation disorder, chronic inflammation and lipid disturbance (Baker and Lundgren, 2011; Boccara et al., 2013). A few studies have associated HIV-positive status with higher odds of hypertension compared with HIV-negative status

(Gazzaruso et al., 2003; van Zoest et al., 2016), whilst others have reported no such association (Bergersen et al., 2003; Jerico et al., 2005; Baekken et al., 2008).

In SSA, a review of such studies has also shown mixed results. Whilst some studies report of no association between HIV itself and hypertension (Schwartz et al., 2012; Mashinya et al., 2014; Ogunmola et al., 2014), others report of an association (Peck et al., 2014). Malaza et al. (2012), reported of no association between HIV infection and hypertension in men but lower odds of hypertension in women living with HIV compared with their counterparts with HIV-negative status. Interestingly most of the studies conducted in SSA reported of lower odds of hypertension in HIV infected adults compared with their uninfected control adults (Scholten et al., 2011; Schutte et al., 2012; Kayima et al., 2015). A large population study involving 65,000 adults also reported of lower odds of hypertension in HIV-positive adults compared with HIV-negative adults (OR=0.82 [95% CI, 0.70-0.90], p=0.002) (Kwarisiima et al., 2016). A systematic review with meta-analysis of publication of CVDs in SSA reported of lower odds of hypertension in HIV infected adults compared with HIV-negative adults (Dillon et al., 2013). These results clearly indicate that whilst the risk of hypertension is lower in HIV-infected individuals in SSA compared with HIV-negative individuals it is contrary to what has been reported in developed countries.

In terms of the HIV-infection duration on the risk of hypertension, Medina-Torne et al. (2012), and Manner et al. (2010) both reported of an increased odds of hypertension in patients as the duration of the HIV-infection increases. Other researchers have also reported of increasing risk of hypertension in PLHIV as the duration of the HIV-infection increases (Krauskopf et al., 2013; Manner et al., 2013b; De Socio et al., 2014). On the other hand, several other studies have reported of no association between HIV-positive duration and the risk of hypertension in PLHIV (Bergersen et al., 2003; Jerico et al., 2005; Palacios et al., 2006; Baekken et al., 2008; Arruda Junior et al., 2010; Denue et al., 2012; Ikeda et al., 2013; Hejazi et al., 2013 ; Dimala et al., 2016).

Viral load is used as marker of immune suppression in PLHIV. Few studies which have determined the relationship between viral load and hypertension have reported of no association between viral load and hypertension in PLHIV (Bergersen et al., 2003; Thiebaut et al., 2005; Crane et al., 2006; Arruda Junior et al., 2010; Medina-Torne et al., 2012; Krauskopf et al., 2013; Antonello et al., 2015; Kwarisiima et al., 2016).

2.3.5.3.2 CD4+ T-cell count

Several studies have been conducted to determine the association between CD4+ T-cell count and the incidence of hypertension and CVDs. Chronic inflammation in PLHIV has been shown to destabilize atherosclerotic plaques, which leads to CVDs (Kaplan et al., 2008; Hsue et al., 2012). Low CD4+ T-cell count has also been associated with higher risk of CVDs (Kaplan et al., 2008; Lichtenstein et al., 2010; Triant et al., 2010; Manner et al., 2013b).

Studies have shown that microbial translocation from the gut into the systemic circulation during HIV infection leads to an array of immune activation resulting in decline in CD4+ T-cells and inflammation. Microbial translocation has been shown to be associated with hypertension in PLHIV (Manner et al., 2013a). Lipopolysaccharides have also been associated with endothelial dysfunction and atherosclerosis, both of which are involved in the pathogenesis of hypertension (Dauphinee and Karsan, 2006; Solages et al., 2006; Oliviero et al., 2009). Studies have also associated low CD4+ T-cell count with arterial stiffness (Ho et al., 2010) and atherosclerosis (Hsue et al., 2004), both which involved in the pathogenesis of hypertension. Despite these mechanisms postulated to be involved in the association of low CD4+ T-cell count with hypertension, several observational studies indicate of no association between low CD4+ T-cell count and hypertension (Bergersen et al., 2003; Jerico et al., 2005; Thiebaut et al., 2005; Palacios et al., 2006; Arruda Junior et al., 2010; Medina-Torne et al., 2012; Ikeda et al., 2013; Hejazi et al., 2013 ; Antonello et al., 2015).

Studies conducted in SSA have also not associated low CD4+ T-cell count with hypertension (Denue et al., 2012; Diouf et al., 2012; Ogunmola et al., 2014; Okello et al., 2015; Sander et al., 2015; Dimala et al., 2016). However, a few studies have associated low CD4+ T-cell count (<200 cells/μL) with increased odds of hypertension (adjusted OR=1.60 [95% CI, 1.05-2.41]) (De Socio et al., 2014). Similarly, other studies have associated Nadir CD4+ T-cell count of < 50 cells/μL with increased odds of hypertension (adjusted OR=2.31 [95% CI, 1.17-4.56], p=0.015) (Manner et al., 2013b). Two studies actually associated higher levels of CD4+ T-cell count with increasing odds of hypertension (Peck et al., 2014; Njelekela et al., 2016).

2.3.5.3.3 Antiretroviral therapy

Worldwide, several studies have been conducted in PLHIV in the area of hypertension in PLHIV. However, the association between ART and hypertension in PLHIV remains debatable with conflicting results. In a Norway study, antiretroviral treatment duration appeared to be an associated factor for hypertension, but the roles of the various ARVs were not investigated (Baekken et al., 2008). A study conducted in Spain indicated that a rise in blood pressure was reported after 48 weeks of ART (Palacios et al., 2006) and another study reported by Jerico et al. (2005) indicated no association between ART and hypertension. However, Gazzaruso et al. (2003) reported of a higher prevalence of hypertension in patients on ART compared with ART-naive patients (34.2% versus 11.9%; p<0.0001).

A systematic review and meta-analysis of 39 studies (which included 11 studies from SSA) involving 44,903 PLHIV indicated that the prevalence of hypertension in ART-exposed is 14.5% whilst that of ART-naive is 10.5% regardless of the socio-demographic differences between the studies (Nduka et al., 2016a). The review also indicated increased odds of hypertension in ART-exposed patients (OR=1.68 [95% CI, 1.35-2.10], I^2=81.5%) compared with ART-naive patients.

In the SSA region, divergent results have also been reported in terms of the relationship between ART and hypertension. Table 5 shows a summary of studies conducted in SSA on the relationship between ART and hypertension. Whilst studies from Ghana (Ngala and Fianko, 2014), Cameroon (Nsagha et al., 2015; Dimala et al., 2016) and Nigeria (Nduka et al., 2016b) and indicate an association between ART and hypertension in PLHIV, a study from Nigeria reported otherwise (Ogunmola et al., 2014). In terms of prevalence, whilst studies from Botswana (Shapiro et al., 2012), Nigeria (Muhammad et al., 2013), Cameroon (Ekali et al., 2013; Dimala et al., 2016) indicate of significant difference in hypertension prevalence between ART-exposed and ART-naive study participants, other studies (Edward et al., 2013; Dimodi et al., 2014; Sander et al., 2015) reported otherwise of difference in hypertension prevalence between ART-exposed and ART-naive study participants. A study from Tanzania reported of differences in prevalence of hypertension between ART-exposed and ART-naive patients (30.0% vs. 21.9% respectively, p=0.010) (Kagaruki et al., 2014)

Worth noting is that a retrospective cohort study in Kenya (Bloomfield et al., 2011) which involved a large sample size of 12,194 PLHIV did not report of an association between length of PI usage and hypertension. Table 4 shows a summary of the studies in SSA reviewed on the epidemiological relationship between ART and hypertension.

Table 5. Studies assessing the relationship between highly active anti-retroviral therapy and hypertension in PLHIV in sub-Saharan Africa.

Country	Authors	Year	Study-design	Sample size of PLHIV	% Female	Relationship between ART and hypertension/blood pressure values
Botswana	Shapiro et al.	2012	Cross-sectional	62	100	Hypertension prevalence significantly higher in ART-exposed compared with ART-naive
Cameroon	Ekali et al.	2013	Cross-sectional	143	72.0	Hypertension prevalence significantly higher in ART-exposed compared with ART-naive
	Dimodi et al.	2014	Cross-sectional	463	74.7	No significant difference in hypertension prevalence between ART-exposed and ART-naive
	Nsagha et al.	2015	Cross-sectional	215	74.9	ART is associated with hypertension
	Dimala et al.	2016	Cross-sectional	200	70.0	Hypertension prevalence significantly higher in ART-exposed compared with ART-naive; ART is associated with hypertension
Ghana	Ngala and Fianko	2014	Cross-sectional	305	68.2	ART is associated with hypertension
Kenya	Bloomfield et al.	2011	Cohort	12,194	64.8	No association between length of PI use and hypertension
Nigeria	Edward et al.	2013	Cross-sectional	265	67.5	No significant difference in hypertension prevalence between ART-exposed and ART-naive
	Muhammad	2013	Cross-sectional	200	53.0	Hypertension prevalence significantly higher in ART-exposed compared with ART-naive
	Ogunmola et al.	2014	Cross-sectional	250	62.4	No significant difference in hypertension prevalence between ART-exposed and ART-naive
	Nduka et al.	2016a	Cross-sectional	406	68.5	ART is related to increase in both systolic and diastolic blood pressure values using PSM analysis
Tanzania	Kagaruki et al.	2014	Cross-sectional	671	70.5	Hypertension prevalence significantly higher in ART-exposed compared with ART-naive
Uganda	Sander et al.	2015	Cross-sectional	426	71.0	No significant difference in hypertension prevalence between ART-exposed and ART-naive

ART=Antiretroviral Therapy; PI=protease inhibitor; PLHIV=Persons Living with HIV; PSM=Propensity score-matching

2.3.6 Pathogenesis/pathophysiology of hypertension in PLHIV

In addition to the known risk factors of hypertension in the general population, HIV itself and ARVs used in ART have been implicated in the pathogenesis and pathophysiology of hypertension and other CVDs in PLHIV. This interaction is further made complex with environmental and genetic factors. Figure 4 shows a hypothetical model postulated by Hemkens and Bucher (Hemkens and Bucher, 2014) showing the various patho-physiological pathways by which HIV and ART promote hypertension and other cardiovascular diseases in PLHIV.

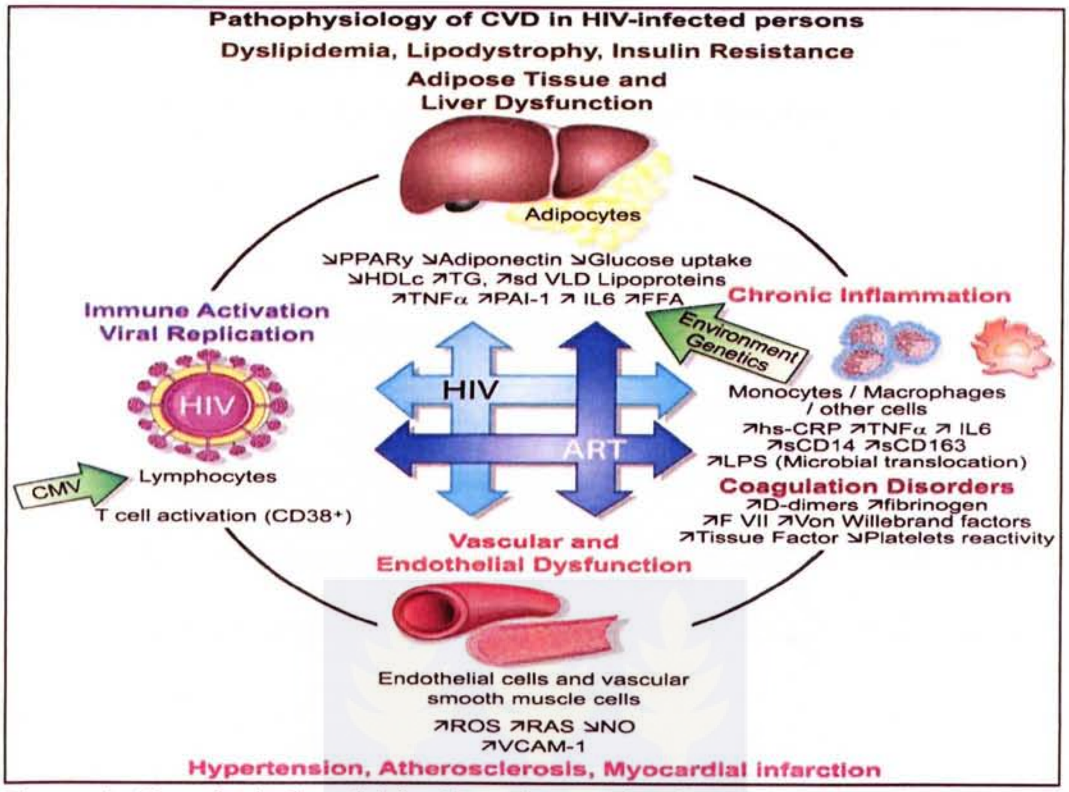

Figure 4. Hypothetical model for the pathogenesis of cardiovascular disease in HIV-infected persons taking antiretroviral therapy Source: (Hemkens and Bucher, 2014)

"HIV and antiretroviral treatment (ART) might affect cardiovascular disease (CVD) through various pathophysiological pathways (together with environmental and genetic factors). There is a very complex interaction of various related factors. HIV and ART have direct effects on adipose tissue and liver function with subsequent dyslipidemia, lipodystrophy and insulin resistance. Other direct impact includes effects on endothelial cells and vascular smooth muscle cells leading to vascular and endothelial dysfunction with subsequent hypertension, atherosclerosis and myocardial infarction. Continuous immune activation and viral replication might lead to a permanent T cell activation, which might also be affected by a reactivation of other viruses, e.g. Cytomegalovirus (CMV). ART and HIV might also stimulate a chronic status of inflammation and have a complex interaction with coagulation factors. These pathways itself are more or less interrelated and mediate indirect effects of HIV and ART on CVD" (Hemkens and Bucher, 2014)

Abbreviations: ART=Antiretroviral therapy; hs-CRP: high-sensitivity; C-reactive protein; F VII: Factor VII; FFA: Free fatty acids; HDLc: High-density lipoprotein cholesterol; IL6: Interleukin 6; LPS: lipopolysaccharide; NO: Nitrogen oxide; PAI-1: Plasminogen activator inhibitor type 1; PPARy: peroxisome proliferator-activated receptors; RAS: Renin angiotensin system; ROS: Reactive oxygen species; sCD14: Soluble CD14; sCD163: Soluble CD163.

2.3.6.1 The HIV-infection

The HIV infection itself can promote atherosclerosis through immune activation, chronic inflammation, coagulation disorders and lipid disturbances as follows (Baker and Lundgren, 2011; Boccara et al., 2013);

- The virus has been reported to enhance endothelial injury resulting in endothelial dysfunction through the production of molecules which enhance angiogenesis like adhesion molecules (de Gaetano Donati et al., 2004) and HIV Tat protein (Gresele et al., 2012).
- HIV also stimulates the production of human vascular smooth muscle cells, which is implicated in the development of atherosclerosis (Eugenin et al., 2008).
- The onset of coagulation disorders (a "prothrombic state") which is associated with HIV leads to increased levels of D dimers, fibrinogen, factor VII, von Willebrand and tissue factors and abnormal platelet reactivity (Baker et al., 2011; Gresele et al., 2012).
- HIV infection is also associated with known atherogenic dyslipidemia observed as increased levels of triglycerides (results of impaired lipase activity) and decreased levels of HDL-C and correlated high concentration of cytokines (Grunfeld et al., 1992).

2.3.6.2 Anti-retrovirals used in ART

Although it remains debatable due to conflicting results, several reports have reported the association between ARVs used in ART and hypertension/CVDs in PLHIV. The pathogeneses involved in ARVs inducing hypertension (and other CVDs) in PLHIV are as follows;

- The use of ART leads to immune activation and may lead to low-grade inflammation, which can promote atherosclerosis (Fisher et al., 2006; Coll et al., 2007; Boccara et al., 2013).
- During immune activation there is an increased translocation of intestinal bacterial from the gut into the systemic circulation which impacts on the promotion of atherosclerosis (Redd et al., 2011).
- Several studies have implicated ART involvement in lipid and glucose metabolism leading to adipocyte dysfunction which results in lipodystrophy syndrome (Grinspoon and Carr, 2005; Capeau, 2007; Boccara et al., 2010). Protease inhibitors (PIs) have also been associated with activation of the adipocyte RAS (Boccara et al., 2010)
- Studies have also reported of PIs inducing endothelial injury, and this has been associated with dyslipidaemia, oxidative stress and senescence (Lefevre et al., 2010). However, contradicting results from the AIDS Clinical Trials Group 5152 indicate that, endothelial dysfunction rather improved over a ART course of 24 weeks (Torriani et al., 2008). This has led to the postulation of the different effect of PIs on the risk of CVDs dependent on the length of usage, be it short term or long term.

2.4 Propensity score-matching analysis

Propensity score-matching (PSM) analysis refers to a statistical method of estimating average treatment effect on an outcome in a bid to infer a causal link. The conceptual foundation of PSM analysis was first propagated by Donald B. Rubin in what is now known as the "Rubin causal model" (RCM) after a series of publications on methods to remove bias and estimate causal effect in observational studies (Rubin, 1974; Rosenbaum and Rubin, 1983a; Rosenbaum and Rubin, 1983b; Rosenbaum and Rubin, 1984; Holland, 1986; Rubin, 2007; Austin, 2011b). The Rubin causal model is based on the Neyman potential outcomes framework and the idea that depending on a particular treatment assignment, very individual or participant has a potential outcome, which is expressed in the form of counterfactual conditional statements. The model holds that the causal effect of being exposed to a treatment as opposed to being unexposed to that treatment at any given time, is the difference between the outcome measure with and without treatment assuming no significant difference in the baseline characteristics between the two groups (Rubin, 1974; Imbens, 2004).

PSM analysis involves the use of an estimated propensity score which is a single score assigned to each individual in the treatment group and it represents the conditional probability of receiving a treatment, given a set of observed covariates or vector of covariates (Garrido et al., 2014). The ultimate aim of creating a propensity score is to be able to balance the observed covariates between individuals in the treatment group and individuals in the comparison group. Thus, PSM analysis mimics randomised control trial using statistical balancing of baseline covariates between the treated group and the untreated/comparison group and this makes it easier to isolate and thereafter infer high level of effect of a treatment or intervention on an outcome of interest. Although PSM analysis has become very popular in the area of developmental economics and econometrics, its usage in the health sciences is gradually picking up due to its ability to answer most health interventions impact assessment/analysis. The interest in the use of PSM analysis in health research is growing as a valuable tool to infer or otherwise a plausible causal effect of treatment i.e. cause-effect relationships, especially in situations where RCT is not practicable due to logistical constraints or ethical reasons (Rosenbaum and Rubin, 1985; Austin, 2011a; Austin, 2011b). The concept of causation in epidemiology has gone through a period of evolution and expansion and has gone beyond and above the simple relationships established by "Hill's Criteria of Causation" (Hill, 1965; Lucas and McMichael, 2005; Mirtz et al., 2009) to the use of statistical methods in testing causal hypothesis (Rosenbaum and Rubin, 1985; Austin, 2011b; Austin, 2011a). PSM analysis is thus a useful tool in observational studies where there is a need to infer a causal relationship between treatment and an outcome.

The method of matching individuals in a treatment group to individuals in a comparison group based on an estimated propensity score can account for selection bias due to observable characteristics used in the matching process. Rosenbaum and Rubin (Rosenbaum and Rubin, 1983b) demonstrated that this matching gives an unbiased estimate of the effect treatment. Despite these demonstrations, three caveats and assumptions are observed when using PSM analysis. The first is the independent and identically distributed sampling assumption (i.i.d) which ensures that for a given dataset, the potential outcome and treatment status of each individual in the dataset is not dependent on the potential outcome and treatment status of other individuals in the dataset. The second assumption is the conditional independence assumption (c.i.), which means that once the propensity has been estimated and used to balance all observable covariates, the potential outcomes are independent of treatment assignment/model. The third assumption is the overlap assumption, which ensures that each individual has a positive probability of receiving treatment. However, the non-inclusion of unobservable covariates or "hidden bias" which may affect treatment allocation is a drawback on the PSA method. The extent of this "hidden bias" can be estimated by doing post-estimation analysis using the *rbound* syntax in Stata.

2.4.1 Steps used in propensity score-matching analysis

There are five steps used in propensity score-matching analysis after which the effect of treatment on an outcome is estimated (Austin, 2011b; Garrido et al., 2014). The five steps are

1. selection of covariates to include in estimating propensity scores for each study participant
2. balance of estimated propensity scores across treatment and comparison groups
3. balance of covariates across treatment and comparison group within blocks of estimated propensity scores
4. choosing a matching or weighting strategy to match each treated study participant to a control based on individually estimated propensity score
5. assessment of balance of covariates after matching/weighting the samples using the estimated propensity scores

2.4.1.1 Selection of covariates to include in estimating propensity score

The first step in PSM analysis is to select the covariates to be used in estimating propensity score for each study participant. This selection process is very important and involves both theorised and hypothesised approaches. Variables associated with both treatment and outcome are considered as confounders and included in the selection. Variables associated with the outcome but not the treatment are also included to reduce bias (Austin, 2011b). Although it is encouraged to include all variables that are potentially related to the outcome, in smaller dataset the inclusion of potentially irrelevant covariates may introduce too much "noise" and obscure any reduction in bias that would have been achieved by their inclusion (Austin, 2011b). However, the inclusion of variables that are hypothesised to be associated with the treatment but not with the outcome can decrease estimation of the treatment effect (Austin, 2011b; Garrido et al., 2014). Of caution is to exclude covariates that are affected by the treatment and also covariates that do predict treatment status perfectly as the distribution of covariates needs to be balanced between the treatment group and the comparison group. After the selection of covariates, a logit or probit regression with treatment as the outcome variable and the potential confounders (covariates) as the explanatory variables is used to estimate the propensity score for each individual in the study population.

2.4.1.2 Balance of estimated propensity score across treatment and comparison groups

After estimating the propensity score for each individual, the estimated propensity scores are assessed to have similar distribution across treatment and comparison groups. This is to ensure that there is overlap in the range of the estimated propensity scores across treatment and comparison groups, commonly called "common support". "Common support" is assessed subjectively by the examination of a graph showing the range of the estimated propensity score across the treatment and comparison using a box plot. In addition, the estimated propensity scores are tested to have similar distribution in the treated and comparison group using a t-test. This is achieved by splitting the study participants into quintiles and the balance of the estimated propensity scores tested for each quintile by a t-test.

2.4.1.3 Balance of covariates across treatment and comparison group within blocks of the estimated propensity score

This step is done to assess that each covariate is balanced between treatment and comparison group. Some covariates at this stage may be dropped, re-categorised, interaction terms introduced or higher-level splines introduced. Although there is no agreeable test for balance of covariates, Austin (Austin, 2009) and Stuart et al. (Stuart et al., 2013) have proposed that the maximum standardised difference for each covariate should range between 10% and 25%.

2.4.1.4 Choosing a matching or weighting strategy

The choice of a matching or weighting strategy is a trade-off between quality and quantity. Notable strategies include regression adjustment, inverse-probability weighting, augmented inverse-probability weighting and inverse-probability-weighted regression adjustment. Others are nearest-neighbour matching, radius matching, propensity-score matching and kernel-weighting/matching strategies. There is no universal "best" strategy as each strategy has its own merits and limitations. These merits and limitations are in terms of how close a match is acceptable, whether every individual in the treatment group should have one or matches in the comparison group, whether individuals in the treatment group should be matched with or without replacement and whether matching should be "greedy" or "optimal". In this study, the kernel weighting strategy was used to match individuals in the treatment group to the comparison group. Also known as kernel matching, the kernel weighting strategy is gradually gaining prominence in health research where other matching or weighting strategies may not be viable options (Imbens, 2000; Dugoff et al., 2014). The kernel weighting strategy involves assigning each individual in the treatment group a weight of one (1). For each such individual, a weighted composite of individuals in the comparison group is used to create a match based on their distance in the propensity score from the individual in the treatment group. This distance is however done with a range or bandwidth such that only comparison group observations outside the bandwidth of "common support" are discarded (Garrido, 2014). Thus, kernel weighting strategy maximizes precision with the retention of most individuals sampled but without worsening bias (as the weighting criteria gives greater weight to better matches). Due to the methods used, kernel weighting lends itself to estimating the average treatment on the treated (ATT) rather than the average treatment effect on the entire study participants (ATE) (Garrido, 2014).

2.4.1.5 Assessment of balance of covariates after matching or weighting the sample using the estimated propensity score

This step ensures that checks are made to evaluate how well the treatment group and the comparison group are balanced in the matched/weighted samples. Methods used to evaluate this balance assessment include;

a. **Comparing standardised differences for each covariate before and after matching/weighting:** Although, there is no universal agreement among researchers as to the threshold of the standardised difference acceptable, a standardised difference of less than 10% in the matched/weighted sample will indicate a negligible difference in the mean, median or proportion of a covariate between treatment group and comparison group (Normand et al., 2001; Austin, 2011b).

b. **Balance diagnosis using graphs:** With weighted data, the density functions of continuous covariates in treatment and comparison groups can be graphed together and compared subjectively (Austin, 2009). In addition, a dot graph can be used to assess visually, the standardised difference.

c. **Evaluation of ratio of variances:** The ratio of variance of covariates in the treated group to the variance of covariates in the comparison group should optimally be one (1) if covariates are balance in the matched/weighted sample. Rubin has however indicated that a ratio ≤0.5 or ≥2.0 are far too extreme to be accepted for propensity score-matching analysis (Rubin, 2001).

2.4.2 Analysis of data matched or weighted by the propensity score

After the deletion of individuals outside the "common support" and the method of matching or weighting employed, the estimation of the treatment effect is done. Treatment effect is referred to as the causal effect of a given treatment or intervention on an outcome of interest (Austin, 2011b; Garrido, 2014). There are generally three treatment effects of interest;

a. **Average Treatment Effect on the entire sample (ATE):** This refers to the average effect, at population level, of moving an entire population from untreated to treated (Austin, 2011b).

b. **Average Treatment Effect on the Treated (ATT or ATET):** This refers to the average effect of the treatment on an individual in the treatment group (Austin, 2011b).

c. **Average Treatment Effect on the Untreated (ATU):** This refers to the average effect of the treatment on an individual in the untreated or comparison group (Austin, 2011b).

Although both ATE and ATT entails a statistical approach to defining causal effect based on the Rubin causal model (Rubin, 1974), ATE is used mostly in randomised control trial and regardless of the context of the research, PSM analysis is reserved for estimating ATT (Austin, 2011b; Nduka et al., 2016b).

2.4.3 Post-estimation sensitivity analysis

From an epidemiological perspective, post-estimation sensitivity analysis in propensity score-matching analysis is required as a tool to evaluate the extent to which a significant relationship found between a treatment and an outcome could be due to unobserved confounding. These tests are used to quantify the strengths of any association between hypothetical unobserved covariates and the exposure and outcome (Liu et al., 2013). Thus, the sensitivity analysis aims to use hypothetical unobserved covariates to achieve a true association between an exposure and an outcome with varying levels of sensitivity parameters (Liu et al., 2013).

From a statistical approach, sensitivity analysis in PSM analysis uses a sensitivity parameter to measure the difference in the odds of exposure for two study participants with the same estimated propensity score but diverge on unobserved covariates (Liu et al., 2013). The analysis yields results that estimate the smallest value of the sensitivity parameter that will change the p-value of the "true" exposure-outcome association from a significant level to a non-significant level (Liu et al., 2013). The Rosenbaum's approach to sensitivity analysis is the most widely used method in matched analysis including PSM analysis and this determines the threshold of the association between unobserved covariates and the exposure and/or the threshold of the association between unobserved covariates and the exposure that would render the determined test statistics insignificant.

2.5 Cardiovascular risk scoring systems

Cardiovascular disease affects most adults and is common in the general population. Cardiovascular disease includes diseases like coronary heart disease, peripheral arterial disease and aortic disease. Although the risk of CVDs increases with age, predicting the risk of CVD in an individual can lead to interventions to reduce the occurrence of future events. Cardiovascular risk scoring systems give an estimate of the probability that an individual will develop CVD within a specified length of time. Cardiovascular risk scoring systems are very useful tools both to individual patients and to attending clinicians in helping decide on when to initiate appropriate life-style modifications and preventive medical treatment.

Several cardiovascular risk-scoring systems on individuals have been developed in different study populations targeted at different ethnic groups. These include the Framingham Risk Score, the SCORE CVD death risk score, the QRISK CVD risk estimator, the Reynolds CVD risk score for women and for men, the ACC/AHA pooled cohort hard CVD risk calculator and the JBS3 risk calculator (Wilson, 2017). Others are the MESA risk score, the China-PAR risk predictor, the Rama-EGAT risk score, the WHO/ISH risk prediction chart and the D:A:D risk score. The most popular and widely used of these CVD risk assessment scores is the FRS, which was modelled from the Framingham Heart Study (Wilson, 2017). With the exception of the D:A:D 5-year cardiovascular risk scoring system meant for the HIV-positive population, the rest of the scoring systems are designed for the general population. However, with the HIV-positive sub population, issues on the effect of HIV itself and the administration of ART on the risk of CVD have raised appropriateness of the use of general CVD risk scores in PLHIV. A commentary by D'Agostino (D'Agostino, 2012) reviewed the use of the FRS and the D:A:D CVD risk equation in HIV-positive population and suggested that whilst FRS can be used for general CVD risk assessment in PLHIV, more specific assessment tools like the D:A:D must be developed for the HIV-positive population.

2.5.1 The Framingham 10-year general cardiovascular disease risk score

The Framingham risk score (FRS) is a sex specific cardiovascular risk scoring system used in estimating the 10-year cardiovascular risk of an individual. First published in 1998 (Framingham Coronary Heart Disease Risk Score) (Wilson et al., 1998) with subsequent edited versions of it published in 2002 (ATP III hard CHD Risk Score) (NCEP, 2002) and 2008 (General Framingham CVD risk score) (D'Agostino et al., 2008), the FRS is the most popular and widely used CVD risk score. The FRS was developed from the Framingham Heart study and it has been validated in different populations/ethnic groups in the USA (D'Agostino et al., 2001). Although, there has been studies with claims of improvement over the FRS, a study indicated little evidence to back such improved prediction over the FRS (Tzoulaki et al., 2009). However, a review of studies, which compared different CVD risk score tools, indicated that due to the different study populations, reporting style and documentation it was difficult to be conclusive on the superiority of any CVD predictive model (Siontis et al., 2012).

The current version of the FRS takes into consideration for each individual CVD risk assessment the following parameters; age, total cholesterol, smoking status, HDL-cholesterol, systolic blood pressure, treatment for hypertension or not and it is sex-specific (D'Agostino et al., 2008). A modified version of the general FRS takes into account a positive history of premature cardiovascular disease in a first degree relative before the age of 55 years (for men) or 65 years (for women) (Genest et al., 2009).

2.5.2 The D:A:D 5-year cardiovascular disease risk score

The data Collection on Adverse Events of anti-HUV drugs (D:A:D) cardiovascular risk scoring system was developed from the D:A:D study and published in 2010 (Friis-Moller et al., 2010) and subsequently updated in 2016 (Friis-Moller et al., 2016). The D:A:D risk score is a specific cardiovascular risk score developed from a cohort of HIV-positive patients taking into consideration the type and duration of ARVs administered. The DA:D study used a 5-year prediction model based on the fact that models based on time-updated data may more accurately capture and predict individual's current risk. The full model takes into consideration age, sex, family history of CVD, smoking status, diabetes status, total cholesterol level, HDL-cholesterol level, systolic blood pressure, CD4 T-cell count, years of exposure to a protease inhibitor (lopinavir), years of exposure to a NRTI and exposure to abacavir or not (Friis-Moller et al., 2016).

2.5.3 The WHO/ISH risk prediction charts

The World Health Organisation/International Society of Hypertension (WHO/ISH) risk prediction chart is a cardiovascular risk scoring system tool developed for assessment and prediction of cardiovascular risk in different populations (Mendis et al., 2007). It is developed based on a 10-year modelling approach from the WHO comparative risk assessment study and incorporates the factors age, sex, diabetes status, systolic blood pressure, smoking stats and total serum cholesterol (Ezzati et al., 2003). With specific charts designed specifically for non-Western countries where cohort data and resources are believed to be unavailable, the WHO/ISH prediction charts uses information on the relative risk of each risk factor, along with population level estimate of absolute risk to develop a risk prediction chart which is regionally-based and thus can be used for LMIC. The charts are divided into the 14 WHO epidemiological sub-regions; Africa (AFR D and E), The Americas (AMR A, B and D), Eastern Mediterranean (EMR B and D), Europe (EUR A, B and C), South-East Asia (SEAR B and D) and Western pacific (WP A and B) (WHO, 2007).

CHAPTER THREE

3.0 METHODS

3.1 Study design

A hospital-based cross sectional study was conducted at the HIV Clinic of the KBTH in Accra, Ghana, from February 2016 to May 2016. All consenting HIV-positive patients aged 18 years and above, non-pregnant (for females) and have been in attendance at the HIV clinic for at least 6 months were eligible for recruitment into the study. Patients excluded from the study were patients with prior diagnosis of hypertension before HIV infection diagnosis or patients with sub-optimal adherence to HIV clinic follow-up visits/ART medication or patients on hospitalisation /diagnosed with AIDS. A simple random sampling technique was used to recruit potential study participants into the study based on the routine clinic attendance. After going through the eligibility criteria (inclusion/exclusion criteria), patients were recruited as study participants. A questionnaire was administered to study participants to collect data on socio-demographic characteristics, life-style characteristics and family history of cardiovascular disease. Blood pressure and anthropometric measurements were made and fasting blood samples taken for metabolic/biochemical parameters. Retrospective chart review of clinical folders was done for baseline variables of each study participant. HIV and ART-related data were extracted from the clinical folders of the study participants. The prevalence of hypertension was estimated among the study participants and the socio-demographic, life-style, anthropometric, metabolic and HIV/ART-related factors associated with hypertension were determined by logistic regression modelling. PSM-analysis was used to determine the ATT of ART on hypertension and an estimation of the level of risk of CVD using cardiovascular risk score assessment tools (10-year Framingham risk score; 10-year WHO/ISH risk prediction chart for fatal or non-fatal cardiovascular event and the 5-year D:A:D CVD risk score) were made.

3.2 Study location

The study site was the HIV Clinic at the Korle-Bu Teaching Hospital. KBTH (Latitude 5 degrees, 36 minutes north; Longitude 0 degrees, 10 minutes east) is located at Guggisberg Avenue (10 minutes' drive under normal traffic from the central business centre of Accra) in the Ablekuma District of the Accra Metropolis in Greater Accra Region of Ghana. Accra is the capital city of Ghana with an estimated population of 4 million, making it the eleventh largest metropolis in Africa. Accra is located in the coastal savannah ecological zone, in the south-eastern end of Ghana with a land size of about 173 km^2. The average daily temperature is around 30°C (86°F) and receives an annual rainfall of between 600 mm and 800 mm.

The HIV Clinic is located in the Fever's Unit under the Department of Medicine, KBTH. Korle-bu Teaching Hospital was established on October 9, 1923 and it has grown from an initial 200 bed capacity to about 2,000. It is currently the third largest hospital in Africa and the leading national referral centre in Ghana. It has currently 17 clinical and diagnostic departments/units and an average daily attendance of 1,500 patients with about 250 daily patient admissions. It has three centres of excellence, the National Cardiothoracic Centre, the National Reconstructive Plastic Surgery and Burns Centre and the National Radiotherapy Centre. In addition, it is the premier tertiary hospital in Ghana and serves as a research and training facility for students and researchers of the University of Ghana.

Currently the KBTH HIV Clinic has a 24-bed capacity and runs the largest cohort of HIV patients in Ghana. Presently about 20,000 patients attend the clinic of which about 11,000 are on ART. The Korle Bu Teaching Hospital has been providing ART services to PLHIV since December 2003. The hospital runs the HIV Clinic three days in a week (Mondays, Wednesdays and Fridays) and operates an institutionalised electronic database which stores all clinic visits as well as medications, laboratory investigations and other patients' data. Currently the staff strength at the clinic is 5 clinicians, 30 nurses, 3 public health nurses, 8 pharmacists, 4 biomedical scientists, 6 volunteers, 8 counsellors and 5 data room staff. The fever's unit also houses cases of rabies and tetanus (3-bed capacity).

3.3 Study population

The study population is the 20,000 HIV-positive patients who attend the HIV clinic and the sampling frame is the electronic register of patients. The patient population is made up of about 11,000 on ART with the rest on care. Each patient is scheduled to attend the clinic once every three months (at a minimum) for both clinical assessment and dispensing of medication (for patients on ARVs). Some patients have been on treatment for the past 11 years.

At HIV clinic enrolment, patients routinely present with baseline clinical and laboratory evaluations like physical examinations, full blood count, liver enzymes, serum creatinine, and CD4+ T-cell count. Follow-ups are done every 3 months whilst occasional viral load is requested for when treatment failure is suspected since it is expensive and patients are unable to afford as a routine laboratory investigation. The recommended baseline CD4 + T-cell count for initiating ART was a count of 250 cells/μL or less and WHO clinical stage III/IV regardless of CD4+ count. This changed later to 350 cells/ μL or less in the 2011 guidelines and is presently pecked at 500 cells/ μL (NACP et al., 2014). Patients receive comprehensive care at a minimum cost of $3.00 or receive free care when registered under the National Health Insurance. Irrespective of these requirements, patients not meeting the criteria are not excluded from receiving continuous care. The care included medical review, laboratory examinations, adherence counselling and general education on the disease and its management. Adherence is reviewed at every clinic visit and documented and is considered satisfactory when patients' self-report of compliance tallies with pill count.

3.4 Variables

Tables 6, 7, 8, 9 and 10 below summarises a list of socio-demographic variables, family history of CVD and lifestyle variables, blood pressure and anthropometric variables, metabolic/biochemical variables, and ART/HIV-related and other variables measured or extracted respectively.

Table 6. Socio-demographic variables measured

Variable	Definition	Type of variable	Scale of measurement
Age	Current age (years) of study participant	Explanatory	1. Binary • <40 years • ≥40 years 2. Continuous
Sex	Sex of study participant	Explanatory	Binary • Female • Male
Religion	Religious affiliation of study participant	Explanatory	Categorical • Christianity • Moslem • Others
Educational level	Highest educational level attained by study participant	Explanatory	Categorical • None • Basic • Secondary • Tertiary/Professional
Marital status	Marital status of study participant	Explanatory	Categorical • Single • Married/co-habiting • Divorced/widowed/separated
Employment	Employment status of study participant	Explanatory	Binary • Unemployed • Employed

Table 7. Family history of cardiovascular disease and life-style variables measured

Variable	Definition	Type of variable	Scale of measurement
Family history of hypertension/CVD	Family history of hypertension or CVD in parents or siblings	Explanatory	Binary • Present • Absent
Tobacco smoking status	Smoking of any form of tobacco including cigarettes	Explanatory	Binary • Ever smoker • None smoker
Alcohol drinking status	Drinking of alcohol regularly	Explanatory	Binary • Drinker • Abstainer
Fruit consumption	This a measure of how frequent study participant consumes fruits	Explanatory	Binary • Never/rarely • Most at times
Engagement in physical activity	This a measure of how frequent study participant engages in physical activities	Explanatory	Binary • Never/rarely • Most at times

CVD=Cardiovascular disease

Table 8. Blood pressure readings measured or extracted from clinical folder

Variable	Definition	Type of variable	Scale of measurement
Hypertension status	Current blood pressure readings were measured and categorised as per WHO and European Society of Hypertension/European Society of Cardiology recommendations (Whitworth, 2003; Mancia et al., 2013; WHO, 2013c). Hypertension was defined as current systolic blood pressure (sBP) ≥140 mmHg and/or diastolic blood pressure (dBP) ≥90 mmHg on two different days and/or self-reported/medical record history of current antihypertensive therapy.	Dependent	Binary • Hypertensive • Non-hypertensive
Baseline systolic blood pressure	Systolic blood pressure readings as at enrollment into HIV clinic or at initiation of ART	Explanatory	Continuous
Baseline diastolic blood pressure	Diastolic blood pressure readings as at enrollment into HIV clinic or at initiation of ART	Explanatory	Continuous

dBP=Diastolic blood pressure; sBP=Systolic blood pressure; ART=Antiretroviral Therapy

Table 9. Anthropometric variables measured

Variable	Definition	Type of variable	Scale of measurement
Weight	Current weight (in kg) of study participant	Explanatory	Continuous
Height	Current height (in meters) of study participant	Explanatory	Continuous
Waist circumference	Current waist circumference (in cm) of study participant	Explanatory	Continuous
Hip circumference	Current hip circumference (in cm) of study participant	Explanatory	Continuous
Current body mass index (BMI)	Current BMI was calculated using the Quetelet index: weight divided by height squared (kg/m^2) and classified as (WHO, 1995): • <25.0 kg/m^2=underweight/normal • ≥25.0 kg/m^2=overweight/obese	Explanatory	Binary • <25.0 kg/m^2 • ≥25.0 kg/m^2
Baseline body mass index (BMI)	Baseline BMI (at enrolment into HIV clinic or at initiation of ART) was calculated using the Quetelet index: weight (as at HIV clinic enrolment or at initiation of ART) divided by height squared (kg/m^2) and classified as (WHO, 1995): • <25.0 kg/m^2=underweight/normal • ≥25.0 kg/m^2=overweight/obese	Explanatory	Binary • <25.0 kg/m^2 • ≥25.0 kg/m^2
Current abdominal obesity (Waist-to-Hip ratio)	Current abdominal obesity was defined as (WHO, 2012) • waist-to-hip ratio of ≥0.85 for women and • waist-to-hip ratio of ≥0.90 for men	Explanatory	Binary • Abdominal obesity present • Abdominal obesity absent
Current abdominal obesity (Waist circumference)	Current abdominal obesity was defined as (WHO, 2012) • waist circumference >88 for women and • waist circumference >102 for men	Explanatory	Binary • Abdominal obesity present • Abdominal obesity absent

BMI=Body mass index; ART=Antiretroviral Therapy

Table 10. Metabolic/biochemical variables measured

Variable	Definition	Type of variable	Scale of measurement
Fasting plasma glucose (FPG)	Fasting plasma glucose was classified according to the American Diabetes Association guidelines (ADA, 2012) as; • Elevated FPG ≥126.1 mg/dL (≥7.0 mmol/L) • Normal FPG <126.1 mg/dL (≥7.0 mmol/L)	Explanatory	Binary • Elevated FPG • Normal FPG
Estimated glomerular filtration rate (eGFR)	eGFR was estimated according to the CKD-EPI creatinine equation (Levey et al., 2009) and classified; • Normal eGFR : ≥60 min/mL/1.73 m^2 • Reduced eGFR: <60 min/mL/1.73 m^2	Explanatory	Binary • Normal eGFR • Reduced eGFR
Total cholesterol	Total cholesterol was classified using the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) (NCEP, 2002) • Hypercholesterolemia: Total cholesterol level ≥5.17 mmol/L • Normal total cholesterol: Total cholesterol level <5.17 mmol/L	Explanatory	Binary • Hypercholesterolemia • Normal total cholesterol
HDL-cholesterol	HDL-cholesterol level was classified using NCEP/ATP III (NCEP, 2002) • Abnormal HDL-C: HDL-cholesterol level <1.03 mmol/L • Normal HDL-C: HDL-cholesterol level ≥1.03 mmol/L	Explanatory	Binary • Abnormal HDL-C • Normal HDL-C
LDL-cholesterol	LDL-cholesterol level was classified using NCEP/ATP III (NCEP, 2002) as • Elevated LDL-C: LDL-cholesterol level ≥3.36 mmol/L • Normal LDL-C: LDL-cholesterol level <3.36 mmol/L	Explanatory	Binary • Elevated LDL-C • Normal LDL-C
Triglycerides	Triglycerides level was classified using NCEP/ATP III (NCEP, 2002) • Elevated triglycerides: Triglycerides level ≥2.26 mmol/L • Normal triglycerides: Triglycerides level <2.26 mmol/L	Explanatory	Binary • Elevated triglycerides • Normal triglycerides

HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; NCEP/ATP III=National Cholesterol Education Program, Adult Treatment Panel III; FPG=Fasting plasma glucose

Table 11. HIV/ART-related variables measured or extracted from clinical folder

Variable	Definition	Type of variable	Scale of measurement
Current CD4+ T-cell count	Current CD4+ T-cell count of study participant	Explanatory	Binary • ≤350 cells/μL • >350 cells/μL
Nadir CD4+ T-cell count	Lowest ever CD4+ T-cell count of study participant	Explanatory	Binary • ≤350 cells/μL • >350 cells/μL
Baseline CD4+ T-cell count	CD4+ T-cell count of study participant at HIV diagnosis/at enrolment into HIV clinic or at initiation of ART	Explanatory	Binary • ≤350 cells/μL • >350 cells/μL
HIV positive duration	Time since HIV diagnosis and study participation (in years)	Explanatory	Continuous
ART exposure	ART-exposed was defined as the administration of either two NRTIs (or one NRTI and one NtRTI) + one NNRTI or 2 NRTIs (or one NRTI and one NtRTI) + one PI.	Explanatory	Binary • ART-exposed • ART-naive
Duration of ART	Cumulative exposure to ART (in months)	Explanatory	Continuous
Presence of co-morbid condition	Any other chronic diagnosed disease like diabetes, TB, hepatitis B or C, chronic kidney disease, within the last 6 months as documented in clinical folder	Explanatory	Binary • Present • Absent

ART=Antiretroviral Therapy; NRTI=Nucleoside reverse transcriptase inhibitor; NtRTI=Nucleotide reverse transcriptase inhibitor; NNRTI=Non-nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor

3.5 Sampling

3.5.1 Sample size calculation

A minimum sample size was calculated based on the estimation of a population parameter for cross sectional studies (Charan and Biswas, 2013).

$$\text{Sample size} = \frac{(Z_{1-\alpha/2})^2 \, p\,(1-p)}{d^2}$$

Where

- $Z_{1-\alpha/2}$= 1.96 at Type I error of 5% i.e. 95% confidence interval
- p = expected proportion of hypertension in PLHIV =25.6% (Ngala and Fianko, 2014)
- d=absolute error = 5%

$$\text{Sample size} = \frac{1.96^2 \times 0.256\ (1-0.256)}{0.05^2}$$

The calculated initial minimum sample size was 293 study participants. Given that, several characteristics of ART-exposed and ART-naive study participants were to be matched on the propensity score, which will lead to deletion of study participants "off support" a 5% adjustment was added to the initial minimum sample size calculated (Nduka et al., 2016b). The final minimum sample size calculated was 308. A total of 311 patients attending the HIV clinic at the KBTH were recruited as study participants for this study.

3.5.2 Sampling procedure

3.5.2.1 Inclusion criteria

1. Both sexes.
2. Patients $\geq$ 18 years of age.
3. Patients who have been enrolled into the HIV clinic for a minimum of 6 months and have had at least 3 clinic visits.

3.5.2.2 Exclusion criteria

1. Patients diagnosed with hypertension before HIV-positive status diagnosis or before enrolment into the HIV clinic.
2. Females who are pregnant and those who had given birth in the last 6 months as at the time of study
3. Patients with clinical AIDS or on hospitalisation
4. Patients with sub-optimal adherence to follow-up visits to HIV clinic (<95%). Adherence was measured using proportion of days covered (PDC) (Ankrah et al., 2015).

3.5.2.3 Selection of study participants

A simple random sampling technique was used for the selection of study participants as follows. The sampling unit were individuals attending the HIV clinic. The clinic operates 3 days in a week (Mondays, Wednesdays and Fridays) and attends to about 150 patients on each of these days and the sampling frame are the patients booked for each clinic day.

The maximum cycle of a patient attending the HIV clinic is 3 months i.e. 12 clinic weeks results in a cycle of 36 clinic days at a minimum. This means a patient is likely to present to the clinic at least once every 36-clinic days. The sampling was done to give every patient an equal chance of being represented; hence, the number of patients sampled per clinic day was eight (8).

Computer generated random sequence of eight unique code numbers was generated from the sampling frame for each clinic day for 40 clinic days and these were the patients to be recruited into the study. The sampling frame was the list of patients booked for a clinic day. Every patient in a particular day's list (sampling frame) was given a unique code number (extracted from folder number). Previously sampled patients were excluded from subsequent sampling frame using date of last clinic attendance. After recruitment, patients were taken through the consent process and after satisfying the study selection criteria. Recruited patients who did not satisfy the inclusion/exclusion criteria or who refused to take part in the study on any particular study day were not replaced but the enrolment procedure continued until the sample size estimated was reached. A total of 40 clinic days were used for the recruitment of study participants.

3.6 Data collection techniques

3.6.1 Consenting process and participation in study

In this study, randomly selected potential study participants were recruited whilst waiting to see the clinician. Each recruited study participant was privately informed about the objectives and purpose of the study, risks and benefits of participating in the study and that his/her participation will be purely voluntary and there will be no negative effect for not consenting to participate in the study. After the consenting process, each participant was administered the questionnaire, blood pressure readings taken, anthropometric measurements done and asked to come back the following morning fasted for blood sampling. Follow-up telephone calls were made to recruited patients and they were reminded to fast before coming for blood sampling the following day.

3.6.2 Data collection from study participants

A questionnaire adopted from WHO STEPwise approach to chronic disease risk-factor surveillance (WHO, 2008a) was modified and used for the collection of study participants' data. In addition, other relevant clinical characteristics were obtained from the medical history record (clinical folder) of the study participants. Information obtained from the study participants were classified under the following groupings:

1. Socio-demographic and life-style characteristics
2. Blood pressure, anthropometric and biochemical measurements
3. HIV/ART-related and other data extracted from clinical folders

3.6.2.1 Socio-demographic and life-style characteristics

Data on age, sex, employment, educational level attained and marital status were obtained from the study participants through an interviewer-administered questionnaire.

Life-style characteristics in terms of alcohol consumption, smoking status, fruit consumption and engagement in physical activity were obtained from the study participants through interviewer-administered questionnaire. Data on family history of cardiovascular disease were also obtained.

3.6.2.2 Blood pressure, anthropometric and biochemical measurements

3.6.2.2.1 Blood pressure measurement

Blood pressure readings were taken by a trained nurse in the outpatient clinic with a new calibrated analogue mercury sphygmomanometer (Tycoo®, USA) having an adjustable cuff. Blood pressure measurements were made with study participants seated in an upright position and relaxed. On the day of enrolment, study participants were made to sit for 10 minutes or more before blood pressure readings were made. In accordance with the WHO STEPwise approach to chronic disease risk-factor surveillance protocol (WHO, 2008a), two measurements were taken 3 minutes apart on alternating arms and the average of these two readings estimated and used in the analysis. This is in accordance with WHO recommendation to use the average of blood pressure readings at one visit in risk factor surveys (WHO, 2008a). An additional blood pressure measurement was made on each study participant four weeks after the first measurement using the same procedure.

3.6.2.2.2 Weight measurement

The body weight of study participants was measured using a calibrated digital Seca® 813 electronic weight measuring scale (Seca, Hamburg, Germany). The scale was placed on an even surface and study participants were made to stand in the centre of the scale's platform bare-footed with their weight distributed evenly to both feet. Two measurements were made to the nearest 0.1 kg and the average estimated.

3.6.2.2.3 Height measurement

The height of study participants was measured using a wall mounted Seca® 213 stadiometer (Seca, Hamburg, Germany). Study participants were asked to remove their footwear and cap and made to stand upright with their back to the height rule and head in a Frankfurt horizontal plane. Readings were made in a position to avoid parallax error. Two measurements were made to the nearest 0.1cm and the average estimated.

3.6.2.2.4 Waist circumference measurement

The waist circumferences of study participants were measured using an inelastic but flexible 203 cm Seca® standard tape measure (Seca, Hamburg, Germany). Study participants were made to stand with their feet close together and their weight equally distributed to each leg. Measurements were done at a level midway between the lower rib margin and iliac crest with the tape all around the body in horizontal position. Two measurements were made to the nearest 0.1cm.and the average estimated.

3.6.2.2.5 Hip circumference measurement

Hip circumference of study participants was measured with a 203 cm Seca® standard tape measure (Seca, Hamburg, Germany). Study participants were made to stand with their feet close together and their weight equally distributed to each leg and hip circumference measured as the maximal circumference over the buttocks. Two measurements were made to the nearest 0.1cm and the average estimated.

3.6.2.2.6 Sample collection and preparation for biochemical measurements

After an overnight fast (minimum of 12 hours), 7 mL of blood was drawn from the median cubital vein on the anterior forearm of each study participant and aliquot into plain tube, fluoride oxalate tube and gel separator tube (BD Vacutainer®). Blood samples in the plain tube were gently mixed for 5 minutes and analysed for CD4+ T-cell count. Blood samples in the fluoride oxalate tubes were gently mixed for 5 minutes and centrifuged at 2500g for 10 minutes at room temperature. The plasma was separated and analysed for fasting plasma glucose. Blood samples in the gel separator tubes were allowed to clot for 30 minutes and then centrifuged at 2500g for 10 minutes, at room temperature. The serum was then separated and analysed for creatinine concentration, total cholesterol concentration, HDL-cholesterol concentration and triglycerides concentration.

3.6.2.2.7 CD4+ T-cell count

CD4+ T-cell count was determined by flow cytometry using anti-CD4, anti-CD14 and anti-CD15 monoclonal antibodies with the Becton Dickinson FACSCount® analyser (BD Biosciences, San Jose, CA 95131, USA) following the manufacturer's protocol.

CD4+ T-cell count was determined with BD FACSCountTM CD4/CD3 reagent kits (BD Bioscience, San Jose, USA), using BD FACSCount System analyzer (BECTON

DICKINSON, USA). The FACSCount® system is a single-platform instrument designed specifically for enumerating absolute CD4+ T-cell count in no-lyse, no-wash whole blood. The flow cytometry assay works on the principle of scattering of light due to different sizes, granularity of the cells passing through the laser beam, and also by the fluorescence emitted by the cells after staining with the specific monoclonal antibodies to cell surface markers that are tagged with fluorescence dyes. A volume of 20 μL of MultiTEST CD3/CD8/CD45/CD4 reconstituted working reagent was added to 50 μL whole blood, mixed and incubated for 15 minutes at room temperature. FACS lysing solution (450 uL) was then added, mixed gently, incubated at room temperature and then readings made with the auto analyser.

3.6.2.2.8 Fasting plasma glucose

Fasting plasma glucose concentration was determined by the glucose oxidase-peroxidase colorimetric method (GOD-POD) using Randox RX Monza® chemistry auto analyser (Randox laboratories Ltd.). A volume of 50 μL of plasma was pipetted into the sample well and assayed for glucose concentration. The principle behind the method involves the oxidation of glucose to gluconate and hydrogen peroxide (H_2O_2) by glucose oxidase (GOD). The H_2O_2 produced is then coupled with phenol and 4-aminoantipyrine (4-AP) in the presence of peroxidase (POD) to yield the coloured complex quinoneimine, which is measured at 505 nm. The intensity of the coloured complex formed is directly proportional to the concentration of glucose in the sample.

$$\beta\text{-D-Glucose} + O_2 + H_2O \xrightarrow{\text{Glucose oxidase}} \text{Gluconate} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4H_2O$$

3.6.2.2.9 Total cholesterol

Serum concentration of total cholesterol was measured by the enzymatic endpoint method using Randox RX Monza® chemistry auto analyser (Randox laboratories Ltd.). A volume of 50 µL of serum was pipetted into the sample well and assayed for total cholesterol concentration. The enzymatic endpoint method involves the conversion of esterified cholesterol to cholesterol by the enzyme, cholesterol ester hydrolase. The resulting cholesterol is then acted upon cholesterol oxidase to yield cholest-4-en-3-one and H_2O_2. The H_2O_2 produced is then coupled with 4-aminoantipyrine (4-AP) in the presence of peroxidase (POD) to yield the coloured complex quinoneimine, which is measured at 505 nm. The intensity of the coloured complex formed is directly proportional to the concentration of total cholesterol in the sample.

$$\text{Cholesteryl ester} + H_2O \xrightarrow{\text{Cholesterol ester hydrolase}} \text{Cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{Cholesterol oxidase}} \text{Cholest-4-en-3-one} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4H_2O$$

3.6.2.2.10 High-density lipoprotein cholesterol

High-density lipoprotein cholesterol was measured by the direct enzymatic colorimetric method using Randox RX Monza® chemistry auto analyser (Randox laboratories Ltd.). A volume of 50 µL of serum was pipetted into the sample well and assayed for high-density lipoprotein cholesterol concentration. The principle behind the method involves the reaction of apoB containing lipoprotein in the sample with a blocking agent, a detergent. This renders them non-reactive and thus the non-HDL lipoprotein LDL, very low density lipoprotein and chylomicrons are inhibited from reacting with the enzymatic cholesterol reagent. This ensures HDL-cholesterol alone is measured in the reaction assay. The enzymatic endpoint method involves the conversion of esterified

HDL-cholesterol to unesterified HDL-cholesterol by the enzyme PEG cholesterol esterase. The resulting unesterified HDL-cholesterol is acted upon cholesterol oxidase to yield cholestone and H_2O_2. The H_2O_2 produced is then coupled with 4-aminoantipyrine (4-AP) in the presence of peroxidase (POD) to yield the coloured complex quinoneimine, which is measured at 600 nm. The intensity of the coloured complex formed is directly proportional to the concentration of total cholesterol in the sample.

$$\text{HDL-cholesteryl ester} + H_2O \xrightarrow{\text{PEG Cholesterol esterase}} \text{HDL-unesterified cholesterol} + \text{fatty acid}$$

$$\text{Unesterified cholesterol} + O_2 \text{ PEG} \xrightarrow{\text{Cholesterol oxidase}} \text{Cholestone} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4H_2O$$

3.6.2.2.11 Triglycerides

Triglycerides concentration was measured by the GPO-PAP method using Randox RX Monza® chemistry auto analyser (Randox laboratories Ltd.). A volume of 50 µL of serum was pipetted into the sample well and assayed for triglycerides concentration. Triglycerides concentration was determined after enzymatic hydrolysis with lipases to yield glycerol and fatty acids. The glycerol is phosphorylated to glycerol-3-phospahte by coupled reaction with adenosine triphosphate (ATP) (converted to adenosine diphosphate-ADP) catalysed by glycerol kinase. Glycerol-3-phosphate is then oxygenated to dihydroxyacetone phosphate and H_2O_2 by the enzyme glycerol-3-phosphate oxidase. The H_2O_2 produced is then coupled with 4-aminoantipyrine (4-AP) and 4-chlorophenol in the presence of peroxidase (POD) to yield the coloured complex quinoneimine, which is measured at 505 nm. The intensity of the coloured complex formed is directly proportional to the concentration of total triglycerides in the sample.

$$\text{Triglycerides} + H_2O \xrightarrow{\text{Lipase}} \text{Glycerol} + \text{fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerol kinase}} \text{Glycerol -3-phosphate} + \text{ADP}$$

$$\text{Glycerol -3-phosphate} + O_2 \xrightarrow{\text{Glycerol-3-phosphate oxidase}} \text{Dihydroxyacetone phosphate} + H_2O_2$$

$$2H_2O_2 + \text{4-chlorophenol} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4H_2O + HCl$$

3.6.2.2.12 Low-density lipoprotein cholesterol

LDL-C serum concentration was calculated using the Friedewald equation as follows: [LDL-C] = [Total Cholesterol]-[HDL-C] - ([Triglycerides]/2.2) where all concentrations are in mmol/L (Friedewald et al., 1972).

3.6.2.2.13 Creatinine

Serum creatinine concentration was measured by the enzymatic method using Randox RX Monza® chemistry auto analyser (Randox laboratories Ltd.). A volume of 50 µL of serum was pipetted into the sample well and assayed for creatinine concentration. Creatinine is converted to creatine by the enzyme creatininase. Creatine is then converted to sarcosine by creatine amidinohydrolase (creatinase). The sarcosine formed is then oxidised to produce H_2O_2, which is coupled with 4-aminoantipyrine (4-AP) and N-Ethyl-N-(2-Hydroxy-3-sulfopropyl)m-toluidine (TOOS) in the presence of peroxidase (POD) to yield the coloured complex quinoneimine. The coloured complex is measured at 550 nm and the intensity of it is directly proportional to the concentration of creatinine in the sample.

$$\text{Creatinine} + H_2O \xrightarrow{\text{Creatininase}} \text{Creatine}$$

$$\text{Creatine} + H_2O \xrightarrow{\text{Creatinase}} \text{Sarcosine} + \text{Urea}$$

$$\text{Sarcosine} + O_2 \xrightarrow{\text{Sarcosine oxidase}} \text{Glycine} + \text{HCHO} + H_2O_2$$

$$2H_2O_2 + \text{TOOS} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4H_2O$$

3.6.2.3 HIV/ART-related and other data extracted from clinical folders

ART/HIV-related data were extracted from patients' folders with the assistance of a trained in-house pharmacist. Data extracted included blood pressure measurements at enrolment into HIV clinic or at initiation of ART (baseline systolic and diastolic blood pressures) and body mass index at enrolment into HIV clinic or at initiation of ART (baseline BMI). Others were duration of HIV infection, type of HIV infection and WHO HIV stage at diagnosis, date of ART initiation, ARVs administered and duration, presence of co-morbidities, current administration of antihypertensive treatment, CD4+ T-cell count at HIV diagnosis or at enrolment initiation of ART (baseline CD4 T-cell count) and Nadir CD4+ T-cell count.

Medication adherence level of patients on ART was obtained from the pharmacy records comparing the appointed dates for ART refill and the actual reporting dates of refill. The sum of default days as a proportion of days covered (PDC) was calculated and used as a marker of level of medication adherence (Ankrah et al., 2015).

3.6.3 Quality control

A one-day training session was held with all study personnel on data collection with emphasis on data quality and strict accountability system. A pre-test of the study questionnaire was done with 20 volunteers at the diabetes clinic of the KBTH and all challenges with the wording of specific questions addressed appropriately. A database was developed in Microsoft Access® and was used to double-check all logic discrepancies to validate the data. All laboratory analyses were conducted to follow standard operating procedures and all equipment calibrated according to manufacturers' specification. Daily controls were run during laboratory assay of study participants' blood samples.

3.7 Data management and statistical analysis

3.7.1 Data management

Data were double entered into Microsoft Access® database. Standardized queries were used to conduct range and logic checks, and discrepant entries were rectified after a review of collected data. Data management techniques used involved sorting, merging, appending and data reorganization to suit the statistical routines used. After double data entry, comparison of the two datasets was done and tagging, or dropping duplicate observation effected. String variables were encoded into numeric and vice versa. Verification of truth of claim was done between information obtained from questionnaire and institutional database. In addition, required data was converted from wide to long form and vice versa and categorical variables recoded as needed.

3.7.2 Statistical analysis

Stata® 14 software was used to analyse the data. Continuous variables were reported as mean ± SD or median with interquartile range if not normally distributed. Continuous variables were modelled in class or after log transformation. Categorical variables were reported as percentages and proportions and were compared using Pearson chi-square statistics. The statistical analyses conducted in this study were in four parts:

1. Descriptive analysis to determine the prevalence of hypertension in entire study participants and in different sub-groups
2. Propensity score-matching analysis to estimate average treatment effect (on the treated) of ART exposure on hypertension and blood pressure values

3. Logistic regression modelling to determine factors associated with hypertension in study participants

4. Analysis to estimate risk of cardiovascular disease in study participants using the 10-year general Framingham cardiovascular risk score, the 5-year D:A:D cardiovascular risk score and the 10-year WHO/ISH risk prediction chart

3.7.2.1 Descriptive analyses to determine prevalence of hypertension

Variables used in estimating prevalence of hypertension in entire study participants and in sub-groups were; current hypertension status, age, sex and ART-exposure. Prevalence of hypertension was calculated for entire study population and sub-groups of age (<40 years and ≥40 years), sex (male and females) and ART exposure (ART-naive and ART-exposed). The z-test of proportionality was used to test for homogeneity of proportion of hypertensive subjects across the sub-groups of age, sex and ART exposure.

3.7.2.2 Logistic regression modelling to determine factors associated with hypertension

The variables used in determining factors associated with hypertension in the regression analysis were current hypertension status (outcome variable), ART-exposure (main exposure variable), age, sex, religion, employment status, marital status, educational level, family history of hypertension/CVD, smoking status, alcohol, physical activity and fruit intake. Other covariates were HIV infection duration, duration of ART administration, HIV-type, presence of co-morbidity, current BMI, abdominal obesity, fasting plasma glucose, total cholesterol level, HDL-C level, LDL-C level, triglycerides level, eGFR, current CD4+ T cell count and nadir CD4+ T-cell count.

A logistic regression analysis was carried out to determine the factors associated with hypertension. The preliminary univariate analysis was designed to determine the associated factors as grouped under socio-demographic and life-style factors, anthropometric and metabolic/biochemical factors and HIV/ART-related factors. Thereafter, a multiple logistic regression model was generated using the ***purposeful selection of covariates method*** (Hosmer and Lemeshow, 2000; Bursac et al., 2008). The purposeful selection of variables (deleting, refitting, and verifying) was done as follows (Bursac et al., 2008):

1. A preliminary univariate analysis was done in and all variables found to be associated with the outcome at a p-value of <0.20 were selected to be part of the initial multiple regression analysis.
2. An initial multiple logistic regression analysis was then run with selected variables from the univariate analysis
3. This was followed by an iterative process of purposeful removal of covariates in the multiple regression analysis based on their non-significance at p>0.1
4. Confounders were then purposefully removed from the remaining list of variables if they did not change parameter estimate by at least 15%
5. At the end of these iterative processes, only significant covariates and confounders were in the multiple regression model.
6. The multiple regression analysis model (containing the significant covariates and confounders) was then run again to include one at a time all variables initially not included in the iterative process (deleted during the univariate analysis because they were non-significant at p>0.20). Significance of these re-entered variables was tested as covariates and as

confounders as previously done in 3 and 4 above, but this time on only the re-entered variables.

7. At the end of this final step, the multiple logistic regression analysis contains preliminary main effects model.

The performance of the final model was assessed on "calibration" using the Hosmer-Lemeshow goodness-of-fit test statistic. This was used to test the level of agreement between predicted probabilities and the 'true probabilities' using the mean of the observed outcomes within predefined groups of study participants (Hosmer and Lemeshow, 2000). This is done after the observations has been sorted (according to their expected probability) and partitioned into 10 groups of equal sizes. The C-goodness-of-fit statistic gives a large "H" value with a corresponding small (Hosmer-Lemeshow χ^2) *p*-value if there is a significant difference between the observed outcome and the predicted outcome and this indicates evidence of lack of fit of the variables involved in the final model.

The performance of the final model was also assessed on discrimination using the Receiver Operating Characteristics (ROC) area under the curve (AUC). This was used to verify whether a set of predictor variables in the final model were able to distinguish hypertension from non-hypertension and the AUC refers to the probability that a hypertensive person has a higher predicted probability than those who were non-hypertensive using the variables involved in the final model. The discrimination of the variables was considered; perfect if AUC=1.00, good if AUC is 0.81-0.99, moderate if AUC is 0.60-0.80 and poor if AUC < 0.6 (Dodoo et al., 2009).

3.7.2.3 Propensity score-matching analysis to estimate average treatment effect of ART on hypertension and blood pressure values

Variables used in estimating ATT of ART on hypertension were; current hypertension status (outcome variable) and ART exposure (treatment variable). The covariates used were age, sex, religion, employment status, marital status, educational level, family history of hypertension/CVD, smoking status, alcohol intake, baseline BMI, physical activity, fruit intake, HIV infection duration, HIV-type, baseline sBP, baseline dBP, baseline CD4 T-cell count, administration of antihypertensive medication and presence of co-morbidity. A logistic regression was used (with ART exposure as the outcome variable and covariates/confounders as exploratory variables) to estimate a propensity score for each study participant. The balance of the estimated propensity scores across the treatment group (ART-exposed) and the comparison group (ART-naive) for common support was checked visually by a box plot and objectively by Student's t-test. Balance of covariates across treatment group and comparison group was checked using a standardised difference of not more than 10%. This iterative process was repeated several times (deleting, re-categorisation and inclusion of interaction terms of covariates) until the estimated propensity scores were balanced across treatment and comparison groups and the entered covariates also balanced across treatment and comparison groups within blocks of the estimated propensity scores.

The average treatment effect on the treated was estimated using the kernel matching or weighting strategy with a bandwidth of 0.06. Thereafter, standard errors were bootstrapped with 150 replications. The balance of covariates after the kernel weighting strategy were checked by comparing the standardised differences before and after matching/weighting (achieving <10% standardised difference), evaluation of ratio of variances (between 0.5 and 2.0) and graphically using a dot graph. Post-estimation analysis for the extent of influence of unobserved covariates (sensitivity test) was done using Rosenbaum bounds (the *rbounds* syntax in Stata®).

3.7.2.4 Analysis to estimate cardiovascular disease risk scores

The variables used in estimating the cardiovascular risk scores were age, sex, current systolic blood pressure, FPG level/diagnosis of diabetes, total cholesterol level HDL-C level, smoking status, family history of CVD, duration on indinavir, duration on lopinavir and administration of abacavir. Analysis of data was done to estimate the 10-year general Framingham cardiovascular risk score (FRS), the 5-year D:A:D cardiovascular risk score and the 10-year WHO/ISH cardiovascular risk prediction score of study participants. The FRSs were classified as low risk (<10%), moderate risk (10% to <20%) and high risk (≥ 20%) (Genest et al., 2009; Anderson et al., 2013). The D:A:D CVD risk scores were classified as low risk (<1%), moderate risk (1% to <5%) and high/very high risk (≥5%) (Friis-Moller et al., 2016). The WHO/ISH cardiovascular risk prediction scores were classified as low risk (<10%), moderate risk (10% to <20%) and high risk (≥20%). Comparisons of the cardiovascular risk scoring systems were determined using Cohen's Kappa coefficient (K) with 95% confidence interval. Kappa was interpreted as perfect agreement (>0.80), substantial agreement (0.61-0.80), moderate agreement (0.41-0.60), fair agreement (0.21-0.40) and poor agreement (≤0.20) (Edward et al., 2013; Mashinya et al., 2015). For the comparison of the D:A:D 5-year score with the FRS and the WHO/ISH scores, it was assumed that the 5-year D:A:D prediction was constant over a 10 year period.

3.8 Ethical consideration

3.8.1 Ethical clearance from Institutional Review Board

The proposal was submitted to the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana and was given ethical clearance [Protocol Identification Number: MS-Et/M.3-P 4.4/2015-2016] (Appendix IV).

3.8.2 Consent from HIV clinic

Permission was obtained from the clinician-in-charge of the Fevers Unit at the KBTH giving assurance of data protection and anonymity of patients' medical records.

3.8.3 Informed consent from study participants

Informed consent was sought and obtained from each individual study participant informing him/her on the aim and purpose of the study, risks and benefits of participating in the study (Appendix II and III).

3.8.4 Data safety

Patients' data were de-identified during data capture, entry, analysis and storage by ensuring only the study codes were used consistently throughout the project cycle. Research assistants and laboratory personnel for data collection were staff of the HIV Clinic. Apart from the research team and the HIV Clinic staff, data were not accessible to any other person. Each study participant's results were relayed to the attending physician for appropriate care and health education.

CHAPTER FOUR

4.0 RESULTS

4.1 Description of study participants

4.1.1 Socio-demographic and life-style characteristics of study participants

A total of 311 PLHIV were recruited as study participants. This was made up of 76.2% females (Table 12). Most of the study participants were 40 years and above (73.0%, n=227) (Table 12). Majority of the study participants do not smoke tobacco (95.8%, n=298) or drink alcohol (68.5%, n=213) (Table 12). Presence of hypertension or other cardiovascular disease in first-degree family members (parents/siblings) was absent in over eighty percent of the study participants (Table 12).

Table 12. Socio-demographic and life-style characteristics of study participants

Characteristics		**Frequency N=311 n (%)**
Age, median (Interquartile range) (years)		44.0 (39.0-51.0)
Age group		
	<40 years	84 (27.0)
	≥40 years	227 (73.0)
Sex		
	Female	237 (76.2)
	Male	74 (23.8)
Highest educational level attained		
	None	44 (14.2)
	Basic	163 (52.4)
	Secondary	95 (30.5)
	Tertiary/Professional	9 (2.9)
Marital status		
	Single	57 (18.3)
	Married/Co-habiting	134 (43.1)
	Widowed/Divorced/Separated	120 (38.6)
Employment status		
	Unemployed	38 (12.2)
	Employed	273 (87.8)
Family history of hypertension/cardiovascular disease		
	Present	39 (12.5)
	Absent	272 (87.5)
Tobacco smoking status		
	Ever smoker	13 (4.2)
	Never smoker	298 (95.8)
Alcohol drinking status		
	Ever drinker	98 (31.5)
	Abstainer	213 (68.5)
Fruit intake		
	Rare/Never	99 (31.8)
	Most at times	212 (68.2)
Engagement in physical activity/exercising		
	Rare/Never	216 (69.5)
	Most at times	95 (30.5)

IQR=Interquartile range; N=Total number of study participants; n=Number of respondents per characteristic

4.1.2 Blood pressure levels, anthropometric and biochemical indices of study participants

A total of 114 study participants (36.7%) were hypertensive with their median current systolic and diastolic blood pressure values being 148.5 mmHg (IQR, 142.0-163.0) and 95.0 mmHg (IQR, 90.0-101.3) respectively (Table 13). The median of their baseline systolic and diastolic blood pressure values were 132.0 mmHg (IQR, 125.8-137.0) and 81.0 mmHg (IQR, 75.0-86.3) respectively. Ten percent (10%) of the study participants had elevated fasting plasma glucose of ≥7.00 mmol/L, whilst 15.4% had reduced estimated glomerular filtration rate of <60 min/mL/1.73m^2 (Table 13).

Table 13. Blood pressure levels, anthropometric and biochemical indices of study participants

Characteristics		**Frequency N=311 n (%)**
Current systolic blood pressure (sBP), median (IQR), mmHg		130 (113-144)
Current diastolic blood pressure (dBP), median (IQR), mmHg		80 (70-91)
Current blood pressure category		
	Non-hypertensive	197 (63.3)
	Hypertensive	114 (36.7)
Current body mass index		
	<25.0 (kg/m^2)	189 (60.8)
	≥25.0 (kg/m^2)	122 (39.2)
Abdominal obesity (Waist-to-hip ratio)		
	Absent (WHR <0.85 for women; WHR <0.90 for men)	196 (63.0)
	Present (WHR ≥0.85 for women; WHR ≥0.90 for men)	115 (37.0)
Abdominal obesity (Waist circumference)		
	Absent (WC ≤88 for women; WC ≤102 for men)	254 (81.7)
	Present (WC >88 for women; WC >102 for men)	57 (18.3)
Fasting plasma glucose		
	Normal FPG (FPG <7.0 mmol/L)	280 (90.0)
	Elevated FPG (FPG ≥7.0 mmol/L)	31 (10.0)
Total cholesterol		
	Normal total cholesterol (TC <5.17 mmol/L)	148 (47.6)
	Hypercholesterolemia (TC ≥5.17 mmol/L)	163 (52.4)
High-density lipoprotein cholesterol		
	Normal (HDL-C ≥1.03 mmol/L)	280 (90.0)
	Abnormal (HDL-C <1.03 mmol/L)	31 (10.0)
Low-density lipoprotein cholesterol		
	Normal (LDL-C <3.36 mmol/L)	195 (62.7)
	Elevated (LDL-C ≥3.36 mmol/L)	116 (37.3)
Triglycerides		
	Normal (TG <2.26 mmol/L)	300 (96.5)
	Elevated (TG ≥2.26 mmol/L)	11 (3.5)
Estimated glomerular filtration rate		
	Normal eGFR (eGFR ≥60 min/mL/1.73 m^2)	263 (84.6)
	Reduced eGFR (eGFR <60 min/mL/1.73 m^2)	48 (15.4)

dBP=Diastolic blood pressure; eGFR=Estimated glomerular filtration rate; FPG=Fasting plasma glucose; HDL-C=High-density lipoprotein cholesterol; IQR=Interquartile range; LDL-C=Low-density lipoprotein cholesterol; N=Total number of study participants; n=Number of respondents per characteristic; sBP=Systolic blood pressure; TC=Total cholesterol; TG=Triglycerides; WC=Waist circumference; WHR=Waist-to-hip ratio

4.1.3 HIV/ART related characteristics of study participants

Most of the study participants (73.6%) had current CD4+ T-cell count of >350 cells/μL (Table 14). The median duration of HIV-infection for the study participants was 7.9 years and the median duration of ART administration (for ART-exposed group) was 6.8 years. Majority of the study participants were on ART (81.0%) of which the administration of either AZT/3TC/NVP or AZT/3TC/EFV constitutes over fifty percent (Table 14).

Table 14. HIV/ART-related characteristics of study participants.

Characteristics		**Frequency N=311 n (%)**
Baseline CD4+ T-cell count		
	≤350 cells/µL	176 (56.6)
	>350 cells/µL	135 (43.4)
Current CD4+ T-cell count		
	≤350 cells/µL	82 (26.4)
	>350 cells/µL	229 (73.6)
Nadir CD4+ T-cell count		
	≤350 cells/µL	220 (70.7)
	>350 cells/µL	91(29.3)
Duration since HIV-positive diagnosis, median (IQR) (years)		7.9 (4.5-10.6)
HIV-type		
	Type I only	228 (73.3)
	Type II only	7 (2.3)
	Mixed (Type I and II)	76 (24.4)
Presence of co-morbidities (excluding hypertension)		
	Absent	243 (78.1)
	Present	68 (21.9)
ART exposure status		
	ART-naive	59 (19.0)
	ART-exposed	252 (81.0)
ARV composition of ART administered (N=252)		
	TDF/FTC/EFV	8 (3.2)
	TDF/3TC/NVP	13 (5.2)
	TDF/3TC/EFV	57 (22.6)
	TDF/3TC/LPV-r	32 (12.7)
	TDF/3TC/ATV-r	3 (1.2)
	AZT/3TC/NVP	58 (23.0)
	AZT/3TC/EFV	81 (32.1)
Cumulative exposure to ART, median (IQR) (years) (N=252)		6.8 (5.9-7.5)

3TC=Lamivudine; ARV=Anti-retrovirals; ATV-r=Ritonavir boosted atazanavir; AZT=Zidovudine; EFV=Efavirenz; FTC=Emtricitabine; ART=Antiretroviral Therapy; IQR=Interquartile range; LPV-r=Ritonavir boosted lopinavir; N=Total number of study participants; n=Number of respondents per characteristic; NNRTI=Non-nucleoside reverse transcriptase inhibitor; NVP=Nevirapine; PI=Protease inhibitor; TDF=Tenofovir; WHO=World Health Organisation

4.2 Prevalence of hypertension in study participants

The overall prevalence of hypertension in the 311 study participants was 36.7% (95% CI, 31.3-42.3) (Table 15). The prevalence of hypertension in study participants aged ≥40 years (40.5%, [95% CI, 34.1-46.9]) was significantly higher compared with the prevalence in study participants aged <40 years (26.2%, [95% CI, 16.8-35.6]). The prevalence of hypertension in ART-exposed study participants (41.3% [95% CI, 35.2-47.3]) was significantly higher compared with the ART-naive study participants (16.9%, [95% CI, 7.4-26.5]) (p<0.001) (Table 15). There was no statistical difference in the prevalence of hypertension between male and female study participants.

Table 15. Prevalence of hypertension in study participants

Group		Total number (N)	Number of hypertensives (n)	Prevalence [95% CI]	p-value
All study participants		311	114	36.7 [31.3-42.3]	-
Age group					
	<40 years	84	22	26.2 [16.8-35.6]	0.020
	≥40 years	227	92	40.5 [34.1-46.9]	
Sex					
	Male	74	30	40.5 [29.4-51.7]	0.427
	Female	237	84	35.4 [29.4-41.5]	
ART exposure					
	ART-naive	59	10	16.9 [7.4-26.5]	<0.001
	ART-exposed	252	104	41.3 [35.2-47.3]	

CI=Confidence interval; ART= Anti-retroviral Therapy

4.3 Logistic regression modelling of factors associated with hypertension in study participants

4.3.1 Univariate analysis of factors associated with hypertension

Analysis of Table 16 indicates that the median age of study participants who were hypertensive (49.0 years; IQR, 40.8-57.0) was significantly higher than that for the non-hypertensive (42.0 years; IQR, 37.0-48.0). Exercising, employment status and presence of family history of cardiovascular disease were associated with hypertension in the univariate analysis (Table 16). Table 17 shows that current body mass index of ≥25.0 kg/m^2 and abdominal obesity (waist circumference) were both associated with increased odds of hypertension in the univariate analysis. Of the biochemical indices measured, elevated levels of total cholesterol and LDL-cholesterol and reduced levels of estimated glomerular filtration rate were associated with hypertension in the univariate analysis (Table 17). HIV/ART-related factors associated with hypertension in the univariate analysis were exposure to ART, duration of both HIV infection and ART exposure (Table 18).

Table 16. Univariate analysis of socio-demographic and life-style factors associated with hypertension in study participants.

		Blood pressure status			
		Hypertensive (N=114) n (%)	Non-hypertensive (N=197) n (%)	Crude odds ratio [95% CI]	p-value
Age (years), median (Interquartile range)		49.0 [40.8-57.0]	42.0 [37.0-48.0]	1.07 [1.06-1.10]	<0.001
Sex	Male	30 (26.3)	44 (22.3)	1.24 [0.73-2.12]	0.427
	Female	84 (73.7)	153 (77.7)	1.00	
Educational level	Tertiary/Professional	4 (3.5)	5 (2.5)	0.96 [0.23-4.06]	0.956
	Secondary	31 (27.2)	64 (32.5)	0.58 [0.28-1.21]	0.146
	Basic/Primary	59 (51.8)	104 (52.8)	0.68 [0.35-1.34]	0.263
	None	20 (17.5)	24 (12.2)	1.00	
Religion	Moslem	16 (14.0)	19 (9.6)	1.53 [0.75-3.11]	0.240
	Christianity	98 (86.0)	178 (90.4)	1.00	
Marital status	Single	21 (18.4)	36 (18.3)	1.12 [0.59-2.13]	0.739
	Widowed/Divorced/Separated	47 (41.2)	73 (37.1)	1.23 [0.74-2.05]	0.424
	Married/Co-habiting	46 (40.4)	88 (44.7)	1.00	
Employment status	Unemployed	20 (17.5)	18 (9.4)	2.12 [1.07-4.19]	0.032
	Employed	94 (82.5)	179 (90.9)	1.00	
Smoking status	Ever smoker	5 (4.4)	8 (4.1)	1.08 [0.35-3.40]	0.890
	Never-smoker	109 (95.6)	189 (95.9)	1.00	
Alcohol consumption	Drinker	37 (32.5)	61 (31.0)	1.07 [0.65-1.76]	0.785
	Abstainer	77 (67.5)	136 (69.0)	1.00	
Family history of CVD	Present	21 (18.4)	18 (9.1)	2.25 [1.14-4.42]	0.019
	Absent	93 (81.6)	179 (90.9)	1.00	
Fruit intake	Rare/Never	79 (31.4)	20 (33.9)	0.89 [0.49-1.62]	0.705
	Most at times	173 (68.7)	39 (66.1)	1.00	
Exercising	Rare/Never	88 (77.2)	128 (65.0)	1.82 [1.08-3.09]	0.025
	Most at times	26 (22.8)	69 (35.0)	1.00	

CI=Confidence interval; CVD=cardiovascular disease

Table 17. Univariate analysis of anthropometric and metabolic/biochemical factors associated with hypertension in study participants

Characteristic		Blood pressure status: Hypertensive (N=114) n (%)	Blood pressure status: Non-hypertensive (N=197) n (%)	Crude odds ratio [95% CI]	p-value
Current body mass index	≥25.0 kg/m^2	67 (58.8)	88 (44.7)	1.77 [1.12-2.82]	0.017
	<25.0 kg/m^2	47 (41.2)	109 (55.3)	1.00	
Abdominal obesity (WHR)	Present	44 (38.6)	71 (36.0)	1.12 [0.69-1.80]	0.653
	Absent	70 (61.4)	126 (64.0)	1.00	
Abdominal obesity (WC)	Present	26 (22.8)	31 (15.7)	1.58 [0.88-2.83]	0.122
	Absent	88 (77.2)	166 (84.3)	1.00	
Fasting plasma glucose	Elevated	13 (11.4)	18 (9.1)	1.28 [0.60-2.72]	0.521
	Normal	101 (88.6)	179 (90.9)	1.00	
Total Cholesterol	Hypercholesterolemia	72 (63.2)	91 (46.2)	2.00 [1.24-3.20]	0.004
	Normal total cholesterol	42 (36.8)	106 (53.8)	1.00	
HDL-cholesterol	Abnormal	10 (8.8)	21 (10.7)	0.81 [0.37-1.78]	0.593
	Normal	104 (91.2)	176 (89.3)	1.00	
LDL-cholesterol	Elevated	51 (44.7)	65 (33.0)	1.64 [1.02-2.64]	0.040
	Normal	63 (55.3)	132 (67.0)	1.00	
Triglycerides	Elevated	5 (4.4)	6 (3.1)	1.46 [0.44-4.90]	0.540
	Normal	109 (95.6)	191 (96.9)	1.00	
Estimated glomerular filtration rate	Reduced	26 (22.8)	22 (11.2)	2.35 [1.26-4.38]	0.007
	Normal	88 (77.2)	175 (88.8)	1.00	

CI=Confidence interval; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; WC=Waist circumference; WHR=Waist-to-hip ratio

Table 18. Univariate analysis of HIV/ART-related factors associated with hypertension in study participants

Characteristic		**Blood pressure status**		**Crude odds ratio**	
		Hypertensive (N=114) n (%)	Non-hypertensive (N=197) n (%)	**[95% CI]**	**p-value**
HIV sub-type	HIV-II only	1 (0.9)	6 (3.1)	0.31 [0.04-2.61]	0.280
	Mixed (Type I and II)	33 (28.9)	43 (21.8)	1.42 [0.84-2.41]	0.294
	HIV-I only	80 (70.2)	148 (75.1)	1.00	
Nadir CD4+ T-cell count	<350 cells/μL	82 (71.9)	138 (70.1)	1.10 [0.66-1.82]	0.726
	≥350 cells/μL	32 (28.1)	59 (29.9)	1.00	
Current CD4+ T-cell count	<350 cells/μL	32 (28.1)	50 (25.4)	1.15 [0.68-1.93]	0.604
	≥350 cells/μL	82 (71.9)	147 (74.6)	1.00	
ART exposure	ART-exposed	104 (91.2)	148 (75.1)	3.44 [1.67-7.11]	0.001
	ART-naive	10 (8.8)	49 (24.9)	1.00	
Duration of HIV infection (years), median (IQR)		9.3 [5.7-11.4]	7.0 [4.1-10.2]	1.11 [1.04-1.18]	0.002
Duration of ART administration (years), median (IQR)		7.0 [3.4-10.0]	4.3 [0.0-8.1]	1.14 [1.08-1.21]	<0.001
Presence of co-morbidities	Present	27 (23.7)	41 (20.8)	1.18 [0.68-2.05]	0.555
	Absent	87 (76.3)	156 (79.2)	1.00	

CI= Confidence interval; ART=Highly Active Anti-retroviral Therapy; IQR=Interquartile range

4.3.2 Multiple logistic regression analysis of factors associated with hypertension

Table 19 shows result of the multiple logistic regression of factors associated with hypertension using a purposeful selection of variables method. Among the socio-demographic and life-style factors studied, age, positive family history of cardiovascular disease and exercising were significantly associated with hypertension (Table 19). Current body mass index of ≥25.0 kg/m^2 and abdominal obesity due to high waist circumference were also significantly associated with hypertension. Presence of hypercholesterolemia was significantly associated with hypertension but not elevated levels of LDL-cholesterol (Table 19). Among the HIV/ART-related factors examined, ART exposure and duration of ART administration were associated with hypertension. Study participants who were ART-exposed had increased odds of hypertension compared with those who were ART-naive (aOR=5.84 [95% CI, 2.23-15.31]; p<0.001) and the odds of hypertension increases by 15% (95% CI, 1.09-1.22; p=001) for every one-year increase in ART administration (Table 19).

Table 19. Multiple logistic regression analysis of factors associated with hypertension

Characteristic		**Adjusted odds ratio [95% CI]**	**p-value**
Age (years)		1.10 [1.06-1.14]	**<0.001**
Family history of hypertension/CVD			
	Present	2.23 [1.02-4.86]	**0.045**
	Absent	1.00	
Exercising			
	Rare/Never	1.94 [1.06-3.55]	**0.032**
	Most at times	1.00	
Current body mass index			
	$\geq$25.0 kg/m^2	2.18 [1.24-3.83]	**0.007**
	<25.0 kg/m^2	1.00	
Abdominal obesity (waist circumference)			
	Present	2.15 [1.08-4.27]	**0.029**
	Absent	1.00	
Total cholesterol			
	Hypercholesterolemia	2.86 [1.30-6.28]	**0.009**
	Normal total cholesterol	1.00	
LDL-cholesterol			
	Elevated	0.69 [0.32-1.53]	0.365
	Normal	1.00	
ART exposure			
	ART-exposed	5.84 [2.23-15.31]	**<0.001**
	ART-naive	1.00	
Nadir CD4+ T-cell count			
	$\leq$350 cells/µL	0.51 [0.25-1.04]	0.064
	>350 cells/µL	1.00	
Duration of ART administration (years)		1.15 [1.09-1.22]	**0.001**
Duration of HIV infection (years)		1.05 [0.97-1.13]	0.194

CI=Confidence interval; CVD=cardiovascular disease; ART= Anti-retroviral Therapy; LDL=Low-density lipoprotein

Post-estimation analysis indicated that the generated logistic model was "good" on "discrimination" with an area under the receiver operating characteristics curve of 0.81 (95% CI, 0.75-0.85; p<0.001) (Figure 5). In terms of "calibration", the generated model gave a Hosmer-Lemeshow goodness-of-fit test χ^2 value of 4.49 (p=0.810) indicating no evidence of lack of goodness of fit between the predicted probabilities and the "true" probabilities.

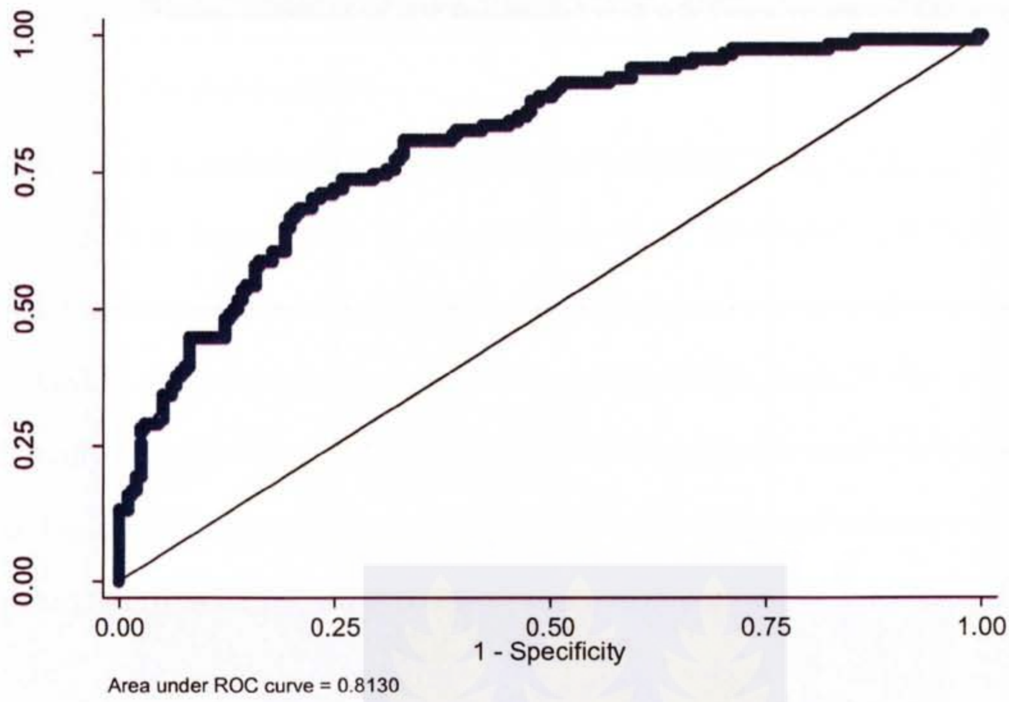

Figure 5. Receiver operating characteristics for "calibration" of final multiple logistic regression model of factors associated with hypertension

4.4 Propensity score-matching analysis of ATT of ART on hypertension

4.4.1 Characteristics of ART-exposed and ART- naive study participants in the PSM analysis

A total of 18 covariates (covariates either hypothesised to be associated with both ART exposure and hypertension or hypothesised to be associated with hypertension; excluding covariates which are affected by ART exposure/treatment) were examined for inclusion in estimating the propensity scores (Table 20). Table 20 analysis indicates that only baseline CD4 T-cell count was significantly different (at $\alpha=0.05$) between the ART-exposed group and the ART-naive group, suggesting its potential as a confounder to the effect of ART treatment and thus needed to be adjusted.

Table 20. Characteristics of study participants in propensity score-matching analysis

Characteristics		**ART-exposed N=252**	**ART-naive N=59**	**p-value**
Age (years), mean ± SD		45.6 ± 9.7	43.8 ± 8.7	0.147
Sex, n (%)				
	Female	193 (76.6)	44 (74.6)	
	Male	59 (23.4)	15 (25.4)	0.744
Education, n (%)				
	None	35 (13.9)	9 (15.2)	
	Basic	139 (55.2)	24 (40.7)	
	Secondary	70 (27.8)	25 (42.4)	
	Tertiary	8 (3.2)	1 (1.7)	0.129
Religion				
	Christianity	225 (89.3)	51 (86.4)	
	Moslem	27 (10.7)	8 (13.6)	0.534
Employment, n (%)				
	Unemployed	31 (12.3)	7 (11.9)	
	Employed	221 (87.7)	52 (88.1)	0.926
Marital status, n (%)				
	Single	47 (18.6)	10 (16.9)	
	Married/Co-habiting	104 (41.3)	30 (50.9)	
	Divorced/Separated/Widowed	101 (40.1)	19 (32.2)	0.394
Smoking status, n (%)				
	Never smoker	242 (96.0)	56 (94.9)	
	Ever smoker	10 (4.0)	3 (5.1)	0.700
Alcohol status, n (%)				
	Abstainer	175 (69.4)	38 (64.4)	
	Drinker	77 (30.6)	21 (35.6)	0.453
Family history of CVD, n (%)				
	No	219 (86.9)	53 (89.8)	
	Yes	33 (13.1)	6 (10.2)	0.541
Exercise, n (%)				
	Never/Rare	175 (69.4)	41 (69.5)	
	Most times	77 (30.6)	18 (30.5)	0.994
Fruit intake, n (%)				
	Never/Rare	79 (31.4)	20 (33.9)	
	Most times	173 (68.6)	39 (66.1)	0.705
Baseline BMI (kg/m^2), mean ± SD		25.7 ± 5.1	25.5 ± 5.2	0.836
BMI category, n (%)				
	<25.0 kg/m^2	128 (50.8)	28 (47.5)	
	≥25.0 kg/m^2	124 (49.2)	31 (52.5)	0.645

BMI=Body mass index; CVD=Cardiovascular disease; N=Total number of study participants; n=Number of respondents per characteristic; SD=Standard deviation

Table 20 cont'. Characteristics of study participants in propensity score-matching analysis

Characteristics		ART-exposed N=252	ART-naive N=59	p-value
HIV-type				
	HIV-I	184 (73.0)	44 (74.6)	0.937
	HIV-II	6 (2.4)	1 (1.7)	
	Mixed (HIV-I and HIV-II)	62 (24.6)	14 (23.7)	
Duration of HIV infection (years), mean ± SD		7.8 ± 3.7	7.2 ± 3.7	0.271
Baseline CD4 T-cell count, mean ± SD		302.0 ± 147.7	384.2 ± 165.6	<0.001
Baseline CD4 T-cell count, n (%)				
	≤350 cells/μL	150 (59.5)	26 (44.1)	
	>350 cells/μL	102 (40.5)	33 (55.9)	0.031
Baseline sBP, mean ± SD (mmHg)		113.6 ± 17.6	116.1 ± 17.0	0.322
Baseline dBP, mean ± SD (mmHg)		69.3 ± 11.5	71.5 ± 11.8	0.199
Antihypertensive treatment, n (%)				
	No	209 (82.9)	49 (83.0)	
	Yes	43 917.1)	10 (17.0)	0.983
Co-morbid condition, n (%)				
	No	197 (78.2)	46 (78.0)	
	Yes	55 (21.8)	13 (22.0)	0.972

BMI=Body mass index; dBP=diastolic blood pressure; N=Total number of study participants; n=Number of respondents per characteristic; sBP=systolic blood pressure; SD=Standard deviation

4.4.2 Estimation of propensity scores for ART-exposed and ART-naive study participants in the PSM analysis

A logistic regression model was used to estimate the propensity score for each study participant with the covariates; age, sex, education, marital status, employment, smoking status, alcohol drinking status, family history of CVD, fruit intake, exercising, baseline BMI category, HIV type, baseline systolic blood pressure, baseline diastolic blood pressure, anti-hypertensive medication and baseline CD4 T-cell count. The mean ± standard deviation of the estimated propensity scores was 0.81 ± 0.08 and the median was 0.82 (IQR, 0.76-0.87). Although this may indicate skewness of the estimated propensity scores, the skewness value of -0.80 is within the range of -1.0 to 1.0 and thus considered good to demonstrate a normal distribution (Nduka et al., 2016b). The results also indicate that the estimated propensity scores were grouped into five optimal blocks. The "common support" for ART-exposed ranged from 0.5599 to 0.9616 with a mean of 0.8186 and for ART-naive ranged from 0.5128 to 0.9182 with a mean of 0.7748. A box-plot, a k-density plot and a histogram of the estimated propensity scores indicating the region of "common support" are shown in figures 6, 7 and 8 respectively. Visual analysis of the box plot (Figure 6) indicate a wide area (over 70%) of estimated propensity scores overlap between the ART-exposed and the ART-naive study participants as depicted by their median points. Figure 7 further collaborates this observation as the shapes of the normal distribution of the estimated propensity scores for ART-exposed and HAAT-naive were similar. Figure 8 confirms the visual inspection of the distribution of the estimated propensity scores being normally distributed and further indication of a high likelihood of achieving a region of common support. In addition, test of balancing property of the estimated propensity scores for each covariate was balanced for all the 18 covariates.

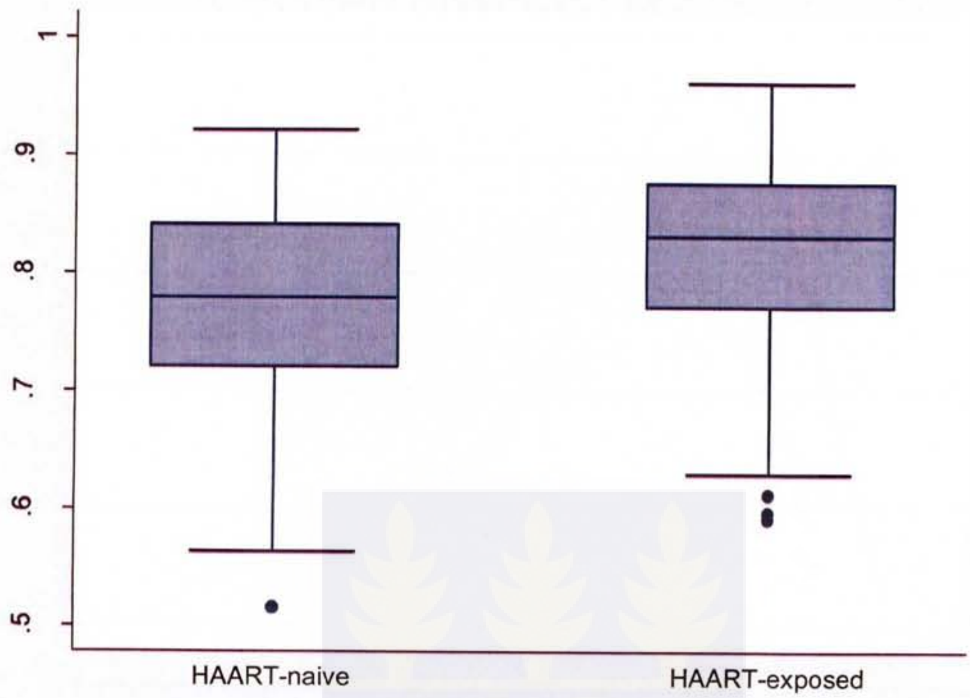

Figure 6. Box-plot of estimated propensity score among ART-exposed and ART-naive study participants before matching

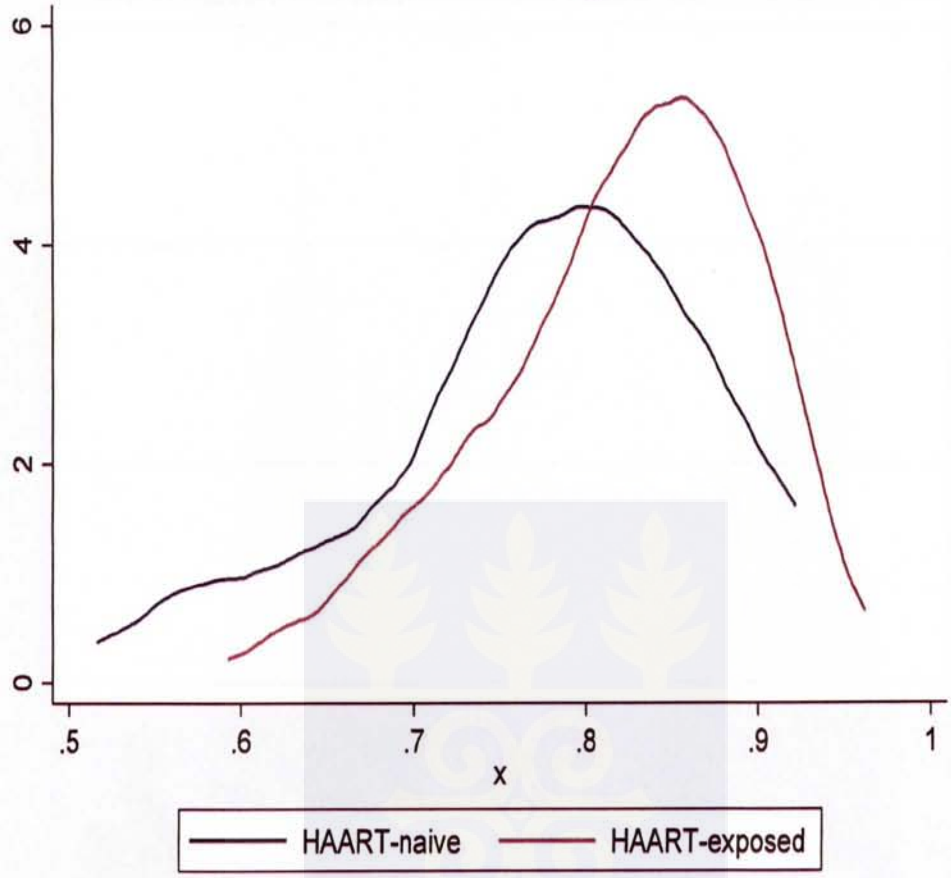

Figure 7. K-density plot of estimated propensity scores among ART-exposed and ART- naive study participants before matching

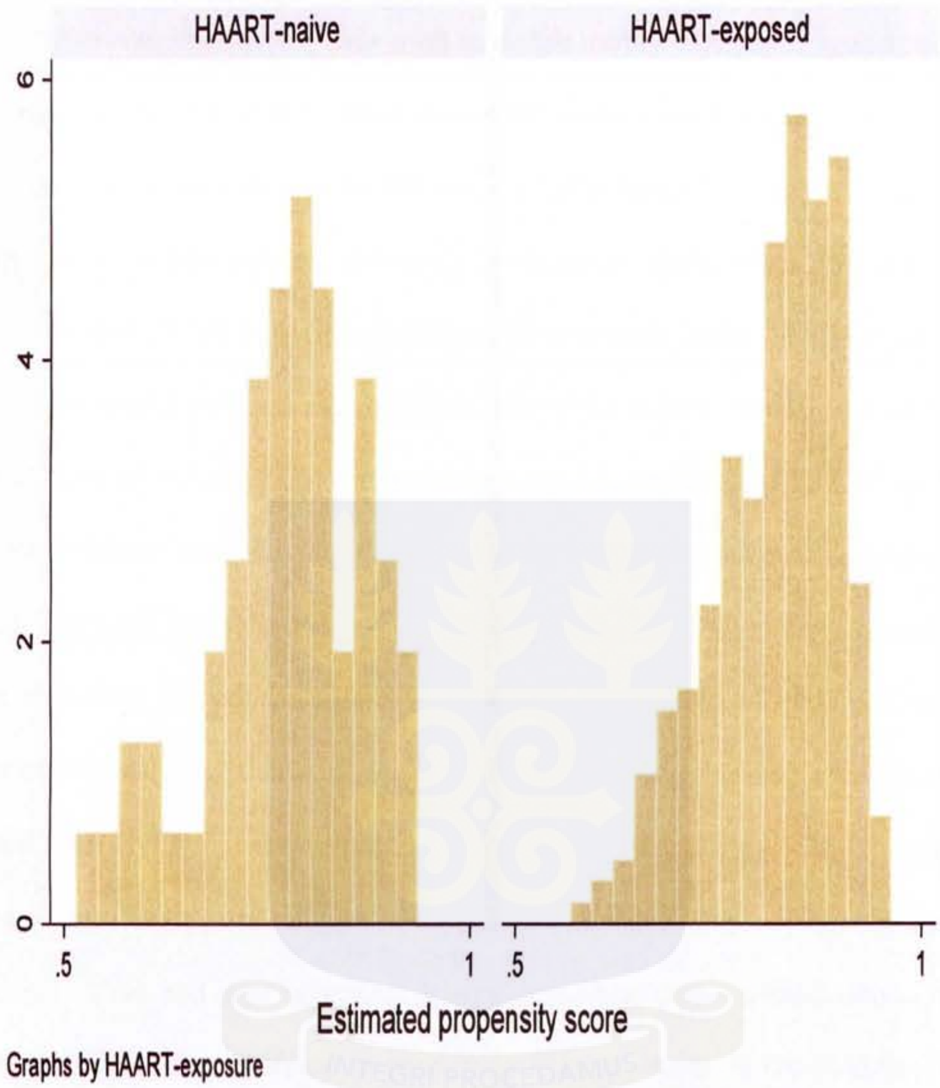

Figure 8. Histogram of estimated propensity score among ART-exposed and ART-naive study participants before matching

4.4.3 Matching of ART-exposed to ART-naive study participants using the estimated propensity scores in the PSM analysis

The kernel weighting strategy was used to match the ART-exposed group to the ART-naive group with a common bandwidth of 0.06. There were 311 study participants (252 ART-exposed individuals and 59 ART-naive individuals) before matching. Matching on the kernel weight yielded 295 study participants made up of 236 ART-exposed individuals and 59 ART-naive individuals (final model). Table 21 shows the variance ratios of the unmatched and matched data. The mean and the median standardised bias reduced from 10.5% and 8.9% respectively in the unmatched data to 4.1% and 3.8% in the matched data. The individual variance ratio in the matched data ranged from 0.92 to 1.22. The total variance ratio of the matched data was 1.72 indicating acceptability of the matching procedure. Figure 9 shows the distribution of estimated propensity scores before and after matching which indicates a good matching between the ART-exposed and ART-naive study participants with a minimal loss of individuals due to lack of "common support". Figure 10 shows the standardized percentage bias across all covariates before and after matching. Visual inspection shows a reduction in bias after matching as seen by a decrease in percentage bias spread from about -20 to 30 in the unmatched data to about -8 to 8 in the matched data (Figure 10). Figure 11 shows the standardized percentage bias for each covariate before and after matching also indicating a successful matching of the ART-exposed to the ART-naive study participants. Analysis of Figure 11 indicate a reduction in standardized percentage bias for 14 included covariates after matching.

Table 21. Covariates balance indicators in the propensity score-matching study participants

Covariate	ART-exposed (Means)	ART-naive (Means)	p-value	% bias	Variance ratio
Age (years)	44.95	45.37	0.613	-4.5	1.05
Sex	0.24	0.23	0.794	2.4	-
Religion	1.11	1.09	0.408	7.1	0.81
Education	2.22	2.28	0.342	-8.6	0.95
Marital status	1.94	1.96	0.786	-2.5	1.00
Employment status	1.12	1.11	0.706	3.4	1.09
Smoking	0.04	0.04	0.741	2.8	-
Alcohol	0.31	0.31	0.977	0.3	-
Family history of CVD	0.11	0.12	0.847	-1.8	-
Fruit intake	1.33	1.31	0.654	4.1	1.03
Exercising	1.71	1.68	0.483	6.4	0.95
Baseline BMI category	1.51	1.51	0.971	-0.3	1.00
HIV type	1.52	1.58	0.426	-7.5	0.94
Duration of HIV infection (years)	7.54	7.80	0.544	-7.0	0.92
Baseline sBP (mmHg)	114.57	114.66	0.953	-6.1	1.03
Baseline dBP (mmHg)	70.03	70.75	0.503	-6.1	0.92
On anti-hypertensive treatment	0.17	0.16	0.825	2.0	-
Baseline CD4 T-cell count category	1.58	1.55	0.494	6.3	0.98

BMI=Body mass index; CVD=Cardiovascular disease; dBP=diastolic blood pressure; sBP=systolic blood pressure

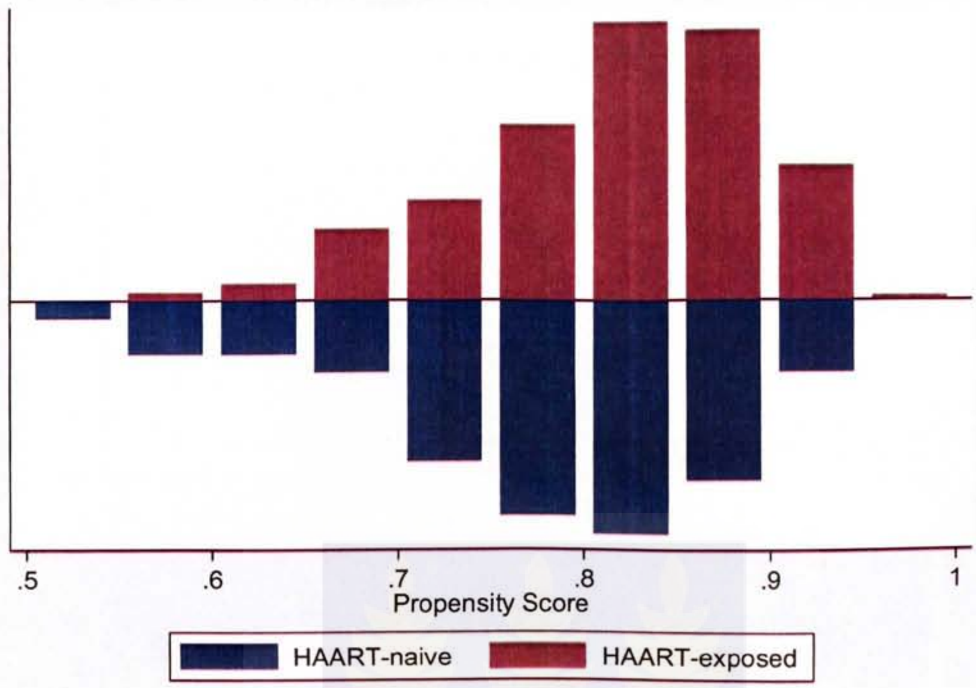

Figure 9a. Distribution of estimated propensity score before matching

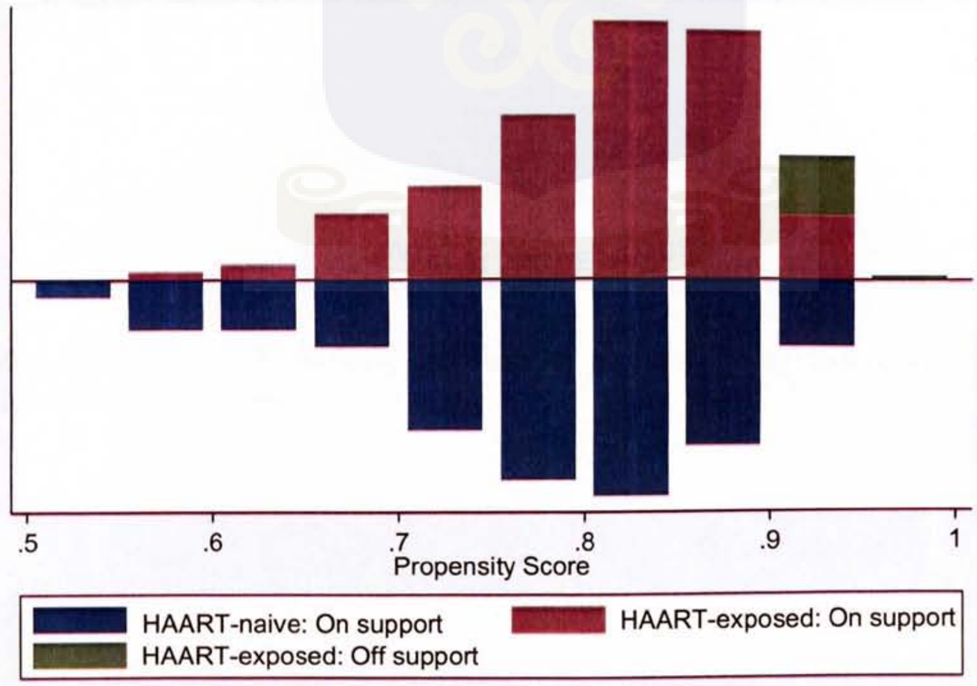

Figure 9b. Distribution of estimated propensity score after matching

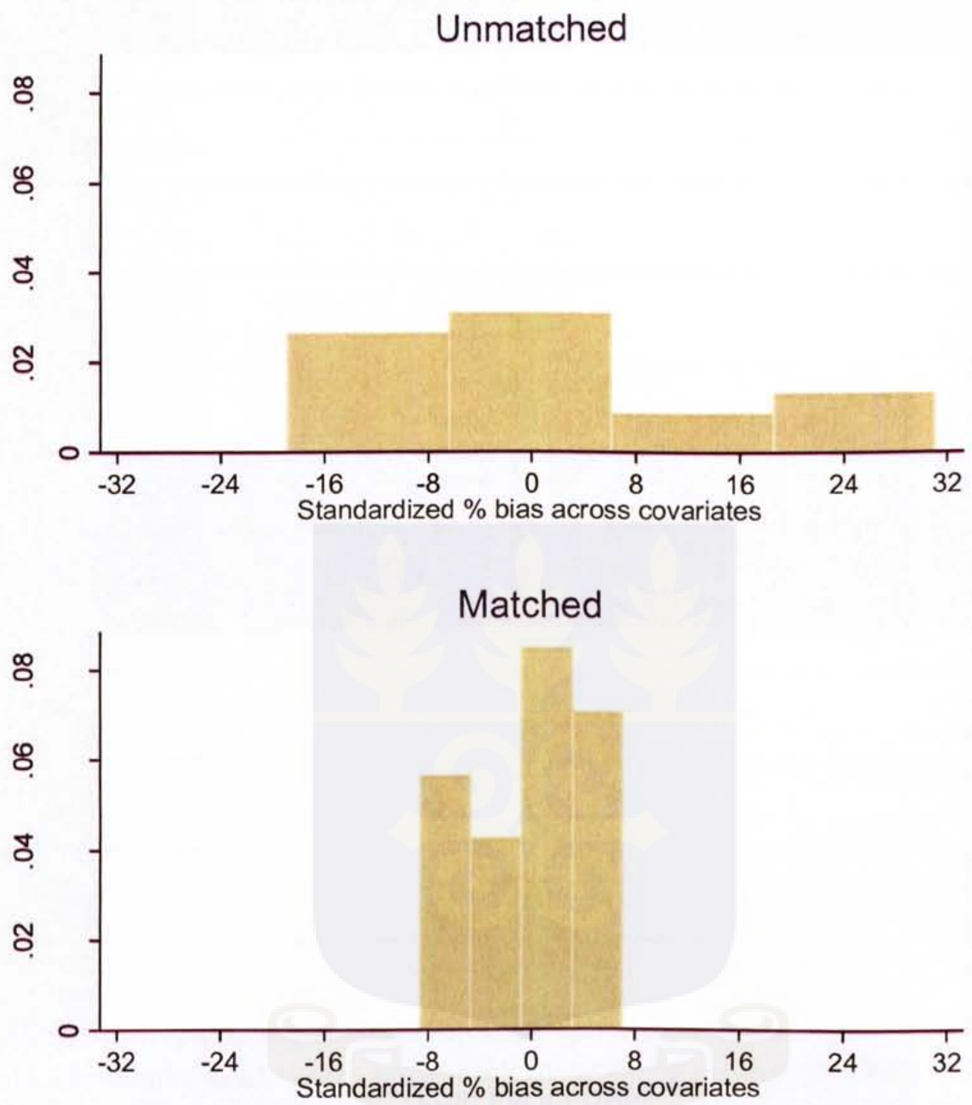

Figure 10. Histogram showing standardized percentage bias before and after propensity score matching

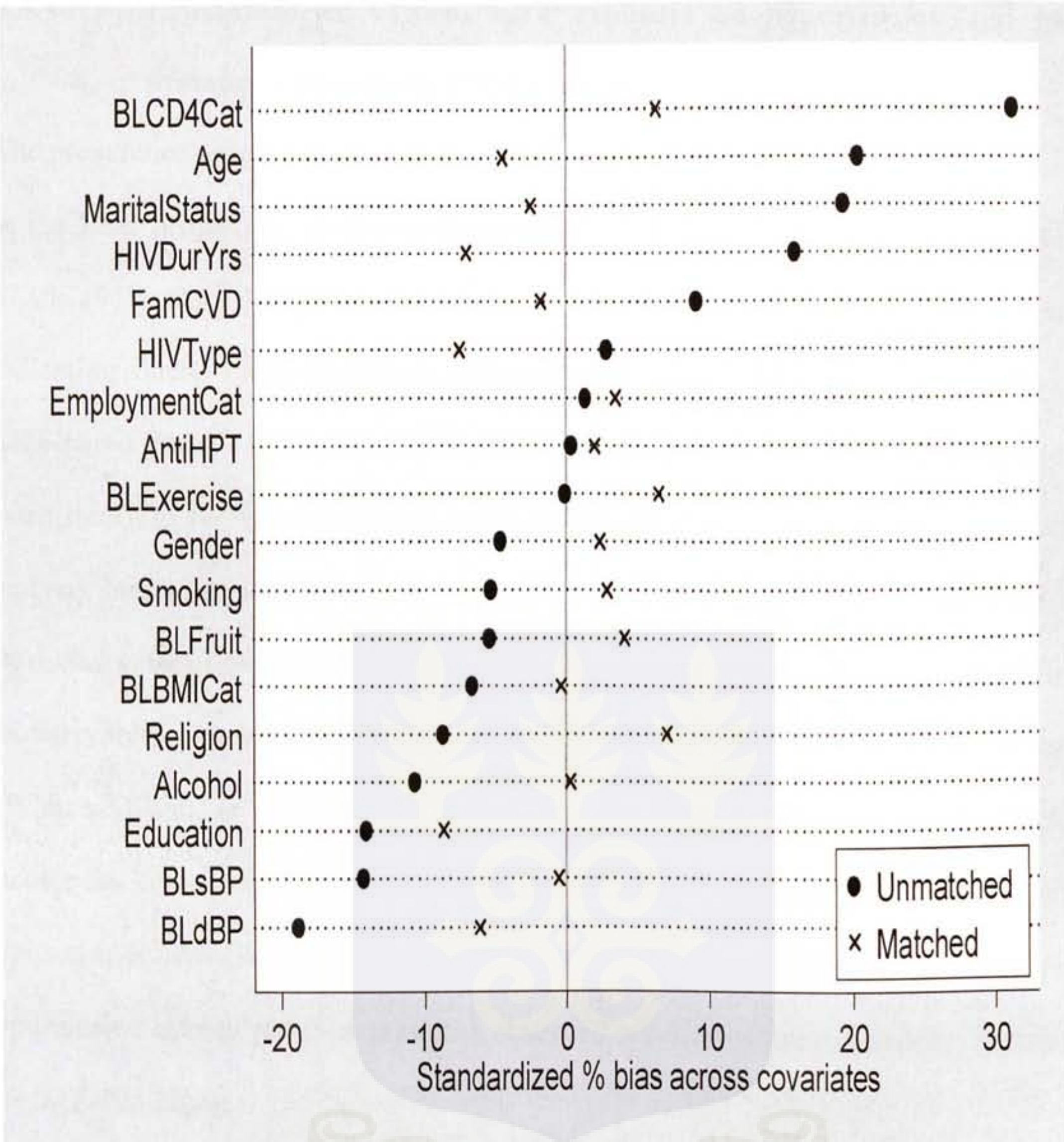

Figure 11. Standardised % bias across each covariate before and after matching

4.4.4 Estimation of ATT of ART exposure on hypertension and blood pressure values in the PSM analysis

The prevalence of hypertension in the ART-exposed and ART-naive study participants in the final propensity score-matching sample was 42.4% (95% CI, 36.2-48.8) and 17.0% (95% CI, 9.3-28.9) respectively and the estimated ATT was 26.2% ($p<0.001$) indicating a statistically significant difference between the ART-exposed group and the ART-naive group (Table 22). Thus, ART-exposed patients were 26.2 percent points more likely to be hypertensive compared with ART-naive patients. Post estimation analysis indicated a gamma level of 1.6 at 95% confidence interval meaning the estimated average treatment effect of ART exposure on hypertension is sensitive to an unobservable covariate, which will increase the odds of ART exposure by 60% (Table 22). In addition, at gamma (Γ) level of 2.1, the Hodges-Lehmann point estimates encompass zero indicating that a high increase in the likelihood of being an ART-exposed individual due to an unobservable characteristic which also increases being hypertensive is required to explain the observed level of estimated average treatment effect (Table 22).

The estimated ATT on systolic blood pressure was 12.0 mmHg (95% CI, 5.7-18.3; $p<0.001$) indicating a significant difference in systolic blood pressure between the ART-exposed group and the ART-naive group (Table 18). Similarly, the estimated ATT on diastolic blood pressure was 6.1 mmHg (95% CI, 1.3-10.8; $p=0.012$) indicating a statistically significant difference in diastolic blood pressure between the ART-exposed group and the ART-naive group (Table 22). Post estimation sensitivity analyses indicate a gamma level of 2.5 and 1.9 at 95% confidence interval respectively for systolic blood pressure and diastolic blood pressure (Table 22). Gamma levels for Hodges-Lehmann point estimates were 3.4 for systolic blood pressure and 2.4 for diastolic blood pressure (Table 22), indicating results of the estimated treatment effect of ART exposure on systolic and diastolic blood pressures were insensitive to selection on unobservable covariates i.e. unlikely that such confounding variables would not have been observed.

Table 22. Estimated average treatment effect of ART exposure on hypertension and blood pressure values

Outcome	Estimated ATT [95% CI]	p-value	Gamma (Γ) 95% CI	Gamma (Γ) Hodges-Lehmann
Hypertension, %	26.2 [13.3-39.1]	<0.001	1.6	2.1
Systolic blood pressure (mmHg)	12.0 [5.7-18.3]	<0.001	2.5	3.4
Diastolic blood pressure (mmHg)	6.1 [1.3-10.8]	0.012	1.9	2.4

ATT=Estimated Average treatment effect on the treated; CI=Confidence interval

4.5 Cardiovascular disease risk score assessment

Table 23 shows the various CVD risk score assessment classified as low, medium or high. Majority of the study participants were classified as low risk of cardiovascular disease in the 10-year FRS (79.4%) and 10-year WHO/ISH prediction chart (86.8%). With the 5-year D:A:D risk score, over 50% of the study participants were classified as moderate to high risk of CVD (Table 23).

Table 23. Cardiovascular risk assessment score

Cardiovascular risk scoring system		All participants n, %[1]	Comparison with D:A:D score Kappa	Kappa	Kappa
Modified FRS	Low	24 7 (79.4)			
	Moderate	47 (15.1)	0.34	<0.001	64.0%
	High	17 (5.5)			
WHO/ISH risk prediction score	Low	270 (86.8)			
	Moderate	19 (6.1)	0.10	<0.001	50.2%
	High	22 (7.1)			
D:A:D risk score	Low	148 (47.6)			
	Moderate	148 (47.6)	-	-	-
	High	15 (4.8)			

[1]Column percentages within each super row; D:A:D=Data Collection on Adverse Events of Anti-HIV Drugs; FRS=Framingham risk score; ISH=International Society for Hypertension; WHO=World Health Organisation

4.6 Summary of results

The key findings of this study involving 311 study participants of which 76.5% were females and 73.0% were ≥40 years were as follows;

1. The prevalence of hypertension in the study participants was 36.7% [95% CI, 31.3-42.3]. The prevalence of hypertension in study participants aged ≥40 years was 40.5% [95% CI, 16.8-35.6] which was significantly higher than the prevalence in the study participants aged <40 years (26.2% [95% CI, 16.8-35.6]). Similarly, the prevalence of hypertension in ART-exposed group (41.3% [95% CI, 35.2-47.3]) was significantly higher than the prevalence in the ART-naive group (16.9% [95% CI, 7.4-26.5]).
2. Propensity score-matching analysis indicated that the estimated average treatment effect (on the treated-ATT) of ART on hypertension was significant at 26.2 percent points. Similarly, the ATT of ART on systolic blood pressure and diastolic blood pressure values were significant at 12.0 mmHg and 6.1 mmHg respectively.
3. Regression modelling showed that the socio-demographic and life-style factors associated with hypertension were increasing age (aOR=1.10 [95% CI, 1.06-1.14]), positive family history of CVD/hypertension (aOR=2.23 [95% CI, 1.02-4.86]) and minimal exercising (aOR=1.94 [95% CI, 1.06-3.55]). Anthropometric and Metabolic/biochemical factors associated with hypertension were current body mass index of ≥25.0 kg/m^2 (aOR=2.18 [95% CI, 1.24-3.83]), abdominal obesity (high waist circumference) (aOR=2.15 [95% CI, 1.08-4.27]) and total cholesterol level ≥5.17 mmol/L (aOR=2.86 [95% CI, 1.30-6.28]). HIV/ART-related factors associated with

hypertension were exposure to ART (aOR=5.84 [95% CI, 2.23-15.31]) and increasing duration of ART exposure (aOR=1.15 [95% CI, 1.09-1.22]).

4. Risk of CVD was estimated using three different CVD risk-scoring systems. Whilst 20.6% and 13.1% of the study participants were of moderate to high risk of CVD using the 10-year general FRS and the 10-year WHO/ISH risk prediction chart respectively, as many as 52.4% were of moderate to high risk of CVD using the 5-year D:A:D CVD risk score.

CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

The present study was undertaken to determine the prevalence of hypertension and associated factors among patients attending HIV clinic at the KBTH in Accra. Results indicate that the prevalence of hypertension was 36.7% and the factors associated with hypertension were increasing age, positive family history of CVD/hypertension, minimal exercising, current BMI ≥25.0 kg/m^2, total cholesterol level ≥5.17 mmol/L, exposure to ART and increasing duration of ART exposure. Findings from the propensity score-matching analysis indicate that treatment with ART results in an estimated average increase in both systolic blood pressure and diastolic blood pressure values (12.0 mmHg and 6.1 mmHg respectively) and a further increase in the risk of hypertension of 26.2%. Estimation of cardiovascular disease risk score indicate 52.4% of the study participants were of moderate to high risk of CVD using the 5-year D:A:D CVD risk score.

5.2 General characteristics of study participants

Results of the present study indicate a study population with majority (73%) of them aged ≥40years. This is similar to the age structure reported in most cross-sectional or cohort studies in HIV-infected persons in SSA (Denue et al., 2012; Diouf et al., 2012; Schwartz et al., 2012; Kagaruki et al., 2014; Mashinya et al., 2014; Nsagha et al., 2015). Current report from the Ghana National AIDS Control Programme indicate the age group 45-49 years constitute the highest prevalence (5.7%) of HIV-positive patients in Ghana (NACP, 2017). This clearly shows an ageing population of PLHIV in Ghana and SSA in general and therefore the need to focus additionally on age-related morbidities including cardiovascular events and its associated factors in order to sustain the gains made in the roll out of ART programme in HIV care.

More than three-quarters of the study participants in this study were females (76.2%) which is comparable to other studies in SSA (Awotedu et al., 2012; Ekali et al., 2013; Bloomfield et al., 2014b; Dimodi et al., 2014; Sander et al., 2015; Dimala et al., 2016). This high proportion of females in studies in PLHIV in SSA could be attributed to several factors including the health seeking behaviours of SSA populations and the policy of screening (HIV testing) all consenting pregnant women in order to manage all HIV-infected pregnant women to prevent mother-to-child HIV transmission. In Ghana, prevalence and incidence rates of HIV infection are obtained from sentinel sites, which are mostly antenatal service centres. Additionally, the main route of HIV transmission in SSA is heterosexual unlike most European and North America countries, making women more vulnerable to HIV infection than men.

In this cross sectional study, 81% of the study participants were on ART. Although this figure is high, it is comparable to similar observational studies conducted in SSA (Ekali et al., 2013; Dimodi et al., 2014; Nsagha et al., 2015; Nduka et al., 2016b). A cross sectional study of 265 PLHIV in Nigeria reported of an ART-exposed group of 80.8% (Edward et al., 2013). Contributing factors to this high proportion of ART-exposed group could be the continuous policy modification of the CD4+ T cell count threshold for initiation of ART in Ghana (based on WHO recommendations) which has shifted from an initial <200 cell/μL to a current threshold of ≤500 cells/μL thereby incorporating more HIV-positive individuals to start ART (WHO, 2013c; NACP et al., 2014).

5.3 Prevalence of hypertension in patients attending HIV clinic at KBTH

The present study revealed that the prevalence of hypertension in PLHIV attending HIV clinic at KBTH in Accra was 36.7%. Hypertension is the leading risk factor for CVD and cerebrovascular mortality (WHO, 2009b) and has been reported to be common among PLHIV (Barbaro, 2006). Several prevalence figures of hypertension in PLHIV have been reported globally ranging from 19.9% in Brazil (Silva et al., 2009; Arruda Junior et al., 2010) to 31.5% in Southern America Cohort (Cahn et al., 2010). Studies from most developed countries suggest prevalence of hypertension among PLHIV between 8% and 39% (Jerico et al., 2005; Barbaro, 2006). Among patients on ART, studies in Europe and North America report of hypertension prevalence between 20% and 40 % (Bergersen et al., 2003; Gazzaruso et al., 2003; Palacios et al., 2006; Baekken et al., 2008; Coloma Conde et al., 2008; Mothe et al., 2009). Reports have cited a higher burden of hypertension (in the general population) in sub-Saharan Africa compared with other sub-regions (Addo et al., 2007). An estimate of the burden of NCDs in SSA put the prevalence of hypertension in the general population at 16.2% (Twagirumukiza et al., 2011; Ogah and Rayner, 2013). Results of other studies in sub-Saharan Africa among PLHIV (ART-exposed and ART-naive combined) indicate prevalence of hypertension ranging from a low of 14.0% in Botswana to a high of 32.0% in Kenya (Nyabera et al., 2011). The prevalence of hypertension in this study is therefore comparable to other studies in PLHIV in SSA.

In relation to Ghana, systematic reviews have cited prevalence of hypertension in the general population to be between 19.3% and 54.6% (Bosu, 2010; Addo et al., 2012) and a 2011 annual hospital-based report from the Ministry of Health indicate a prevalence of hypertension between 30% and 40% (MOH, 2011). The present hypertension prevalence can therefore be said to be a reflection of the current high prevalence of hypertension in Ghana, especially as the study was conducted in a hospital setting and in patients with a chronic infectious disease.

The present study also indicated a hypertension prevalence of 40.5% in study participants' aged ≥40 years which is comparable to a combined analysis of data from MACS and Women's Interagency HIV Study (WIHS) report of a 35%-41% prevalence of hypertension in patients ≥40 years of age (Kaplan et al., 2007).

In the present study, the 41.3% prevalence of hypertension in ART-exposed study participants was significantly higher compared with the ART-naive group. The current study prevalence of hypertension in ART-exposed PLHIV is comparable with other studies reported in sub-Saharan Africa of 65% in Botswana (Shapiro et al., 2012), 38.0% in Cameroon (Dimala et al., 2016) and 34.9% in Zimbabwe (Mutede et al., 2015). A hypertension prevalence of 45% in ART-exposed individuals in Malaysia has been reported (Hejazi et al., 2013). Whilst some studies, both in Europe and SSA have indicated no significant difference in hypertension prevalence between ART-exposed and ART-naive patients (Bergersen et al., 2003; Edward et al., 2013; Dimodi et al., 2014; Ogunmola et al., 2014; Sander et al., 2015), other studies have indicated otherwise (Gazzaruso et al., 2003; Muhammad et al., 2013; Kagaruki et al., 2014; Peck et al., 2014; Dimala et al., 2016). It is important to note that a previous study conducted in Ghana determining the prevalence of hypertension in ART-exposed PLHIV indicated a systolic hypertension prevalence of 15.2% and a diastolic hypertension prevalence of 23.8% (Ngala and Fianko, 2014). Whilst the results of this study is higher than the study reported by Ngala and Fianko (2014), this could be attributed to the fact that present study indicated a mean duration of ART exposure of 84 months and was conducted in the largest cohort of HIV-care in Ghana. Duration of ART exposure has been shown to be associated with hypertension in several studies (Bergersen et al., 2003; Seaberg et al., 2005; Ekali et al., 2013; Ngala and Fianko, 2014; Mutede et al., 2015; Nduka et al., 2016a) and in addition, the mean age of the study participants for the study reported by Ngala and Fianko (2014) was 38 years whilst that for the current study was 45 years. Age is a known risk factor for several cardiovascular diseases and hypertension (especially age ≥40 years). Other factors, which may account for this differential observation, could be differences in geographical locations, study settings, clinical characteristics of study participants and even study design.

Bearing in mind the continuous implication of ARVs and in particular PIs in the pathophysiology of hypertension in PLHIV, it is imperative that with an adequate study sample sizes, there will be significant difference in prevalence of hypertension between ART-exposed groups and ART-naive groups. Both HIV infection and ARVs have been postulated to have direct and indirect effect on the vascular system accelerating atherosclerosis via endothelial dysfunction, vasculitis, HIV nephropathy, lipodystrophy and other metabolic derangements (Bergersen et al., 2003; Hsue et al., 2012; Boccara et al., 2013; Nuesch et al., 2013; Bloomfield et al., 2014b; Chastain et al., 2015; Isa, 2015).

It is worth noting that the observed prevalence of hypertension in this study could be slightly lower than it actually is, given that potential study participants who were already diagnosed with hypertension before enrolment into the HIV clinic were excluded from the study.

5.4 Factors associated with hypertension

Using regression modelling and purposeful selection of covariates method, results from the present study indicate that the factors associated with hypertension were increasing age, family history of cardiovascular disease/hypertension, exercising, body mass index and abdominal obesity. Other factors were total cholesterol, exposure to ART and duration of exposure to ART.

Socio-demographic factors

Among the socio-demographic factors, increasing age is a well-known risk factor for hypertension in the general population and this is particularly evidenced in people of 40 years and above. In the present study, the odds of hypertension increases by 10 % for every additional one-year increase in age. This results is comparable and consistent with several studies conducted in PLHIV in both developed and developing countries (Friis-Moller et al., 2003; Seaberg et al., 2005; Bloomfield et al., 2011; Medina-Torne et al., 2012; Manner et al., 2013b; De Socio et al., 2014; Sander et al., 2015; Dimala et al., 2016; Njelekela et al., 2016). Hejazi et al. (2013) had reported of a 7% increase in odds of hypertension for every one-year increase in age, which is comparable with the results of the present study. The contribution of ageing to the pathogenesis of hypertension has been attributed to arterial stiffness that is reduced elasticity of the large arteries which occurs with ageing (Oparil et al., 2003). This reduced elasticity is attributed to smooth-muscle hypertrophy and thinning, collagen deposition and fragmenting and fracture of the elastin fibres in the arteries (O'Rourke et al., 2000). Ageing has also been associated with endothelial dysfunction which results in isolated systolic hypertension (Safar, 1999). Some studies have argued about an accelerated ageing process in PLHIV but this continues to be a subject of debate and research in the light of the near-normal life expectancy of PLHIV in the present ART era.

In the present study, other socio-demographic characteristics measured including sex, educational level, religious denomination, marital status and employment status were not associated with hypertension. The lack of association between sex and hypertension is consistent with reports from other studies (Jerico et al., 2005; Palacios et al., 2006; Diouf et al., 2012; Medina-Torne et al., 2012; Edward et al., 2013; Ikeda et al., 2013; Ogunmola et al., 2014; Kwarisiima et al., 2016). In a similar way, the lack of association between highest educational status attained and hypertension is similar to reports from other studies (Ikeda et al., 2013; Ogunmola et al., 2014; Kwarisiima et al., 2016). Both Krauskoff et al. (2013) and Hejazi et al. (2013) reported lack of association between employment status and hypertension as also reported in the present study.

Cardiovascular diseases and risk factors have been known to run in families and individuals with parental history of hypertension are classified as high risk targets for interventions to prevent the disease (Whelton et al., 2002; Wang et al., 2008). In the present study, a positive family history of CVD/hypertension was associated with hypertension. This finding is consistent with other studies that have associated positive family history of hypertension with increased odds of hypertension in PLHIV (Arruda Junior et al., 2010; De Socio et al., 2014). Although some studies have reported no such association (Thiebaut et al., 2005; Dimala et al., 2016), the fact that there are several reports on the interaction between genetics, renal dysfunction and the resultant salt and water retention imbalance which leads to hypertension in the general population (Oparil et al., 2003) supports the results of this study.

Life-style factors

Exercising, a life-style factor was established to be associated with hypertension in this study. Several epidemiological studies have demonstrated the relevance of regular physical exercise in reducing the incidence of hypertension in the general population (Carnethon et al., 2010; Warburton et al., 2010; Diaz and Shimbo, 2013;

Thawornchaisit et al., 2013). The results of the present study is therefore consistent with the knowledge that physical inactivity is a risk factor for hypertension and is comparable with the results of other studies conducted in PLHIV in SSA (Mutede et al., 2015). Regular physical exercise is proposed to reduce the incidence of hypertension through several mechanisms including decrease in oxidative stress (and reactive oxygen species), decrease in inflammation and body weight and increase in endothelial function (Diaz and Shimbo, 2013).

Smoking of tobacco is estimated to cause 10% of CVD and is considered a major risk factor for hypertension in the general population. Results of the present study indicated lack of association between smoking and hypertension which is similar to reports from other countries in SSA (Ikeda et al., 2013; Kagaruki et al., 2014; Dimala et al., 2016). This phenomenon could be attributed to the low prevalence of smoking generally in SSA compared with most developed countries and the counselling given to HIV-patients to stop smoking during HIV clinic enrolment. The prevalence of smoking in this study (both current and previous) was 4.2%.

Although alcohol drinking is considered a major risk factor in the incidence of hypertension in the general population, the current study did not indicate such an association. Results from other studies reported such a similar relationship (Arruda Junior et al., 2010; Kagaruki et al., 2014; Mashinya et al., 2015; Dimala et al., 2016; Kwarisiima et al., 2016).

Anthropometric factors

Of the anthropometric parameters investigated in this study, BMI ≥25.0 kg/m^2, and abnormal waist circumference (as a measure of abdominal obesity) were established to be associated with hypertension. Several epidemiological studies have established overweight/obesity as a risk factor for the incidence of hypertension in the general population (Brown et al., 2000; Sakurai et al., 2006), and among PLHIV (Friis-Moller et al., 2003; Seaberg et al., 2005; Thiebaut et al., 2005; Medina-Torne et al., 2012; De Socio et al., 2014). Several studies among PLHIV in SSA have also reported of increased odds of hypertension in overweight/obese individuals (Kagaruki et al., 2014; Mutede et al., 2015; Dimala et al., 2016; Kwarisiima et al., 2016; Njelekela et al., 2016). Results of the present study which indicated an increased odds of hypertension of 2.18 (95% CI, 1.24-3.83) in overweight/obese individuals is comparable to a report by Bloomfield et al. (2012), which studied a cohort of 12,194 HIV-positive study participants in Kenya and indicated an increased odds of hypertension of 2.42 (95% CI, 1.88-3.09) in individuals with BMI ≥25.0 kg/m^2. Many studies have drawn attention to increasing prevalence of overweight/obesity in HIV-positive individuals and this has been attributed to both a general age-related increase in body weight (Denue et al., 2012) and a tendency of PLHIV to be overweight to remove or reduce suspicion and its accompanying stigmatisation of HIV infection (De Socio et al., 2008; Boodram et al., 2009; Aboud et al., 2010; Muronya et al., 2011; Edward et al., 2013). In addition, suggestions have been given that the trend for elevated blood pressure in ART-exposed individuals may be due to both general obesity and distorted lipid profile mediation in the association between ART and hypertension (Palacios et al., 2006; Crane et al., 2009; Bernardino de la Serna et al., 2010; Ekali et al., 2013).

Abnormal waist circumference, a measure of abdominal obesity or body fat distribution, was found to be associated with hypertension in this study. Absolute waist circumference >102 cm (in men) and >88 cm (in women) is classified as abdominal obesity (WHO, 2000; Yusuf et al., 2004). A large body of scientific evidence abounds of the role played by abdominal obesity in the aetiology of cardio-metabolic abnormalities including hypertension, dyslipidaemia, insulin resistance and type 2 diabetes (Van Pelt et al., 2001; Anjana et al., 2004; Janssen et al., 2004; Yusuf et al., 2004; Cameron and Zimmet, 2008; Westphal, 2008). A mediation analysis for lineal model conducted in a study by Nduka et al. (2016c) emphasised the strong impact of central fat distribution in mediating the causal pathway between ART and increased blood pressure (Nduka et al., 2016c). This observation is supported by previous studies that have indicated the mediation role played by waist circumference in the association between ART and hypertension (Shlay et al., 2007; Antonello et al., 2015). The present study is thus consistent with the study by Nduka et al. (2016c) (as both ART and abdominal obesity were associated with hypertension) and other studies (Arruda Junior et al., 2010; Kagaruki et al., 2014).

Waist-to-hip ratio (WHR), another component of the anthropometric parameters was not associated with hypertension, similar to results reported by other studies (Hejazi et al., 2013 ; Mashinya et al., 2014; Mashinya et al., 2015; Dimala et al., 2016).

Metabolic/biochemical factors

Reports from the present study indicate an association between hypercholesterolemia and hypertension. Several studies have been conducted in the field of lipid profile of HIV-infected individuals. Disorder of the lipoprotein metabolism referred to as dyslipidaemia is regarded as a major risk factor for CVD. The most common form of dyslipidaemia is hyperlipidaemia, which is characterised by hypercholesterolemia, elevated concentration of LDL-C, hypertriglyceridemia and reduced level of HDL-C. Results from the present study is thus consistent with several reports which associate hypercholesterolemia with an increased risk of hypertension in the general population (Sesso et al., 2005; Halperin et al., 2006) and among PLHIV (Bergersen et al., 2003;

Thiebaut et al., 2005; Baekken et al., 2008; Diouf et al., 2012; Kagaruki et al., 2014). The pattern of distorted lipid profile among PLHIV is seen mostly in patients on protease inhibitors and PI-based regimens have been shown to be atherogenic more than non PI-based regimens (van der Valk et al., 2001; Grinspoon and Carr, 2005; Buchacz et al., 2008; Dau and Holodniy, 2008; Salami et al., 2009). Lipid abnormalities due to PI-based regimens has been estimated to occur in up to 50% of HIV-infected patients (Fontas et al., 2004) but the degree of this abnormality varies with the type of protease inhibitor involved and the duration of treatment (Carr, 2003; Chastain et al., 2015). However, in this study, the number of individuals on PI-based regimen were few (10.6%, n=35) which may account for the lack of association between the other parameters of the lipid profile measured (i.e. HDL-C, LDL-C and triglycerides) and hypertension. Nonetheless, some studies among PLHIV have reported lack of association between hypertriglyceridemia and hypertension (Thiebaut et al., 2005; Diouf et al., 2012; Medina-Torne et al., 2012; Hejazi et al., 2013), lack of association between HDL-C and hypertension (Bergersen et al., 2003; Palacios et al., 2006; Arruda Junior et al., 2010; Denue et al., 2012; Kagaruki et al., 2014) and lack of association between LDL-C and hypertension (Palacios et al., 2006; Arruda Junior et al., 2010; Denue et al., 2012).

Elevated fasting blood glucose (FPG) and reduced estimated glomerular filtration rate (eGFR) are both recognised indices whose prevalence are high in hypertensive patients in the general population. The prevalence of elevated FPG and reduced eGFR in the present study were 10.0% and 15.4% respectively and these are comparable to other studies in SSA. Studies by Edward et al. (2013) in Nigeria and Diouf et al. (2012) in Senegal had reported a prevalence of elevated FPG of 10.6% and 14.5% respectively. The frequency of reduced eGFR was 15.4%, which is higher than figures from previous studies of 12.6% in ART-naive and 10.7% in ART-exposed patients (Peck et al., 2014) but comparable to a prevalence of 17.0% reported by Baekken et al. (2008). Previous studies have noted that kidney disease is common in HIV-infected adults in SSA (Msango et al., 2011). Literature abounds on the effect of ARVs on the incidence of elevated FPG in association with hypertension and CVD among PLHIV (Chastain et al., 2015). Results from the present study indicate lack of association between both elevated FPG and reduced eGFR and hypertension. This is similar to reports from other studies which indicated lack of association between elevated FPG and hypertension (Bergersen et al., 2003; Baekken et al., 2008; Hejazi et al., 2013) and between reduced eGFR and hypertension (Baekken et al., 2008; Wilson et al., 2009; Denue et al., 2012; Manner et al., 2013b; Peck et al., 2014).

HIV/ART-related factors

Several studies have been conducted in determining the relationship between HIV/ART and hypertension. In studies that have included HIV-negative individuals as controls, the association between HIV status and hypertension has been conflicting. Some studies have reported either a significant difference in hypertension prevalence between HIV-negative controls and HIV-positive group or an association between HIV status and hypertension (Malaza et al., 2012; Peck et al., 2014; Kwarisiima et al., 2016). Most studies on the other hand have reported no association between HIV status and hypertension (Bergersen et al., 2003; Jerico et al., 2005; Baekken et al., 2008; Arruda Junior et al., 2010; Schwartz et al., 2012; Shapiro et al., 2012; Mashinya et al., 2014; Ogunmola et al., 2014; van Zoest et al., 2016). Some reasons, which could account for this disparity, include the differences in population structure between the studies, the prevalence of hypertension in the general population and the duration of infection. However, whilst some studies have associated longer duration of HIV infection with hypertension (Medina-Torne et al., 2012; Manner et al., 2013b; De Socio et al., 2014), others have reported lack of such an association (Baekken et al., 2008; Hejazi et al., 2013). Despite these conflicting results, studies that have associated HIV positive status with hypertension have suggested mechanisms to account for the higher incidence of hypertension in HIV positive individuals. These include the infection inducing a dysregulated and chronic inflammation due to immune suppression and reconstitution, which can lead to endovascular changes (Kaplan et al., 2008; Palella and Phair, 2011; Peck et al., 2014). Other mechanisms are endothelial activation and dysfunction as well as direct infection of the virus on arterial vascular smooth cells (Kline and Sutliff, 2008; Torriani et al., 2008; Mulazzi et al., 2009) and the generation of free radicals leading to oxidative damage to the endothelium and endothelial dysfunction (Torre, 2006). The present study however did not include HIV-negative controls in the design; hence, the relationship between HIV status and prevalent hypertension was not investigated.

Other findings of the present study are the association between exposure to ART and hypertension and the association between duration of ART and hypertension. Although literature abounds in studies on the association between ART exposure and the risk of hypertension, the results have been inconclusive. A systematic review with meta-analysis of 39 studies involving 44,903 participants however concluded that both systolic and diastolic blood pressure values were significantly higher among ART-exposed patients compared with treatment-naive patients (Nduka et al., 2016a). The study also reported of a significant increased risk of hypertension in ART-exposed patients compared with treatment-naive patients. The findings of this study is therefore consistent with several other studies in SSA (Shapiro et al., 2012; Muhammad et al., 2013; Kagaruki et al., 2014; Ngala and Fianko, 2014; Nsagha et al., 2015; Dimala et al., 2016; Nduka et al., 2016b) and other sub-regions (Bergersen et al., 2003; Chow et al., 2003; Seaberg et al., 2005; Crane et al., 2006; Palacios et al., 2006; Baekken et al., 2008; Wilson et al., 2009; De Socio et al., 2014). Whilst it may be overwhelming to notice the amount of literature, including one systematic review and one propensity score-matching analysis, supporting the association between ART and hypertension, other studies have reported the lack of association between ART and hypertension in SSA (Bloomfield et al., 2011; Dimodi et al., 2014; Ogunmola et al., 2014; Edwards et al., 2015; Sander et al., 2015) and in other sub-regions (Bergersen et al., 2003; Friis-Moller et al., 2003; Jerico et al., 2005; Thiebaut et al., 2005; Arruda Junior et al., 2010; Medina-Torne et al., 2012; Ikeda et al., 2013; Krauskopf et al., 2013; Hejazi et al., 2013 ; Antonello et al., 2015). The present study reported of an adjusted odds ratio of 5.84 (95% CI, 2.23-15.31) which is highly comparable with a similar study conducted in Ghana which reported of an increased odds of hypertension of 5.00 in ART-exposed individuals compared with ART-naive individuals (Ngala and Fianko, 2014). The present finding is also supported by the plausible causal effect inferred from the PSM analysis presented earlier in this thesis.

Various mechanisms have been postulated to account for the association between ART and hypertension. These mechanisms include premature and/or accelerated development of atherosclerosis leading to blockage of the blood vessels lumen (Carr, 2003; Fichtenbaum, 2003; Mehta and Reilly, 2005), ART induced immune activation, increased intestinal bacterial translocation and low-grade inflammation which, may promote atherosclerosis and increased arterial stiffness (Hsue et al., 2009; Crowe et al., 2010; Kaplan et al., 2011; Redd et al., 2011; Boccara et al., 2013) and the involvement of ARVs in both lipid and glucose metabolism resulting in lipodystrophy syndrome and the activation of the renin angiotensin system (Boccara et al., 2010). Protease inhibitors in particular have been reported to induce endothelial injury, which is associated with dyslipidaemia, oxidative stress and senescence (Lefevre et al., 2010). However, studies by the AIDS Clinical Trials Group S1S2 which showed that ART rather improved endothelial dysfunction in HIV patients after 24 weeks of therapy (Torriani et al., 2008) has led to the probable differential effect of PIs on the risk of CVDs in general depending on the length of usage.

Another finding in this study is the association between length of antiretroviral usage and the increased risk of hypertension. This results is consistent with other reports of an increased risk of hypertension with increasing duration of ART among PLHIV in SSA (Ekali et al., 2013; Muhammad et al., 2013; Ngala and Fianko, 2014; Mutede et al., 2015) and the results of the systematic review and meta-analysis (Nduka et al., 2016a).

Meanwhile there is there is lack of association between CD4+ T-cell count, HIV duration and hypertension in this study. The relationship between CD4+ T-cell count as a measure of immune system function and hypertension in HIV infected individuals continue to be a subject of ongoing research (Wilson et al., 2009). Large cohort studies have associated lower CD4+ T cell count with incident cardiovascular event in general and posited it could be mediated by a chronic pro-inflammatory state that promotes atherosclerosis (El-Sadr et al., 2006; Friis-Moller et al., 2007; Lichtenstein et al., 2010). On the other hand, a higher CD4+ T cell count, seen as a measure of better immune system function has been associated with hypertension among PLHIV and this phenomenon has been attributed to an overall improved general health and nutritional status (with initiation of ART) such that the association is mediated by confounders like obesity (Bergersen et al., 2003; Crum-Cianflone et al., 2010). Despite the mechanisms suggested to be involved in the association of low CD4+ T-cell count with hypertension, several observational studies indicate lack of association between low CD4+ T-cell count and hypertension. The present results is therefore consistent with several other reports which have indicated lack of association between CD4+ T cell count and hypertension among PLHIV in SSA (Bloomfield et al., 2011; Denue et al., 2012; Diouf et al., 2012; Ogunmola et al., 2014; Okello et al., 2015; Dimala et al., 2016) and other sub-regions (Jerico et al., 2005; Palacios et al., 2006; Medina-Torne et al., 2012; Ikeda et al., 2013; Benjamin et al., 2016; van Zoest et al., 2016).

Another finding in this study is the lack of association between duration of HIV infection and prevalence of hypertension. Even though a cohort study would have been appropriate to investigate a relationship between duration of HIV diagnosis and preferable incident hypertension, nonetheless, the results of the present study is consistent with reports from several previous studies (Jerico et al., 2005; Palacios et al., 2006; Bhaskaran et al., 2008; Denue et al., 2012; Ikeda et al., 2013; Hejazi et al., 2013 ; Dimala et al., 2016).

5.5 Estimated average treatment effect of ART exposure on hypertension and blood pressure values

The study demonstrated that using PSM analysis, the estimated average treatment effect of ART increases the prevalence of hypertension and also increases both systolic and diastolic blood pressure values. This study comes at a time when the association between ART and hypertension is ridden with conflicting results although there are several postulations on the pathophysiology of ART effect on hypertension and CVD in general. The unfortunate dearth of literature on the causal average treatment effect of ART on hypertension as observed by Nduka et al. (2016a) makes it difficult to compare the present results with previous studies. However, this study is the second in line in this analysis direction. A study published by Nduka et al. (2016a) reported an estimated causal average treatment effect (ATT) of 7.85 mmHg and 7.45 mmHg increases in systolic and diastolic blood pressure values. The results of the present study indicate an estimated average treatment effect on the treated (ATT) of 12.0 mmHg on systolic blood pressure and 6.1 mmHg on diastolic blood pressure. Although the ATT on diastolic blood pressure is comparable to the ATT reported by Nduka et al. (2016a), the ATT on systolic blood pressure is higher than the previous study. However, considering the fact that a 20 mmHg point is needed to move a non-hypertensive individual maximum threshold systolic blood pressure from 120 mmHg (non-hypertensive) to 140 mmHg (hypertensive) whilst a 10 mmHg is needed for diastolic blood pressure (from 80 mmHg to 90 mmHg), the present study's ATT on both systolic blood pressure and diastolic blood pressure is plausible.

The present study also reported an estimated ATT of 26.2 percent points on hypertension, which is coherent with conclusions from several studies that is suggestive of a plausible causal relationship between ART and hypertension and related blood pressure levels in PLHIV. Reports from the MACS indicated a temporal relationship between ART and increased blood pressure levels (Seaberg et al., 2005). A systematic review with meta-analysis involving 39 studies (of varied study designs and settings) indicated an epidemiological association between ART and increased levels of systolic and diastolic blood pressure and increased risk of hypertension in PLHIV (Nduka et al., 2016a).

The interest in the use of PSM analysis to infer or otherwise a plausible causal effect of treatment i.e. cause-effect relationships, especially in situations where RCT is not practicable due to logistical constraints or ethical reasons is growing (Rosenbaum and Rubin, 1985; Austin, 2011a; Austin, 2011b). This is consistent with the modifying concept of causation in epidemiology which has expanded and gone beyond the simple relationships established by "Hill's Criteria of Causation" (Hill, 1965; Lucas and McMichael, 2005; Mirtz et al., 2009) to the use of statistical methods in testing causal hypothesis (Rosenbaum and Rubin, 1985; Austin, 2011b; Austin, 2011a). To the best of my knowledge, this study is the second to use propensity score-matched analysis in examining a plausible causal relationship between ART and blood pressure values in PLHIV; the first being the study reported by Nduka et al. (2016a).

The role played by ART in elevating blood pressure values and consequently increasing the risk of hypertension in PLHIV has been attributed to a myriad of interacting patho-physiological pathways including ART-induced vascular and endothelial dysfunction (Seaberg et al., 2005; Dau and Holodniy, 2008; Hemkens and Bucher, 2014), an exaggerated immune response following initiation of ART (Bosamiya, 2011), chronic inflammation and adipose and liver dysfunction (Hemkens and Bucher, 2014). Worth noting is that although animal experimental data is lacking in the reversal or preventive effect of ART on blood pressure (Nduka et al., 2016b), a published clinical trial demonstrated a significant reduction in blood pressure when patients were switched from a first generation NNRTI (nevirapine-NVP, in combination with FTC and TDF-DF) to a second generation NNRTI (rilpivirine-RPV, in combination with FTC and TDF-DF) (Rokx et al., 2015). It has been suggested that the current use of nevirapine as a NNRTI in ART is consistent with the rise in the prevalence of hypertension and associated CVD mortality rates seen since the onset of the ART era (Seaberg et al., 2005; Hooshyar et al., 2007; Bloomfield et al., 2014b; Nduka et al., 2016b).

5.6 Cardiovascular risk score assessment

The introduction of ART for the management of HIV has led to a better health care for PLHIV. However, since the onset of the ART era two decades ago, there is mounting evidence that both HIV infection and ART are risk factors for the development of cardiovascular diseases. In addition to this, most countries in sub-Saharan Africa (SSA) are undergoing a demographic and epidemiologic transition in terms of disease burden from infectious diseases to non-communicable diseases and therefore issues have been raised on the burden of CVD in PLHIV in SSA. Cardiovascular risk scoring systems have been used to estimate the risk of CVD in the general population and several of such tools exist as online calculators. The present study estimated the 10-year FRS, the 5-year D:A:D risk score and the 10-year WHO/ISH risk score in 311 HIV-positive patients without any previous CVD attending the KBTH in Accra. The present study estimated a 10-year moderate to high risk of CVD to be 20.6% and 13.2% using the FRS and the WHO/ISH risk score respectively but D:A:D scored 52.4%. Cardiovascular disease is a leading cause of death in most population and has been recognised as an important cause of morbidity and mortality among PLHIV (Reinsch et al., 2012). In North America and Europe, CVD is the second most common cause of death among HIV-infected persons after AIDS-related mortality, hence a shift in long-term care of PLHIV to include more focused attention on cardiovascular risk assessment, prevention and appropriate management (Bonnet et al., 2002; Boccara et al., 2013; Aberg et al., 2014). The results of the present study indicate that using the FRS and WHO/ISH cardiovascular scoring systems, majority of the study participants were classified as having low risk of CVD. However, the D:A:D cardiovascular scoring system classified more than 50% of the study participants to be of moderate to high risk of CVD. Although the results of the low risk of CVD using the FRS and the WHO/ISH scoring systems are comparable to results of previous studies of 72.3% in Slovenians (Pirs et al., 2014), 60.3% in Germans (Reinsch et al., 2012), 93.3% in South Africans (Mashinya et al., 2015) and 88.3% in Nigerians (Edward et al., 2013), there are arguments on the appropriateness of the use of the FRS in evaluating the cardiovascular risk of HIV-positive individuals. Generally, in the HIV-uninfected individuals, it has been suggested that the FRS overestimates the risk of CVD in Europeans (D'Agostino et al., 2001; Brindle et al., 2003; Hense et al., 2003). This overestimation of the FRS have also been observed in HIV-infected Thais (Edwards-Jackson et al., 2011), Brazilians (Nery et al., 2013) and Europeans (Krikke et al., 2016). This has raised the issue on the appropriateness of use of the FRS in HIV-infected populations.

However, the present study points to an underestimation of risk of CVD using the FRS compared with the D:A:D score in this group of HIV-infected Ghanaian population. This present study estimation of 20.6% moderate to high risk of CVD (FRS) is similar to studies published by Mashinya et al. (2015), which noted that despite the level of agreement between the FRS and the D:A:D score in HIV-infected South Africans, the FRS still underestimates the risk of CVD among PLHIV (Mashinya et al., 2015). The study further iterated that this underestimation if not taken care of might lead to the exclusion of individuals who otherwise will benefit from an aggressive CVD risk prevention or management. The FRS has also been noted to underestimate the risk of CVD in the general HIV-uninfected South African population (Klug, 2012). This clearly shows the inappropriateness of using the FRS in sub-Saharan Africa populations and in particular HIV-infected individuals in this sub-region.

The WHO/ISH prediction chart score is an alternative risk score developed by the WHO for epidemiological sub-regions but has seldom been used in general and in HIV-infected populations in particular. The present study report of 86.7% of the study participants with low risk of CVD using the WHOI/ISH prediction chart is comparable to a study reported in Nigeria of 87.2% (Edward et al., 2013). However, the level of agreement between the FRS and the WHO/ISH score is over 75.0% (data not shown) indicating that it is most probably the WHO/ISH score may also underestimate the level of risk of CVD among PLHIV in sub-Sahara Africa. The sparse amount of literature in this direction however makes this argument debatable.

In the present study, whilst all the three cardiovascular scoring systems relatively had similar scores for individuals with high risk of CVD, the most striking difference between the systems is in the scoring of individuals with either low or moderate risk of CVD. The D:A:D scoring system tend to classify more individuals into the moderate risk class than the FRS and the WHO/ISH risk prediction chart which is similar to results from other studies (Nery et al., 2013). The important aspect of this group of patients who are in the moderate risk category is their relatively shorter progression time to the high-risk group if not managed appropriately because of the HIV-infection and ART. This makes the D:A:D risk scoring system more appropriate to be used in HIV infected individuals and especially in patients on ART. In fact, the D:AD score also indicated that 93.3% and 87.8% of those classified as of high risk or of moderate risk of CVD respectively were on ART (data not shown). Other studies have noted the accuracy of using the D:A:D risk score in identifying HIV-positive individuals with high risk of CVD but a thorough review of this literature has been discussed by D'Agostino (2011).

5.7 General discussion

With the increasing prevalence of HIV in Ghana and as patients grow older, the occurrence of hypertension and other cardiovascular risk factors will be seen among PLHIV especially in patients on ART. In addition, although currently the estimated risk score of cardiovascular event is low or moderate in most patients, up-scaling of the CD4+ T cell count threshold for initiation of ART combined with the ageing of the population of PLHIV, most patients will eventually fall into the high risk group and will need management of these cardiovascular events. HIV care however provides a good opportunity for the management of hypertension and other chronic cardiovascular events with regular assessment. Regular blood pressure measurement, although currently routine in the HIV clinic, should be considered an essential element of HIV care. In addition, studies from South Africa have shown that when non-communicable diseases care is integrated into HIV care, patients on ART do attain better functional ability and health status (Nyirenda et al., 2012; Mutevedzi et al., 2013). Thus, the current changing pattern of co-morbidities especially cardiovascular diseases among PLHIV will require health policies and interventions, which may have to incorporate the integration of chronic disease management into HIV care (Bloomfield et al., 2014b; Bloomfield et al., 2014a; Oni et al., 2014). Although, there is paucity of data in the cost-benefit analysis of such a policy direction, there has been suggestions that integrating chronic disease management into existing HIV care may in the long term be more cost effective compared with the traditional vertical approach and single disease management (Hyle et al., 2014). In fact, such a position is supported by results from a pilot study at a secondary health facility in Nigeria, which concluded that it is feasible and therefore a need to integrate cardiovascular screening and management into HIV care in order to improve life expectancy and sustain gains made in HIV care in the era of ART (Gwarzo et al., 2012).

5.8 Study limitations

The current study used a cross sectional study design to determine prevalence of hypertension and associated factors in patients attending HIV clinic at the KBTH in Accra. Inferences from this study should be done in the context of the study design as temporality cannot be established. There is no information on the timing of the outcome relative to the exposures hence this limits any causal inference including reverse causation (outcome changing exposure) for some of the factors found to be associated with hypertension in the regression modelling analysis. However, in an effort to reduce the effect of reverse causation for HIV/ART-related factors, potential study participants were excluded if they have been diagnosed with hypertension prior to HIV infection diagnosis/initiation of ART.

In addition, some variables used in the PSM analysis were extracted from the clinical folders of study participants and hence their appropriateness depends on the extent of correctness attached to these data when they were collected. Blood pressure readings were performed at two different clinic days and may be subject of fluctuation secondary to human and equipment-related factors; however, this was adjusted in the analysis and any measurement difference would likely be of a non-differential type.

Another limitation of this study is that data were based on measurements taken at one point in time according to clinical indications and will be assumed to reflect their chronic condition. Study participant did not receive a definitive diagnosis of hypertension based on the measurements done, but nonetheless, the 2012 WHO STEPwise approach to chronic disease risk-factor surveillance instrument was used (WHO, 2012).

In addition, factors like family history of CVD/hypertension, smoking, alcohol use, physical inactivity were based on study participants' self-report. Thus it is possible for respondents to be tempted to present themselves in a more favourable way by giving health-conscious answers in what is termed "social desirability"(Dimala et al., 2016). Finally, the study did not include HIV-negative control group for better comparison on HIV-related factors between HIV–positive individuals and HIV-negative individuals.

5.9 Study strengths and contribution to knowledge

This is the first study to the best of my knowledge to associate a plausible causal relationship between ART and increased prevalence of hypertension using propensity score-matching analysis. In addition, this study is the second to the best of my knowledge to infer a plausible causal relationship between ART and increased systolic and diastolic blood pressure values using propensity score-matching analysis. Another strength of this study is the use of a statistical model (propensity score-matching analysis) to investigate a potential causal link between ART and blood pressure which otherwise ethical challenges would have hindered the design of a randomized control trail to investigate the potential causal link. In addition, the inference of causal link using estimated ATT reflects a higher level of evidence and a substantial lower risk of not accounting for residual confounding compared with other observational studies which used regression modelling techniques (Seeger et al., 2007; Austin, 2011b) . Another strength of the study is the methods used in ensuring that the selected covariates in the propensity score-matching sample were sufficiently and appropriately balanced between the ART-naive group and the ART-exposed group using a comprehensive three step process; differences in means or proportions, standardised bias after matching and ratio of variances (Austin, 2011b). In addition, the covariates selected in estimation of the propensity score included the risk factors of hypertension known to persist in the general population.

Also relevant is that this is the first study conducted in Ghana's largest HIV cohort, to assess the general risk of cardiovascular events among PLHIV using recognised cardiovascular risk score assessment tools.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The outcome of this study clearly shows a high prevalence of hypertension in patients attending the HIV clinic at the KBTH. This observed high prevalence of hypertension could be due to an "unmasking" of an already high predisposition to hypertension by the HIV infection itself, the initiation of ARVs and an ageing HIV cohort as figures from the NACP indicate the 45-49 years' age group have the highest prevalence of HIV in Ghana. Due to the ongoing debate on the association between ART and hypertension, a propensity score-matching analysis was employed to examine the average treatment effect of ART on hypertension and blood pressure values. The present finding acknowledges ART-associated increase in blood pressure as an entity and results of the PSM analysis indicate a plausible causal relationship between ART and hypertension with increases in both systolic and diastolic blood pressure values. The reported plausible causal link between ART and hypertension/increases in blood pressure values, which represents a transition from association to causation, could be a significant step in policy formulation in taking preventive action against hypertension and its complications among PLHIV. Regression modelling analysis to determine factors associated with hypertension indicated that the risk factors for hypertension i.e. increasing age, positive family history of CVD/hypertension, inadequate exercising, general overweight/obesity and abdominal obesity were associated with hypertension. In addition, hypercholesterolemia, exposure to ART and duration of this ART exposure were also found to be associated with hypertension. Finally, using D:A:D risk assessment system, it was found that over 50% of the individuals who participated in the study were having a moderate to high risk of CVD. Outcome from this study highlights the need to perform cardiovascular risk assessment before initiation of ART and periodic assessments to ensure prompt detection and management of these risk factors to prevent the occurrence of cardiovascular events. Although the current NACP guidelines recognises the possibility of drug-drug interaction between ARVs administered and some antihypertensive drugs, and adverse events monitoring for metabolic abnormalities, there is no direction on the systematic screening, prevention and management of CVD among PLHIV. As the HIV infected cohort grows in age but cardiovascular events are yet to reach alarming proportions, this presents a rare opportunity to understand and decrease cardiovascular risk among PLHIV. The results of this study will help shape policy considering the magnitude of risk of CVD among PLHIV and the fact that the prevalence of HIV in Ghana is on the ascendency.

6.2 Recommendations

Policy-relevant recommendations

1. A policy framework on CVD risk assessment, prevention and management in patients attending KBTH HIV clinic should be formulated (including the use of D:A:D CVD risk assessment tool)-Such preventive measures are especially crucial for Ghana, where HIV prevalence is increasing, trends in cardiovascular disease risk factors are rising persistently and antiretroviral treatment coverage is anticipated to widen.
2. Research into the feasibility of integration of NCD care into HIV-care so that patients need not seek this care from clinics where they may feel uncomfortable in disclosing their HIV status to attending healthcare givers.

Practice-related recommendations

1. Blood pressure monitoring should move from being routine at the KBTH HIV clinic to more of purposeful screening of patients for hypertension and patients should be encouraged to have regular blood pressure measurements at home and not only when they visit the clinic
2. Waist circumference as a marker of abdominal obesity should be regularly measured in patients attending HIV clinic at the KBTH in Accra.

Further research-related recommendations

1. A longitudinal study is recommended to establish a cohort of patients attending HIV clinic at the KBTH to understand better the treatment effect of specific ARVs on specific cardiovascular events.
2. Future research should look at the incorporation HIV-negative controls in a cohort study for better assessment of effect of HIV status on risk of cardiovascular events in patients receiving HIV care in Ghana.
3. A systematic review and meta-analysis on the burden of CVD risk factors in PLHIV specifically in the SSA region is recommended.
4. Usage of PSM analysis should be encouraged in epidemiological studies involving HIV care in Ghana.

REFERENCES

Aberg, J. A. 2009. Cardiovascular complications in HIV management: past, present, and future. *J Acquir Immune Defic Syndr,* 50, 54-64.

Aberg, J. A., Gallant, J. E., Ghanem, K. G., Emmanuel, P., Zingman, B. S. & Horberg, M. A. 2014. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis,* 58, 1-10.

Abhyankar, L. N., Jones, M. R., Guallar, E. & Navas-Acien, A. 2012. Arsenic exposure and hypertension: a systematic review. *Environ Health Perspect,* 120, 494-500.

Aboud, M., Elgalib, A., Pomeroy, L., Panayiotakopoulos, G., Skopelitis, E., Kulasegaram, R., Dimian, C., F, C. L., Duncan, A., Wierzbicki, A. S. & Peters, B. S. 2010. Cardiovascular risk evaluation and antiretroviral therapy effects in an HIV cohort: implications for clinical management: the CREATE 1 study. *Int J Clin Pract,* 64, 1252-9.

American Diabetes Association (ADA). 2012. Diagnosis and classification of diabetes mellitus. *Diabetes Care,* 35 Suppl 1, S64-71.

Addo, J., Smeeth, L. & Leon, D. A. 2007. Hypertension in sub-saharan Africa: a systematic review. *Hypertension,* 50, 1012-8.

Addo, J., Agyemang, C., Smeeth, L., de-Graft Aikins, A., Edusei, A. K. & Ogedegbe, O. 2012. A review of population-based studies on hypertension in Ghana. *Ghana Med J,* 46, 4-11.

Adeloye, D. & Basquill, C. 2014. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. *PLoS One,* 9, e104300.

AIDSinfo. 2016. *HIV Overview FDA-Approved HIV Medicines* [Online]. Rockville, MD U.S. Department of Health and Human Services (HHS). Available: https://aidsinfo.nih.gov/education-materials/fact-sheets/19/58/fda-approved-hiv-medicines [Accessed 16th May 2016].

Alter, G., Heckerman, D., Schneidewind, A., Fadda, L., Kadie, C. M., Carlson, J. M., Oniangue-Ndza, C., Martin, M., Li, B., Khakoo, S. I., Carrington, M., Allen, T. M. & Altfeld, M. 2011. HIV-1 adaptation to NK-cell-mediated immune pressure. *Nature,* 476, 96-100.

Anderson, T. J., Gregoire, J., Hegele, R. A., Couture, P., Mancini, G. B., McPherson, R., Francis, G. A., Poirier, P., Lau, D. C., Grover, S., Genest, J., Jr., Carpentier, A. C., Dufour, R., Gupta, M., Ward, R., Leiter, L. A., Lonn, E., Ng, D. S., Pearson, G. J., Yates, G. M., Stone, J. A. & Ur, E. 2013. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol,* 29, 151-67.

Anjana, M., Sandeep, S., Deepa, R., Vimaleswaran, K. S., Farooq, S. & Mohan, V. 2004. Visceral and central abdominal fat and anthropometry in relation to diabetes in Asian Indians. *Diabetes Care,* 27, 2948-53.

Ankrah, D. N. A., Lartey, M., Agyepong, I., Leufkens, H. G. M. & Mantel-Teeuwisse, A. K. 2015. Adherence and Treatment Change among HIV/AIDS Patients in Ghana – A Nested Case Control Study. *J AIDS Clin Res,* 6, 510.

Antonello, V. S., Antonello, I. C., Grossmann, T. K., Tovo, C. V., Pupo, B. B. & Winckler Lde, Q. 2015. Hypertension--an emerging cardiovascular risk factor in HIV infection. *J Am Soc Hypertens,* 9, 403-7.

Arguedas, J. A., Perez, M. I. & Wright, J. M. 2009. Treatment blood pressure targets for hypertension. *Cochrane Database Syst Rev*, CD004349.

Aronow, W. S., Fleg, J. L., Pepine, C. J., Artinian, N. T., Bakris, G., Brown, A. S., Ferdinand, K. C., Ann Forciea, M., Frishman, W. H., Jaigobin, C., Kostis, J. B., Mancia, G., Oparil, S., Ortiz, E., Reisin, E., Rich, M. W., Schocken, D. D., Weber, M. A., Wesley, D. J., Harrington, R. A., Bates, E. R., Bhatt, D. L., Bridges, C. R., Eisenberg, M. J., Ferrari, V. A., Fisher, J. D., Gardner, T. J., Gentile, F., Gilson, M. F., Hlatky, M. A., Jacobs, A. K., Kaul, S., Moliterno, D. J., Mukherjee, D., Rosenson, R. S., Stein, J. H. & Weitz, H. H. 2011. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Soc Hypertens,* 5, 259-352.

Arruda Junior, E. R., Lacerda, H. R., Moura, L. C., Albuquerque Mde, F., Miranda Filho Dde, B., Diniz, G. T., Albuquerque, V. M., Amaral, J. C., Ximenes, R. A. & Monteiro, V. S. 2010. Risk factors related to hypertension among patients in a cohort living with HIV/AIDS. *Braz J Infect Dis,* 14, 281-7.

Arts, E. J. & Hazuda, D. J. 2012. HIV-1 antiretroviral drug therapy. *Cold Spring Harb Perspect Med,* 2, a007161.

Aryee, P. A. 2009. *Interaction between anaemia and human immuno-deficiency virus infection in an asymptomatic population in South Africa.* PhD Thesis, University of Southampton.

Austin, P. C. 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med,* 28, 3083-107.

Austin, P. C. 2011a. A Tutorial and Case Study in Propensity Score Analysis: An Application to Estimating the Effect of In-Hospital Smoking Cessation Counseling on Mortality. *Multivariate Behav Res,* 46, 119-151.

Austin, P. C. 2011b. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res,* 46, 399-424.

Awotedu, K. O., Longo-Mbenza, B., Nasila, J. S., Awotedu, A. & Ekpebegh, C. 2012. Cardiometabolic risk, insulin resistance and immunity in HIV/AIDS patients receinving highly active retroviral therapy. *Int J Diabetes Dev Ctries,* 32, 145-150.

Baekken, M., Os, I., Sandvik, L. & Oektedalen, O. 2008. Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy. *J Hypertens,* 26, 2126-33.

Bain, L. E., Kum, A. P., Ekukwe, N. C., Clovis, N. C. & Enowbeyang, T. E. 2016. HIV, cardiovascular disease, and stroke in sub-Saharan Africa. *Lancet HIV,* 3, e341-2.

Baker, J. V. & Lundgren, J. D. 2011. Cardiovascular implications from untreated human immunodeficiency virus infection. *Eur Heart J,* 32, 945-51.

Baker, J. V., Neuhaus, J., Duprez, D., Kuller, L. H., Tracy, R., Belloso, W. H., De Wit, S., Drummond, F., Lane, H. C., Ledergerber, B., Lundgren, J., Nixon, D. E., Paton, N. I. & Neaton, J. D. 2011. Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection. *J Acquir Immune Defic Syndr,* 56, 36-43.

Barbaro, G. 2006. Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection. *Curr HIV Res,* 4, 79-85.

Barre-Sinoussi, F., Chermann, J. C., Rey, F., Nugeyre, M. T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rouzioux, C., Rozenbaum, W. & Montagnier, L. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science,* 220, 868-71.

Bavinger, C., Bendavid, E., Niehaus, K., Olshen, R. A., Olkin, I., Sundaram, V., Wein, N., Holodniy, M., Hou, N., Owens, D. K. & Desai, M. 2013. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One,* 8, e59551.

Becker, A. C., Sliwa, K., Stewart, S., Libhaber, E., Essop, A. R., Zambakides, C. A. & Essop, M. R. 2010. Acute coronary syndromes in treatment-naive black South africans with human immunodeficiency virus infection. *J Interv Cardiol,* 23, 70-7.

Becker, A. C., Jacobson, B., Singh, S., Sliwa, K., Stewart, S., Libhaber, E. & Essop, M. R. 2011. The thrombotic profile of treatment-naive HIV-positive Black South Africans with acute coronary syndromes. *Clin Appl Thromb Hemost,* 17, 264-72.

Beilin, L. J., Puddey, I. B. & Burke, V. 1996. Alcohol and hypertension--kill or cure? *J Hum Hypertens,* 10 Suppl 2, S1-5.

Benjamin, L. A., Corbett, E. L., Connor, M. D., Mzinganjira, H., Kampondeni, S., Choko, A., Hopkins, M., Emsley, H. C., Bryer, A., Faragher, B., Heyderman, R. S., Allain, T. J. & Solomon, T. 2016. HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: A case-control study. *Neurology,* 86, 324-33.

Bergersen, B. M., Sandvik, L., Dunlop, O., Birkeland, K. & Bruun, J. N. 2003. Prevalence of hypertension in HIV-positive patients on highly active retroviral therapy (HAART) compared with HAART-naive and HIV-negative controls: results from a Norwegian study of 721 patients. *Eur J Clin Microbiol Infect Dis,* 22, 731-6.

Bernardino de la Serna, J. I., Zamora, F. X., Montes, M. L., Garcia-Puig, J. & Arribas, J. R. 2010. [Hypertension, HIV infection, and highly active antiretroviral therapy]. *Enferm Infecc Microbiol Clin,* 28, 32-7.

Beyrer, C., Baral, S. D., van Griensven, F., Goodreau, S. M., Chariyalertsak, S., Wirtz, A. L. & Brookmeyer, R. 2012. Global epidemiology of HIV infection in men who have sex with men. *Lancet,* 380, 367-77.

Bhaskaran, K., Hamouda, O., Sannes, M., Boufassa, F., Johnson, A. M., Lambert, P. C. & Porter, K. 2008. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA,* 300, 51-9.

Bloomfield, G. S., Hogan, J. W., Keter, A., Sang, E., Carter, E. J., Velazquez, E. J. & Kimaiyo, S. 2011. Hypertension and obesity as cardiovascular risk factors among HIV seropositive patients in Western Kenya. *PLoS One,* 6, e22288.

Bloomfield, G. S., Khazanie, P., Morris, A., Rabadan-Diehl, C., Benjamin, L. A., Murdoch, D., Radcliff, V. S., Velazquez, E. J. & Hicks, C. 2014a. HIV and noncommunicable cardiovascular and pulmonary diseases in low- and middle-income countries in the ART era: what we know and best directions for future research. *J Acquir Immune Defic Syndr,* 67 Suppl 1, S40-53.

Bloomfield, G. S., Hogan, J. W., Keter, A., Holland, T. L., Sang, E., Kimaiyo, S. & Velazquez, E. J. 2014b. Blood pressure level impacts risk of death among HIV seropositive adults in Kenya: a retrospective analysis of electronic health records. *BMC Infect Dis,* 14, 284.

Boccara, F., Auclair, M., Cohen, A., Lefevre, C., Prot, M., Bastard, J. P., Capeau, J. & Caron-Debarle, M. 2010. HIV protease inhibitors activate the adipocyte renin angiotensin system. *Antivir Ther,* 15, 363-75.

Boccara, F., Lang, S., Meuleman, C., Ederhy, S., Mary-Krause, M., Costagliola, D., Capeau, J. & Cohen, A. 2013. HIV and coronary heart disease: time for a better understanding. *J Am Coll Cardiol,* 61, 511-23.

Boily, M. C., Baggaley, R. F., Wang, L., Masse, B., White, R. G., Hayes, R. J. & Alary, M. 2009. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis,* 9, 118-29.

Bonnet, F., Morlat, P., Chene, G., Mercie, P., Neau, D., Chossat, I., Decoin, M., Djossou, F., Beylot, J. & Dabis, F. 2002. Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy, Bordeaux, France, 1998-1999. *HIV Med,* 3, 195-9.

Boodram, B., Plankey, M. W., Cox, C., Tien, P. C., Cohen, M. H., Anastos, K., Karim, R., Hyman, C. & Hershow, R. C. 2009. Prevalence and correlates of elevated body mass index among HIV-positive and HIV-negative women in the Women's Interagency HIV Study. *AIDS Patient Care STDS,* 23, 1009-16.

Bosamiya, S. S. 2011. The immune reconstitution inflammatory syndrome. *Indian J Dermatol,* 56, 476-9.

Bosu, W. K. 2010. Epidemic of hypertension in Ghana: a systematic review. *BMC Public Health,* 10, 418.

Braitstein, P., Brinkhof, M. W., Dabis, F., Schechter, M., Boulle, A., Miotti, P., Wood, R., Laurent, C., Sprinz, E., Seyler, C., Bangsberg, D. R., Balestre, E., Sterne, J. A., May, M. & Egger, M. 2006. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet,* 367, 817-24.

Briasoulis, A., Agarwal, V. & Messerli, F. H. 2012. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich),* 14, 792-8.

Brindle, P., Emberson, J., Lampe, F., Walker, M., Whincup, P., Fahey, T. & Ebrahim, S. 2003. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ,* 327, 1267.

Brothers, C. H., Hernandez, J. E., Cutrell, A. G., Curtis, L., Ait-Khaled, M., Bowlin, S. J., Hughes, S. H., Yeo, J. M. & Lapierre, D. H. 2009. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr,* 51, 20-8.

Brown, C. D., Higgins, M., Donato, K. A., Rohde, F. C., Garrison, R., Obarzanek, E., Ernst, N. D. & Horan, M. 2000. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res,* 8, 605-19.

Brummett, B. H., Babyak, M. A., Siegler, I. C., Shanahan, M., Harris, K. M., Elder, G. H. & Williams, R. B. 2011. Systolic blood pressure, socioeconomic status, and biobehavioral risk factors in a nationally representative US young adult sample. *Hypertension,* 58, 161-6.

Buchacz, K., Weidle, P. J., Moore, D., Were, W., Mermin, J., Downing, R., Kigozi, A., Borkowf, C. B., Ndazima, V. & Brooks, J. T. 2008. Changes in lipid profile over 24 months among adults on first-line highly active antiretroviral therapy in the home-based AIDS care program in rural Uganda. *J Acquir Immune Defic Syndr,* 47, 304-11.

Bursac, Z., Gauss, C. H., Williams, D. K. & Hosmer, D. W. 2008. Purposeful selection of variables in logistic regression. *Source Code Biol Med,* 3, 17.

Burt, V. L., Whelton, P., Roccella, E. J., Brown, C., Cutler, J. A., Higgins, M., Horan, M. J. & Labarthe, D. 1995. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension,* 25, 305-13.

Busari, O., Opadijo, O. & Adeyemi, O. 2007. Cardiac diseases in HIV and AIDS. *The Internet Journal of Cardiology,* 5.

Busari, O. A. & Busari, O. E. 2013. Cardiac diseases and metabolic syndrome in HIV infection. *Archives Medical Review Journal,* 22, 377-392.

Cahn, P., Leite, O., Rosales, A., Cabello, R., Alvarez, C. A., Seas, C., Carcamo, C., Cure-Bolt, N., L'Italien, G. P., Mantilla, P., Deibis, L., Zala, C. & Suffert, T. 2010. Metabolic profile and cardiovascular risk factors among Latin American HIV-infected patients receiving HAART. *Braz J Infect Dis,* 14, 158-66.

Cameron, A. J. & Zimmet, P. Z. 2008. Expanding evidence for the multiple dangers of epidemic abdominal obesity. *Circulation,* 117, 1624-6.

Campbell, N. R., Lackland, D. T. & Niebylski, M. L. 2014. High blood pressure: why prevention and control are urgent and important: a 2014 fact sheet from the World Hypertension League and the International Society of Hypertension. *J Clin Hypertens (Greenwich),* 16, 551-3.

Capeau, J. 2007. From lipodystrophy and insulin resistance to metabolic syndrome: HIV infection, treatment and aging. *Curr Opin HIV AIDS,* 2, 247-52.

Carnethon, M. R., Evans, N. S., Church, T. S., Lewis, C. E., Schreiner, P. J., Jacobs, D. R., Jr., Sternfeld, B. & Sidney, S. 2010. Joint associations of physical activity and aerobic fitness on the development of incident hypertension: coronary artery risk development in young adults. *Hypertension,* 56, 49-55.

Carr, A. 2003. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. *AIDS,* 17 Suppl 1, S141-8.

Centres for Disease Control (CDC) 1981. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. *MMWR,* 30, 305-8.

Centres for Disease Control (CDC) 1982. A cluster of Kaposi's sarcoma and Pneumocystis carinii pneumonia among homosexual male residents of Los Angeles and Orange Counties, California. *MMWR,* 31, 305-7.

Centres for Disease Control (CDC) 1983. Acquired immune deficiency syndrome (AIDS) in prison inmates-New York, New Jersey. *MMWR,* 31, 700-1.

Centres for Disease Control (CDC) 2015. *About HIV/AIDS* [Online]. Atlanta: Centres for Disease Control and Prevention. Available: http://www.cdc.gov/hiv/basics/whatishiv.html [Accessed 31-03-2016 2016].

Council on Foreign Relations (CFR) 2014. The Emerging Global Crisis: Noncommunicable Diseases in Low- and Middle-Income Countries. *In:* FORCE, I. T. (ed.). 58 East 68th Street, New York, NY 10065: Council on Foreign Relations.

Charan, J. & Biswas, T. 2013. How to calculate sample size for different study designs in medical research? *Indian J Psychol Med,* 35, 121-6.

Chastain, D. B., Henderson, H. & Stover, K. R. 2015. Epidemiology and management of antiretroviral-associated cardiovascular disease. *Open AIDS J,* 9, 23-37.

Cheng, S., Xanthakis, V., Sullivan, L. M. & Vasan, R. S. 2012. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham heart study. *Hypertension,* 60, 1393-9.

Cheung, B. M., Wat, N. M., Man, Y. B., Tam, S., Thomas, G. N., Leung, G. M., Cheng, C. H., Woo, J., Janus, E. D., Lau, C. P., Lam, T. H. & Lam, K. S. 2007. Development of diabetes in Chinese with the metabolic syndrome: a 6-year prospective study. *Diabetes Care,* 30, 1430-6.

Cheung, B. M., Wat, N. M., Tso, A. W., Tam, S., Thomas, G. N., Leung, G. M., Tse, H. F., Woo, J., Janus, E. D., Lau, C. P., Lam, T. H. & Lam, K. S. 2008a. Association between raised blood pressure and dysglycemia in Hong Kong Chinese. *Diabetes Care,* 31, 1889-91.

Cheung, B. M., Wat, N. M., Man, Y. B., Tam, S., Cheng, C. H., Leung, G. M., Woo, J., Janus, E. D., Lau, C. P., Lam, T. H. & Lam, K. S. 2008b. Relationship between the metabolic syndrome and the development of hypertension in the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISPS2). *Am J Hypertens,* 21, 17-22.

Cheung, B. M. 2010. The hypertension-diabetes continuum. *J Cardiovasc Pharmacol,* 55, 333-9.

Cheung, B. M. & Li, C. 2012. Diabetes and hypertension: is there a common metabolic pathway? *Curr Atheroscler Rep,* 14, 160-6.

Chillo, P., Bakari, M. & Lwakatare, J. 2012. Echocardiographic diagnoses in HIV-infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. *Cardiovasc J Afr,* 23, 90-7.

Chin, J. H. 2012. Stroke in sub-Saharan Africa: an urgent call for prevention. *Neurology,* 78, 1007-8.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., Jones, D. W., Materson, B. J., Oparil, S., Wright, J. T., Jr. & Roccella, E. J. 2003. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA,* 289, 2560-72.

Chow, C. K., Teo, K. K., Rangarajan, S., Islam, S., Gupta, R., Avezum, A., Bahonar, A., Chifamba, J., Dagenais, G., Diaz, R., Kazmi, K., Lanas, F., Wei, L., Lopez-Jaramillo, P., Fanghong, L., Ismail, N. H., Puoane, T., Rosengren, A., Szuba, A., Temizhan, A., Wielgosz, A., Yusuf, R., Yusufali, A., McKee, M., Liu, L., Mony, P. & Yusuf, S. 2013. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA,* 310, 959-68.

Chow, D. C., Souza, S. A., Chen, R., Richmond-Crum, S. M., Grandinetti, A. & Shikuma, C. 2003. Elevated blood pressure in HIV-infected individuals receiving highly active antiretroviral therapy. *HIV Clin Trials,* 4, 411-6.

Chow, F. C., Regan, S., Feske, S., Meigs, J. B., Grinspoon, S. K. & Triant, V. A. 2012. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr,* 60, 351-8.

Clavel, F., Guyader, M., Guetard, D., Salle, M., Montagnier, L. & Alizon, M. 1986a. Molecular cloning and polymorphism of the human immune deficiency virus type 2. *Nature,* 324, 691-5.

Clavel, F., Guetard, D., Brun-Vezinet, F., Chamaret, S., Rey, M. A., Santos-Ferreira, M. O., Laurent, A. G., Dauguet, C., Katlama, C., Rouzioux, C. & et al. 1986b. Isolation of a new human retrovirus from West African patients with AIDS. *Science,* 233, 343-6.

Clavel, F. & Hance, A. J. 2004. HIV drug resistance. *N Engl J Med,* 350, 1023-35.

Clumeck, N., Mascart-Lemone, F., de Maubeuge, J., Brenez, D. & Marcelis, L. 1983. Acquired immune deficiency syndrome in Black Africans. *Lancet,* 1, 642.

Coakley, E., Petropoulos, C. J. & Whitcomb, J. M. 2005. Assessing chemokine co-receptor usage in HIV. *Curr Opin Infect Dis,* 18, 9-15.

Coffin, J., Haase, A., Levy, J. A., Montagnier, L., Oroszlan, S., Teich, N., Temin, H., Toyoshima, K., Varmus, H., Vogt, P. & et al. 1986a. Human immunodeficiency viruses. *Science,* 232, 697.

Coffin, J., Haase, A., Levy, J. A., Montagnier, L., Oroszlan, S., Teich, N., Temin, H., Toyoshima, K., Varmus, H., Vogt, P. & et al. 1986b. What to call the AIDS virus? *Nature,* 321, 10.

Cohen, M. S., Hellmann, N., Levy, J. A., DeCock, K. & Lange, J. 2008. The spread, treatment, and prevention of HIV-1: evolution of a global pandemic. *J Clin Invest,* 118, 1244-54.

Coll, B., Parra, S., Alonso-Villaverde, C., Aragones, G., Montero, M., Camps, J., Joven, J. & Masana, L. 2007. The role of immunity and inflammation in the progression of atherosclerosis in patients with HIV infection. *Stroke,* 38, 2477-84.

Colloboration, A. T. C. 2010. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis,* 50, 1387-96.

Coloma Conde, A. G., Alvarez Albarran, M., Roca-Cusachs Coll, A., Domingo Pedrol, P. & Puig Campmany, M. 2008. [Prevalence of arterial hypertension and lipid profile in HIV patients]. *Med Clin (Barc),* 131, 681-4.

Conen, D., Glynn, R. J., Ridker, P. M., Buring, J. E. & Albert, M. A. 2009. Socioeconomic status, blood pressure progression, and incident hypertension in a prospective cohort of female health professionals. *Eur Heart J,* 30, 1378-84.

Cosgrove, C., Ussher, J. E., Rauch, A., Gartner, K., Kurioka, A., Huhn, M. H., Adelmann, K., Kang, Y. H., Fergusson, J. R., Simmonds, P., Goulder, P., Hansen, T. H., Fox, J., Gunthard, H. F., Khanna, N., Powrie, F., Steel, A., Gazzard, B., Phillips, R. E., Frater, J., Uhlig, H. & Klenerman, P. 2013. Early and nonreversible decrease of CD161++ /MAIT cells in HIV infection. *Blood,* 121, 951-61.

Coutsoudis, A., Kwaan, L. & Thomson, M. 2010. Prevention of vertical transmission of HIV-1 in resource-limited settings. *Expert Rev Anti Infect Ther,* 8, 1163-75.

Crane, H. M., Van Rompaey, S. E. & Kitahata, M. M. 2006. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. *AIDS,* 20, 1019-26.

Crane, H. M., Grunfeld, C., Harrington, R. D. & Kitahata, M. M. 2009. Lipoatrophy and lipohypertrophy are independently associated with hypertension. *HIV Med,* 10, 496-503.

Crowe, S. M., Westhorpe, C. L., Mukhamedova, N., Jaworowski, A., Sviridov, D. & Bukrinsky, M. 2010. The macrophage: the intersection between HIV infection and atherosclerosis. *J Leukoc Biol,* 87, 589-98.

Crum-Cianflone, N., Roediger, M. P., Eberly, L., Headd, M., Marconi, V., Ganesan, A., Weintrob, A., Barthel, R. V., Fraser, S. & Agan, B. K. 2010. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. *PLoS One,* 5, e10106.

Currier, J. S., Taylor, A., Boyd, F., Dezii, C. M., Kawabata, H., Burtcel, B., Maa, J. F. & Hodder, S. 2003. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr,* 33, 506-12.

D'Agostino, R. B., Sr., Grundy, S., Sullivan, L. M. & Wilson, P. 2001. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA,* 286, 180-7.

D'Agostino, R. B., Sr., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M. & Kannel, W. B. 2008. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation,* 117, 743-53.

D'Agostino, R. B., Sr. 2012. Cardiovascular risk estimation in 2012: lessons learned and applicability to the HIV population. *J Infect Dis,* 205 Suppl 3, S362-7.

Danaei, G., Finucane, M. M., Lin, J. K., Singh, G. M., Paciorek, C. J., Cowan, M. J., Farzadfar, F., Stevens, G. A., Lim, S. S., Riley, L. M. & Ezzati, M. 2011. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet,* 377, 568-77.

Daskalopoulou, S. S., Rabi, D. M., Zarnke, K. B., Dasgupta, K., Nerenberg, K., Cloutier, L., Gelfer, M., Lamarre-Cliche, M., Milot, A., Bolli, P., McKay, D. W., Tremblay, G., McLean, D., Tobe, S. W., Ruzicka, M., Burns, K. D., Vallee, M., Ramesh Prasad, G. V., Lebel, M., Feldman, R. D., Selby, P., Pipe, A., Schiffrin, E. L., McFarlane, P. A., Oh, P., Hegele, R. A., Khara, M., Wilson, T. W., Brian Penner, S., Burgess, E., Herman, R. J., Bacon, S. L., Rabkin, S. W., Gilbert, R. E., Campbell, T. S., Grover, S., Honos, G., Lindsay, P., Hill, M. D., Coutts, S. B., Gubitz, G., Campbell, N. R., Moe, G. W., Howlett, J. G., Boulanger, J. M., Prebtani, A., Larochelle, P., Leiter, L. A., Jones, C., Ogilvie, R. I., Woo, V., Kaczorowski, J., Trudeau, L., Petrella, R. J., Hiremath, S., Stone, J. A., Drouin, D., Lavoie, K. L., Hamet, P., Fodor, G., Gregoire, J. C., Fournier, A., Lewanczuk, R., Dresser, G. K., Sharma, M., Reid, D., Benoit, G., Feber, J., Harris, K. C., Poirier, L. & Padwal, R. S. 2015. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol,* 31, 549-68.

Dau, B. & Holodniy, M. 2008. The Relationship Between HIV Infection and Cardiovascular Disease. *Curr Cardiol Rev,* 4, 203-18.

Dauphinee, S. M. & Karsan, A. 2006. Lipopolysaccharide signaling in endothelial cells. *Lab Invest,* 86, 9-22.

de-Graft Aikins, A., Unwin, N., Agyemang, C., Allotey, P., Campbell, C. & Arhinful, D. 2010. Tackling Africa's chronic disease burden: from the local to the global. *Global Health,* 6, 5.

de Gaetano Donati, K., Rabagliati, R., Iacoviello, L. & Cauda, R. 2004. HIV infection, HAART, and endothelial adhesion molecules: current perspectives. *Lancet Infect Dis,* 4, 213-22.

de Simone, G., Devereux, R. B., Chinali, M., Roman, M. J., Best, L. G., Welty, T. K., Lee, E. T. & Howard, B. V. 2006. Risk factors for arterial hypertension in adults with initial optimal blood pressure: the Strong Heart Study. *Hypertension,* 47, 162-7.

De Socio, G. V., Parruti, G., Quirino, T., Ricci, E., Schillaci, G., Adriani, B., Marconi, P., Franzetti, M., Martinelli, C., Vichi, F., Penco, G., Sfara, C., Madeddu, G. &

Bonfanti, P. 2008. Identifying HIV patients with an unfavorable cardiovascular risk profile in the clinical practice: results from the SIMONE study. *J Infect,* 57, 33-40.

De Socio, G. V., Bonfanti, P., Martinelli, C., Ricci, E., Pucci, G., Marinoni, M., Vitiello, P., Menzaghi, B., Rizzardini, G. & Schillaci, G. 2010. Negative influence of HIV infection on day-night blood pressure variability. *J Acquir Immune Defic Syndr,* 55, 356-60.

De Socio, G. V., Ricci, E., Maggi, P., Parruti, G., Pucci, G., Di Biagio, A., Calza, L., Orofino, G., Carenzi, L., Cecchini, E., Madeddu, G., Quirino, T. & Schillaci, G. 2014. Prevalence, awareness, treatment, and control rate of hypertension in HIV-infected patients: the HIV-HY study. *Am J Hypertens,* 27, 222-8.

Denue, B. A., Muazu, J., Gashau, W., Mbo, D. N. & Ajayi, N. A. 2012. Effects of highly active antiretroviral therapy (HAART) on blood pressure changes and its associated factors in HAART naive HIV-infected patients in North eastern Nigeria. *Archives of Applied Science Research,* 4, 1447-1452.

Department of Health & Human Services (DHHS) 2010. Stages of HIV. U.S. Department of Health & Human Services.

Di Angelantonio, E., Sarwar, N., Perry, P., Kaptoge, S., Ray, K. K., Thompson, A., Wood, A. M., Lewington, S., Sattar, N., Packard, C. J., Collins, R., Thompson, S. G. & Danesh, J. 2009. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA,* 302, 1993-2000.

Diaz, K. M. & Shimbo, D. 2013. Physical activity and the prevention of hypertension. *Curr Hypertens Rep,* 15, 659-68.

Dillon, D. G., Gurdasani, D., Riha, J., Ekoru, K., Asiki, G., Mayanja, B. N., Levitt, N. S., Crowther, N. J., Nyirenda, M., Njelekela, M., Ramaiya, K., Nyan, O., Adewole, O. O., Anastos, K., Azzoni, L., Boom, W. H., Compostella, C., Dave, J. A., Dawood, H., Erikstrup, C., Fourie, C. M., Friis, H., Kruger, A., Idoko, J. A., Longenecker, C. T., Mbondi, S., Mukaya, J. E., Mutimura, E., Ndhlovu, C. E., Praygod, G., Pefura Yone, E. W., Pujades-Rodriguez, M., Range, N., Sani, M. U., Schutte, A. E., Sliwa, K., Tien, P. C., Vorster, E. H., Walsh, C., Zinyama, R., Mashili, F., Sobngwi, E., Adebamowo, C., Kamali, A., Seeley, J., Young, E. H., Smeeth, L., Motala, A. A., Kaleebu, P. & Sandhu, M. S. 2013. Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Epidemiol,* 42, 1754-71.

Dimala, C. A., Atashili, J., Mbuagbaw, J. C., Wilfred, A. & Monekosso, G. L. 2016. Prevalence of Hypertension in HIV/AIDS Patients on Highly Active Antiretroviral Therapy (HAART) Compared with HAART-Naive Patients at the Limbe Regional Hospital, Cameroon. *PLoS One,* 11, e0148100.

Dimodi, H. T., Etame, L. S., Nguimkeng, B. S., Mbappe, F. E., Ndoe, N. E., Tchinda, J. N., Ebene, J. J. A., Ntentie, F. R., Kingue, G. B. A., Angie, M.-A. M., Paka, G. D., Kouanfack, C., Ngondi, J. L. & Enyong, J. O. 2014. Prevalence of metabolic syndrome in HIV-infected Cameroonian patients. *World J AIDS,* 4, 85-92.

Ding, X., Andraca-Carrera, E., Cooper, C., Miele, P., Kornegay, C., Soukup, M. & Marcus, K. A. 2012. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr,* 61, 441-7.

Diouf, A., Cournil, A., Ba-Fall, K., Ngom-Gueye, N. F., Eymard-Duvernay, S., Ndiaye, I., Batista, G., Gueye, P. M., Ba, P. S., Taverne, B., Delaporte, E. & Sow, P. S. 2012. Diabetes and Hypertension among Patients Receiving Antiretroviral Treatment Since 1998 in Senegal: Prevalence and Associated Factors. *ISRN AIDS,* 2012, 621565.

Dodoo, A. N., Fogg, C., Asiimwe, A., Nartey, E. T., Kodua, A., Tenkorang, O. & Ofori-Adjei, D. 2009. Pattern of drug utilization for treatment of uncomplicated malaria in urban Ghana following national treatment policy change to artemisinin-combination therapy. *Malar J,* 8, 2.

Dube, M. P., Lipshultz, S. E., Fichtenbaum, C. J., Greenberg, R., Schecter, A. D. & Fisher, S. D. 2008. Effects of HIV infection and antiretroviral therapy on the heart and vasculature. *Circulation,* 118, e36-40.

Dugoff, E. H., Schuler, M. & Stuart, E. A. 2014. Generalizing observational study results: applying propensity score methods to complex surveys. *Health Serv Res,* 49, 284-303.

Duprez, D. A., Kuller, L. H., Tracy, R., Otvos, J., Cooper, D. A., Hoy, J., Neuhaus, J., Paton, N. I., Friis-Moller, N., Lampe, F., Liappis, A. P. & Neaton, J. D. 2009. Lipoprotein particle subclasses, cardiovascular disease and HIV infection. *Atherosclerosis,* 207, 524-9.

Edward, A. O., Oladayo, A. A., Omolola, A. S., Adetiloye, A. A. & Adedayo, P. A. 2013. Prevalence of traditional cardiovascular risk factors and evaluation of cardiovascular risk using three risk equations in nigerians living with human immunodeficiency virus. *N Am J Med Sci,* 5, 680-8.

Edwards-Jackson, N., Kerr, S., Tieu, H., Ananworanich, J., Hammer, S., Ruxrungtham, K., Phanuphak, P. & Avihingsanon, A. 2011. Cardiovascular risk assessment in persons with HIV infection in the developing world: comparing three risk equations in a cohort of HIV-infected Thais. *HIV Med,* 12, 510-5.

Edwards, J. K., Bygrave, H., Van den Bergh, R., Kizito, W., Cheti, E., Kosgei, R. J., Sobry, A., Vandenbulcke, A., Vakil, S. N. & Reid, T. 2015. HIV with non-communicable diseases in primary care in Kibera, Nairobi, Kenya: characteristics and outcomes 2010-2013. *Trans R Soc Trop Med Hyg,* 109, 440-6.

Ekali, L. G., Johnstone, L. K., Echouffo-Tcheugui, J. B., Kouanfack, C., Dehayem, M. Y., Fezeu, L., Nouthe, B., Hayes, L., Unwin, N. C. & Sobngwi, E. 2013. Fasting blood glucose and insulin sensitivity are unaffected by HAART duration in

Cameroonians receiving first-line antiretroviral treatment. *Diabetes Metab,* 39, 71-7.

Ekezie, J., Adebisi, S. S. & Danborno, B. 2009. Anthropometric study on the influence of sex and marital status on the Ibo ethnic group., 2009; 6: 70-75. *Bio and Env Sc J for the Trop,* 6, 70-75.

El-Sadr, W. M., Lundgren, J., Neaton, J. D., Gordin, F., Abrams, D., Arduino, R. C., Babiker, A., Burman, W., Clumeck, N., Cohen, C. J., Cohn, D., Cooper, D., Darbyshire, J., Emery, S., Fatkenheuer, G., Gazzard, B., Grund, B., Hoy, J., Klingman, K., Losso, M., Markowitz, N., Neuhaus, J., Phillips, A. & Rappoport, C. 2006. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med,* 355, 2283-96.

Eugenin, E. A., Morgello, S., Klotman, M. E., Mosoian, A., Lento, P. A., Berman, J. W. & Schecter, A. D. 2008. Human immunodeficiency virus (HIV) infects human arterial smooth muscle cells in vivo and in vitro: implications for the pathogenesis of HIV-mediated vascular disease. *Am J Pathol,* 172, 1100-11.

Ezzati, M., Hoorn, S. V., Rodgers, A., Lopez, A. D., Mathers, C. D. & Murray, C. J. 2003. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet,* 362, 271-80.

Fabian, J., Naicker, S., Goetsch, S. & Venter, W. D. 2013. The clinical and histological response of HIV-associated kidney disease to antiretroviral therapy in South Africans. *Nephrol Dial Transplant,* 28, 1543-54.

Farzan, S. F., Chen, Y., Wu, F., Jiang, J., Liu, M., Baker, E., Korrick, S. A. & Karagas, M. R. 2015. Blood Pressure Changes in Relation to Arsenic Exposure in a U.S. Pregnancy Cohort. *Environ Health Perspect,* 123, 999-1006.

Fedele, F., Bruno, N. & Mancone, M. 2011. Cardiovascular risk factors and HIV disease. *AIDS Rev,* 13, 119-29.

Feinstein, M. J., Kim, J. H., Bibangambah, P., Sentongo, R., Martin, J. N., Tsai, A. C., Bangsberg, D. R., Hemphill, L., Triant, V. A., Boum, Y., 2nd, Hunt, P. W., Okello, S. & Siedner, M. J. 2017. Ideal Cardiovascular Health and Carotid Atherosclerosis in a Mixed Cohort of HIV-Infected and Uninfected Ugandans. *AIDS Res Hum Retroviruses,* 33, 49-56.

Ferrannini, E. & Cushman, W. C. 2012. Diabetes and hypertension: the bad companions. *Lancet,* 380, 601-10.

Fichtenbaum, C. J. & Gerber, J. G. 2002. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. *Clin Pharmacokinet,* 41, 1195-211.

Fichtenbaum, C. J. 2003. Antiretrovirals and cardiovascular disease: is HAART bad for your heart? *AIDS Clin Care,* 15, 69-73, 76.

Fisher, N. D. & Williams, G. H. 2005. Hypertensive vascular disease. *In:* KASPER, D. L., BRAUNWALD, E. & FAUCI, A. S. (eds.) *Harrrison's Principles of Internal Medicine.* New York: McGraw-Hill.

Fisher, S. D., Miller, T. L. & Lipshultz, S. E. 2006. Impact of HIV and highly active antiretroviral therapy on leukocyte adhesion molecules, arterial inflammation, dyslipidemia, and atherosclerosis. *Atherosclerosis,* 185, 1-11.

Fontas, E., van Leth, F., Sabin, C. A., Friis-Moller, N., Rickenbach, M., d'Arminio Monforte, A., Kirk, O., Dupon, M., Morfeldt, L., Mateu, S., Petoumenos, K., El-Sadr, W., de Wit, S., Lundgren, J. D., Pradier, C. & Reiss, P. 2004. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis,* 189, 1056-74.

Fourie, C. M., van Rooyen, J. M. & Schutte, A. E. 2011. HIV infection and cardiovascular risk in black South Africans. *Cardiovasc J Afr,* 22, 117-9.

Fourie, C. M., Schutte, A. E., Smith, W., Kruger, A. & van Rooyen, J. M. 2015. Endothelial activation and cardiometabolic profiles of treated and never-treated HIV infected Africans. *Atherosclerosis,* 240, 154-60.

Freiberg, M. S., Chang, C. C., Kuller, L. H., Skanderson, M., Lowy, E., Kraemer, K. L., Butt, A. A., Bidwell Goetz, M., Leaf, D., Oursler, K. A., Rimland, D., Rodriguez Barradas, M., Brown, S., Gibert, C., McGinnis, K., Crothers, K., Sico, J., Crane, H., Warner, A., Gottlieb, S., Gottdiener, J., Tracy, R. P., Budoff, M., Watson, C., Armah, K. A., Doebler, D., Bryant, K. & Justice, A. C. 2013. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med,* 173, 614-22.

Friedewald, W. T., Levy, R. I. & Fredrickson, D. S. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem,* 18, 499-502.

Friis-Moller, N., Sabin, C. A., Weber, R., d'Arminio Monforte, A., El-Sadr, W. M., Reiss, P., Thiebaut, R., Morfeldt, L., De Wit, S., Pradier, C., Calvo, G., Law, M. G., Kirk, O., Phillips, A. N. & Lundgren, J. D. 2003. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med,* 349, 1993-2003.

Friis-Moller, N., Reiss, P., Sabin, C. A., Weber, R., Monforte, A., El-Sadr, W., Thiebaut, R., De Wit, S., Kirk, O., Fontas, E., Law, M. G., Phillips, A. & Lundgren, J. D. 2007. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med,* 356, 1723-35.

Friis-Moller, N., Thiebaut, R., Reiss, P., Weber, R., Monforte, A. D., De Wit, S., El-Sadr, W., Fontas, E., Worm, S., Kirk, O., Phillips, A., Sabin, C. A., Lundgren, J. D. & Law, M. G. 2010. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil,* 17, 491-501.

Friis-Moller, N., Ryom, L., Smith, C., Weber, R., Reiss, P., Dabis, F., De Wit, S., Monforte, A. D., Kirk, O., Fontas, E., Sabin, C., Phillips, A., Lundgren, J. & Law, M. 2016. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur J Prev Cardiol,* 23, 214-23.

Fu, S. Y., Li, W. M., Zhao, Y. J., Dong, L. H., Zhao, J. B., Wang, B. Q., Lu, Y. J. & Yang, B. F. 2010. Prevalence of hypertension and risk factors in Heilongjiang province in 2007. *Chin Med J (Engl),* 123, 752-5.

Gallant, J. E., Winston, J. A., DeJesus, E., Pozniak, A. L., Chen, S. S., Cheng, A. K. & Enejosa, J. V. 2008. The 3-year renal safety of a tenofovir disoproxil fumarate vs. a thymidine analogue-containing regimen in antiretroviral-naive patients. *AIDS,* 22, 2155-63.

Gallo, R. C., Salahuddin, S. Z., Popovic, M., Shearer, G. M., Kaplan, M., Haynes, B. F., Palker, T. J., Redfield, R., Oleske, J., Safai, B. & et al. 1984. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science,* 224, 500-3.

Gao, F., Bailes, E., Robertson, D. L., Chen, Y., Rodenburg, C. M., Michael, S. F., Cummins, L. B., Arthur, L. O., Peeters, M., Shaw, G. M., Sharp, P. M. & Hahn, B. H. 1999. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature,* 397, 436-41.

Garrido, M. M. 2014. Propensity scores: a practical method for assessing treatment effects in pain and symptom management research. *J Pain Symptom Manage,* 48, 711-8.

Garrido, M. M., Kelley, A. S., Paris, J., Roza, K., Meier, D. E., Morrison, R. S. & Aldridge, M. D. 2014. Methods for constructing and assessing propensity scores. *Health Serv Res,* 49, 1701-20.

Gazzaruso, C., Bruno, R., Garzaniti, A., Giordanetti, S., Fratino, P., Sacchi, P. & Filice, G. 2003. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. *J Hypertens,* 21, 1377-82.

Genest, J., McPherson, R., Frohlich, J., Anderson, T., Campbell, N., Carpentier, A., Couture, P., Dufour, R., Fodor, G., Francis, G. A., Grover, S., Gupta, M., Hegele, R. A., Lau, D. C., Leiter, L., Lewis, G. F., Lonn, E., Mancini, G. B., Ng, D., Pearson, G. J., Sniderman, A., Stone, J. A. & Ur, E. 2009. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol,* 25, 567-79.

Ghana Health Service (GHS) 2008. Outpatient morbidity in health services. Accra: Ghana Health Service.

Ghana Health Service (GHS) & National AIDS Control Programme (NACP) 2012. National AIDS Control Programme Bulletin. Accra: National AIDS Control Programme.

Ghana Health Service (GHS) 2012. Strategic objectives and new paradigm of the Ministry of Health. Accra: Ghana Health Service.

Go, A. S., Bauman, M. A., Coleman King, S. M., Fonarow, G. C., Lawrence, W., Williams, K. A. & Sanchez, E. 2014. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *Hypertension,* 63, 878-85.

Goonetilleke, N., Liu, M. K., Salazar-Gonzalez, J. F., Ferrari, G., Giorgi, E., Ganusov, V. V., Keele, B. F., Learn, G. H., Turnbull, E. L., Salazar, M. G., Weinhold, K. J., Moore, S., Letvin, N., Haynes, B. F., Cohen, M. S., Hraber, P., Bhattacharya, T., Borrow, P., Perelson, A. S., Hahn, B. H., Shaw, G. M., Korber, B. T. & McMichael, A. J. 2009. The first T cell response to transmitted/founder virus contributes to the control of acute viremia in HIV-1 infection. *J Exp Med,* 206, 1253-72.

Gravlee, C. C., Dressler, W. W. & Bernard, H. R. 2005. Skin color, social classification, and blood pressure in southeastern Puerto Rico. *Am J Public Health,* 95, 2191-7.

Gresele, P., Falcinelli, E., Sebastiano, M. & Baldelli, F. 2012. Endothelial and platelet function alterations in HIV-infected patients. *Thromb Res,* 129, 301-8.

Gress, T. W., Nieto, F. J., Shahar, E., Wofford, M. R. & Brancati, F. L. 2000. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med,* 342, 905-12.

Grinspoon, S. & Carr, A. 2005. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med,* 352, 48-62.

Grossman, E. & Messerli, F. H. 2012. Drug-induced hypertension: an unappreciated cause of secondary hypertension. *Am J Med,* 125, 14-22.

Grunfeld, C., Pang, M., Doerrler, W., Shigenaga, J. K., Jensen, P. & Feingold, K. R. 1992. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab,* 74, 1045-52.

Grunfeld, C., Kotler, D. P., Arnett, D. K., Falutz, J. M., Haffner, S. M., Hruz, P., Masur, H., Meigs, J. B., Mulligan, K., Reiss, P. & Samaras, K. 2008. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation,* 118, e20-8.

Ghana Statistical Service (GSS), Noguchi Memorial Institute for Medical Research (NMIMR) & ORC Macro 2004. Ghana Demographic and Health Survey 2003. Calverton, Maryland, USA: Ghana Statistical Service, Noguchi Memorial Institute for Medical Research, ORC Macro.

Ghana Statistical Service (GSS), Ghana Health Service (GHS) & ICF 2015. Ghana Demographic and Health Survey 2014. Rockville, Maryland, USA: Ghana Statistical Service, Ghana Health Service, ICF International. 2015.

Gulick, R. M. 2010. Antiretroviral treatment 2010: progress and controversies. *J Acquir Immune Defic Syndr,* 55 Suppl 1, S43-8.

Guyton, A. C. 1991. Blood pressure control--special role of the kidneys and body fluids. *Science,* 252, 1813-6.

Gwarzo, U., Maji, T., Isa-Dutse, S., Ahmed, Y., Obayagona, K., Okechukwu, E., Odafe, S., Khamofu, H., Torpey, K. & Chabikuli, O. 2012. Cardiovascular Disease Risk Factor Profiles of HIV-Infected Clients: Findings from a Pilot Program to Integrate CVD Screening into HIV Services at a Secondary Health Facility in Kano, North-Western Nigeria. *International AIDS Society Conference USA, ,* Abstract MOAE0104.

Hakim, J. G., Matenga, J. A. & Siziya, S. 1996. Myocardial dysfunction in human immunodeficiency virus infection: an echocardiographic study of 157 patients in hospital in Zimbabwe. *Heart,* 76, 161-5.

Halanych, J. H., Safford, M. M., Kertesz, S. G., Pletcher, M. J., Kim, Y. I., Person, S. D., Lewis, C. E. & Kiefe, C. I. 2010. Alcohol consumption in young adults and incident hypertension: 20-year follow-up from the Coronary Artery Risk Development in Young Adults Study. *Am J Epidemiol,* 171, 532-9.

Hall, H. I., McDavid, K., Ling, Q. & Sloggett, A. 2006. Determinants of progression to AIDS or death after HIV diagnosis, United States, 1996 to 2001. *Ann Epidemiol,* 16, 824-33.

Halperin, R. O., Sesso, H. D., Ma, J., Buring, J. E., Stampfer, M. J. & Gaziano, J. M. 2006. Dyslipidemia and the risk of incident hypertension in men. *Hypertension,* 47, 45-50.

Harrison, K. M., Song, R. & Zhang, X. 2010. Life expectancy after HIV diagnosis based on national HIV surveillance data from 25 states, United States. *J Acquir Immune Defic Syndr,* 53, 124-30.

Hartman, T. L. & Buckheit, R. W., Jr. 2012. The Continuing Evolution of HIV-1 Therapy: Identification and Development of Novel Antiretroviral Agents Targeting Viral and Cellular Targets. *Mol Biol Int,* 2012, 401965.

Hatsukami, D. K., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C. & Murphy, S. 2005. Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest,* 128, 2528-37.

Heikinheimo, T., Chimbayo, D., Kumwenda, J. J., Kampondeni, S. & Allain, T. J. 2012. Stroke outcomes in Malawi, a country with high prevalence of HIV: a prospective follow-up study. *PLoS One,* 7, e33765.

Hejazi, N., Huang, M. S., Lin, K. G. & Choong, L. C. 2013 Hypertension among HIV-infected adults receiving highly active antiretroviral therapy (HAART) in Malaysia. *Glob J Health Sci,* 6, 58-71.

Hemkens, L. G. & Bucher, H. C. 2014. HIV infection and cardiovascular disease. *Eur Heart J,* 35, 1373-81.

Hense, H. W., Schulte, H., Lowel, H., Assmann, G. & Keil, U. 2003. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany--results from the MONICA Augsburg and the PROCAM cohorts. *Eur Heart J,* 24, 937-45.

Hill, A. B. 1965. The Environment and Disease: Association or Causation? *Proc R Soc Med,* 58, 295-300.

Hirschhorn, L. R., Kaaya, S. F., Garrity, P. S., Chopyak, E. & Fawzi, M. C. 2012. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS,* 26 Suppl 1, S65-75.

Ho, J. E., Deeks, S. G., Hecht, F. M., Xie, Y., Schnell, A., Martin, J. N., Ganz, P. & Hsue, P. Y. 2010. Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals. *AIDS,* 24, 1897-905.

Hoffmann, M., Berger, J. R., Nath, A. & Rayens, M. 2000. Cerebrovascular disease in young, HIV-infected, black Africans in the KwaZulu Natal province of South Africa. *J Neurovirol,* 6, 229-36.

Holland, P. W. 1986. Statistics and Causal Inference. *J. Amer. Statis. Assoc.,* 81, 945-960.

Hooshyar, D., Hanson, D. L., Wolfe, M., Selik, R. M., Buskin, S. E. & McNaghten, A. D. 2007. Trends in perimortal conditions and mortality rates among HIV-infected patients. *AIDS,* 21, 2093-100.

Hosmer, D. W. & Lemeshow, S. 2000. Applied Logistic Regression. 2nd ed. New York: Wiley and Sons.

Hsue, P. Y., Lo, J. C., Franklin, A., Bolger, A. F., Martin, J. N., Deeks, S. G. & Waters, D. D. 2004. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation,* 109, 1603-8.

Hsue, P. Y., Hunt, P. W., Schnell, A., Kalapus, S. C., Hoh, R., Ganz, P., Martin, J. N. & Deeks, S. G. 2009. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS,* 23, 1059-67.

Hsue, P. Y., Deeks, S. G. & Hunt, P. W. 2012. Immunologic basis of cardiovascular disease in HIV-infected adults. *J Infect Dis,* 205 Suppl 3, S375-82.

Hu, W. S. & Hughes, S. H. 2012. HIV-1 reverse transcription. *Cold Spring Harb Perspect Med,* 2.

Hyle, E. P., Naidoo, K., Su, A. E., El-Sadr, W. M. & Freedberg, K. A. 2014. HIV, tuberculosis, and noncommunicable diseases: what is known about the costs, effects, and cost-effectiveness of integrated care? *J Acquir Immune Defic Syndr,* 67 Suppl 1, S87-95.

Hyle, E. P., Mayosi, B. M., Middelkoop, K., Mosepele, M., Martey, E. B., Walensky, R. P., Bekker, L. G. & Triant, V. A. 2017. The association between HIV and atherosclerotic cardiovascular disease in sub-Saharan Africa: a systematic review. *BMC Public Health,* 17, 954.

International Committee on Taxonomy of Viruses (ICTV) 2002. *Lentivirus and Retroviridae* [Online]. Available: http://www.ictvonline.org/taxonomyReleases.asp [Accessed 10th May 2016].

International Diabetes Federation (IDF), Union for International Cancer Control (UICC) & World Heart Federation 2009. Report on 'Health development: Held back by Non-communicable diseases. *Time to act: The Global Emergency of Non-communicable diseases.*

Ikeda, M. L., Barcellos, N. T., Alencastro, P. R., Wolff, F. H., Brandao, A. B., Fuchs, F. D. & Fuchs, S. C. 2013. Association of blood pressure and hypertension with alcohol consumption in HIV-infected white and nonwhite patients. *ScientificWorldJournal,* 2013, 169825.

Ilyas, M. 2009. Hypetension in adults: Part 1. Prevalence, types, causes and effects. *Southern Sudan Medical Journal,* 2, 9-10.

Imbens, G. W. 2000. The role of the propensity score in estimating dose rsponse functions. *Biometrica,* 87, 706-10.

Imbens, G. W. 2004. Nonparametric estimation of average treatment effects under exogeneity: A review. *Rev Econ Stat,* 86, 4-29.

Isa, S. E. 2015. Cardiovascular disease in HIV-infected patients: a focus on diabetes mellitus and hypertension? *African Journal of Diabetes Medicine,* 23, 5-8.

Islam, F. M., Wu, J., Jansson, J. & Wilson, D. P. 2012. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med,* 13, 453-68.

James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., Lackland, D. T., LeFevre, M. L., MacKenzie, T. D., Ogedegbe, O., Smith, S. C., Jr., Svetkey, L. P., Taler, S. J., Townsend, R. R., Wright, J. T., Jr., Narva, A. S. & Ortiz, E. 2014. 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,* 311, 507-20.

Janssen, I., Katzmarzyk, P. T. & Ross, R. 2004. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr,* 79, 379-84.

Jerico, C., Knobel, H., Montero, M., Sorli, M. L., Guelar, A., Gimeno, J. L., Saballs, P., Lopez-Colomes, J. L. & Pedro-Botet, J. 2005. Hypertension in HIV-infected patients: prevalence and related factors. *Am J Hypertens,* 18, 1396-401.

Jerico, C., Knobel, H., Sorli, M. L., Montero, M., Guelar, A. & Pedro-Botet, J. 2006. [Prevalence of cardiovascular risk factors in HIV-infected patients]. *Rev Clin Esp,* 206, 556-9.

Jervase, E., Barnabas, D., Emeka, A. & Osondu, N. 2008. Sex Differences And Relationship Between Blood Pressure And Age Among The Ibos Of Nigeria. *The Internet J Bio Anthrop,* 3, 1-5.

Jiang, J., Liu, M., Parvez, F., Wang, B., Wu, F., Eunus, M., Bangalore, S., Newman, J. D., Ahmed, A., Islam, T., Rakibuz-Zaman, M., Hasan, R., Sarwar, G., Levy, D., Slavkovich, V., Argos, M., Bryan, M. S., Farzan, S. F., Hayes, R. B., Graziano, J. H., Ahsan, H. & Chen, Y. 2015. Association between Arsenic Exposure from Drinking Water and Longitudinal Change in Blood Pressure among HEALS Cohort Participants. *Environ Health Perspect,* 123, 806-12.

Joshi, R., Jan, S., Wu, Y. & MacMahon, S. 2008. Global inequalities in access to cardiovascular health care: our greatest challenge. *J Am Coll Cardiol,* 52, 1817-25.

Kagaruki, G. B., Mayige, M. T., Ngadaya, E. S., Kimaro, G. D., Kalinga, A. K., Kilale, A. M., Kahwa, A. M., Materu, G. S. & Mfinanga, S. G. 2014. Magnitude and risk factors of non-communicable diseases among people living with HIV in Tanzania: a cross sectional study from Mbeya and Dar es Salaam regions. *BMC Public Health,* 14, 904.

Kahn, J. O. & Walker, B. D. 1998. Acute human immunodeficiency virus type 1 infection. *N Engl J Med,* 339, 33-9.

Kallings, L. O. 2008. The first postmodern pandemic: 25 years of HIV/ AIDS. *J Intern Med,* 263, 218-43.

Kalra, S. & Agrawal, N. 2013. Diabetes and HIV: current understanding and future perspectives. *Curr Diab Rep,* 13, 419-27.

Kaplan, R. C., Kingsley, L. A., Sharrett, A. R., Li, X., Lazar, J., Tien, P. C., Mack, W. J., Cohen, M. H., Jacobson, L. & Gange, S. J. 2007. Ten-year predicted coronary heart disease risk in HIV-infected men and women. *Clin Infect Dis,* 45, 1074-81.

Kaplan, R. C., Kingsley, L. A., Gange, S. J., Benning, L., Jacobson, L. P., Lazar, J., Anastos, K., Tien, P. C., Sharrett, A. R. & Hodis, H. N. 2008. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. *AIDS,* 22, 1615-24.

Kaplan, R. C., Sinclair, E., Landay, A. L., Lurain, N., Sharrett, A. R., Gange, S. J., Xue, X., Hunt, P., Karim, R., Kern, D. M., Hodis, H. N. & Deeks, S. G. 2011. T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. *J Infect Dis,* 203, 452-63.

Kayima, J., Nankabirwa, J., Sinabulya, I., Nakibuuka, J., Zhu, X., Rahman, M., Longenecker, C. T., Katamba, A., Mayanja-Kizza, H. & Kamya, M. R. 2015. Determinants of hypertension in a young adult Ugandan population in epidemiological transition-the MEPI-CVD survey. *BMC Public Health,* 15, 830.

Kearney, P. M., Whelton, M., Reynolds, K., Whelton, P. K. & He, J. 2004. Worldwide prevalence of hypertension: a systematic review. *J Hypertens,* 22, 11-9.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K. & He, J. 2005. Global burden of hypertension: analysis of worldwide data. *Lancet,* 365, 217-23.

Kline, E. R. & Sutliff, R. L. 2008. The roles of HIV-1 proteins and antiretroviral drug therapy in HIV-1-associated endothelial dysfunction. *J Investig Med,* 56, 752-69.

Klug, E. Q. 2012. *South African Dyslipidaemia Guideline Consensus Statement.*

Kolapo, K. O. & Vento, S. 2011. Stroke: a realistic approach to a growing problem in sub-Saharan Africa is urgently needed. *Trop Med Int Health,* 16, 707-10.

Krauskopf, K., Van Natta, M. L., Danis, R. P., Gangaputra, S., Ackatz, L., Addessi, A., Federman, A. D., Branch, A. D., Meinert, C. L. & Jabs, D. A. 2013. Correlates of hypertension in patients with AIDS in the era of highly active antiretroviral therapy. *J Int Assoc Provid AIDS Care,* 12, 325-33.

Krikke, M., Hoogeveen, R. C., Hoepelman, A. I., Visseren, F. L. & Arends, J. E. 2016. Cardiovascular risk prediction in HIV-infected patients: comparing the Framingham, atherosclerotic cardiovascular disease risk score (ASCVD), Systematic Coronary Risk Evaluation for the Netherlands (SCORE-NL) and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) risk prediction models. *HIV Med,* 17, 289-97.

Kumwenda, J. J., Mateyu, G., Kampondeni, S., van Dam, A. P., van Lieshout, L. & Zijlstra, E. E. 2005. Differential diagnosis of stroke in a setting of high HIV prevalence in Blantyre, Malawi. *Stroke,* 36, 960-4.

Kusuma, Y. S., Babu, B. V. & Naidu, J. M. 2002. Blood pressure levels among cross-cultural populations of Visakhapatnam district, Andhra Pradesh, India. *Ann Hum Biol,* 29, 502-12.

Kwarisiima, D., Balzer, L., Heller, D., Kotwani, P., Chamie, G., Clark, T., Ayieko, J., Mwangwa, F., Jain, V., Byonanebye, D., Petersen, M., Havlir, D. & Kamya, M. R. 2016. Population-Based Assessment of Hypertension Epidemiology and Risk Factors among HIV-Positive and General Populations in Rural Uganda. *PLoS One,* 11, e0156309.

Laaksonen, D. E., Niskanen, L., Nyyssonen, K., Lakka, T. A., Laukkanen, J. A. & Salonen, J. T. 2008. Dyslipidaemia as a predictor of hypertension in middle-aged men. *Eur Heart J,* 29, 2561-8.

Lang, S., Mary-Krause, M., Cotte, L., Gilquin, J., Partisani, M., Simon, A., Boccara, F. & Costagliola, D. 2010. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med,* 170, 1228-38.

Lasserson, D. S., Scherpbier de Haan, N., de Grauw, W., van der Wel, M., Wetzels, J. F. & O'Callaghan, C. A. 2016. What is the relationship between renal function and visit-to-visit blood pressure variability in primary care? Retrospective cohort study from routinely collected healthcare data. *BMJ Open,* 6, e010702.

Lawes, C. M., Vander Hoorn, S., Law, M. R., Elliott, P., MacMahon, S. & Rodgers, A. 2006. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. *J Hypertens,* 24, 423-30.

Lazar, J. M., Wu, X., Shi, Q., Kagame, A., Cohen, M., Binagwaho, A., Munyakazi, L., Salciccioli, L., Shi, D. & Anastos, K. 2009. Arterial wave reflection in HIV-infected and HIV-uninfected Rwandan women. *AIDS Res Hum Retroviruses,* 25, 877-82.

Lefevre, C., Auclair, M., Boccara, F., Bastard, J. P., Capeau, J., Vigouroux, C. & Caron-Debarle, M. 2010. Premature senescence of vascular cells is induced by HIV protease inhibitors: implication of prelamin A and reversion by statin. *Arterioscler Thromb Vasc Biol,* 30, 2611-20.

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T. & Coresh, J. 2009. A new equation to estimate glomerular filtration rate. *Ann Intern Med,* 150, 604-12.

Levitt, N. S., Steyn, K., Dave, J. & Bradshaw, D. 2011. Chronic noncommunicable diseases and HIV-AIDS on a collision course: relevance for health care delivery, particularly in low-resource settings--insights from South Africa. *Am J Clin Nutr,* 94, 1690S-1696S.

Levy, J. A. 1993. HIV pathogenesis and long-term survival. *AIDS,* 7, 1401-10.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R. & Collins, R. 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet,* 360, 1903-13.

Lichtenstein, K. A., Armon, C., Buchacz, K., Chmiel, J. S., Buckner, K., Tedaldi, E. M., Wood, K., Holmberg, S. D. & Brooks, J. T. 2010. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis,* 51, 435-47.

Lim, S. S., Gaziano, T. A., Gakidou, E., Reddy, K. S., Farzadfar, F., Lozano, R. & Rodgers, A. 2007. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. *Lancet,* 370, 2054-62.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., Amann, M., Anderson, H. R., Andrews, K. G., Aryee, M., Atkinson, C., Bacchus, L. J., Bahalim, A. N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M. L., Blore, J. D., Blyth, F., Bonner, C., Borges, G., Bourne, R., Boussinesq, M., Brauer, M., Brooks, P., Bruce, N. G., Brunekreef, B., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Bull, F., Burnett, R. T., Byers, T. E., Calabria, B., Carapetis, J., Carnahan, E., Chafe, Z., Charlson, F., Chen, H., Chen, J. S., Cheng, A. T., Child, J. C., Cohen, A., Colson, K. E., Cowie, B. C., Darby, S., Darling, S., Davis, A., Degenhardt, L., Dentener, F., Des Jarlais, D. C., Devries, K., Dherani, M., Ding, E. L., Dorsey, E. R., Driscoll, T., Edmond, K., Ali, S. E., Engell, R. E., Erwin, P. J., Fahimi, S., Falder, G., Farzadfar, F., Ferrari, A., Finucane, M. M., Flaxman, S., Fowkes, F. G., Freedman, G., Freeman, M. K., Gakidou, E., Ghosh, S., Giovannucci, E., Gmel, G., Graham, K., Grainger, R., Grant, B., Gunnell, D., Gutierrez, H. R., Hall, W., Hoek, H. W., Hogan, A., Hosgood, H. D., 3rd, Hoy, D., Hu, H., Hubbell, B. J., Hutchings, S. J., Ibeanusi, S. E., Jacklyn, G. L., Jasrasaria, R., Jonas, J. B., Kan, H., Kanis, J. A., Kassebaum, N., Kawakami, N., Khang, Y. H., Khatibzadeh, S., Khoo, J. P., Kok, C., Laden, F., et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380, 2224-60.

Linneberg, A., Jacobsen, R. K., Skaaby, T., Taylor, A. E., Fluharty, M. E., Jeppesen, J. L., Bjorngaard, J. H., Asvold, B. O., Gabrielsen, M. E., Campbell, A., Marioni, R. E., Kumari, M., Marques-Vidal, P., Kaakinen, M., Cavadino, A., Postmus, I., Ahluwalia, T. S., Wannamethee, S. G., Lahti, J., Raikkonen, K., Palotie, A., Wong, A., Dalgard, C., Ford, I., Ben-Shlomo, Y., Christiansen, L., Kyvik, K. O., Kuh, D., Eriksson, J. G., Whincup, P. H., Mbarek, H., de Geus, E. J., Vink, J. M., Boomsma, D. I., Smith, G. D., Lawlor, D. A., Kisialiou, A., McConnachie, A., Padmanabhan, S., Jukema, J. W., Power, C., Hypponen, E., Preisig, M., Waeber, G., Vollenweider, P., Korhonen, T., Laatikainen, T., Salomaa, V., Kaprio, J., Kivimaki, M., Smith, B. H., Hayward, C., Sorensen, T. I., Thuesen, B. H., Sattar, N., Morris, R. W., Romundstad, P. R., Munafo, M. R., Jarvelin, M. R. & Husemoen, L. L. 2015. Effect of Smoking on Blood Pressure and Resting Heart Rate: A Mendelian Randomization Meta-Analysis in the CARTA Consortium. *Circ Cardiovasc Genet,* 8, 832-41.

Lipowicz, A., Gronkiewicz, S. & Malina, R. M. 2002. Body mass index, overweight and obesity in married and never married men and women in Poland. *Am J Hum Biol,* 14, 468-75.

Liu, W., Kuramoto, S. J. & Stuart, E. A. 2013. An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prev Sci,* 14, 570-80.

Lloyd-Sherlock, P., Beard, J., Minicuci, N., Ebrahim, S. & Chatterji, S. 2014. Hypertension among older adults in low- and middle-income countries: prevalence, awareness and control. *Int J Epidemiol,* 43, 116-28.

Longenecker, C. T., Mondo, C., Le, V. V., Jensen, T. P. & Foster, E. 2011. HIV infection is not associated with echocardiographic signs of cardiomyopathy or pulmonary hypertension among pregnant Ugandan women. *Int J Cardiol,* 147, 300-2.

Longo-Mbenza, B., Tonduangu, K., Kintonki Vita, E. & Seghers, K. V. 1997. [The effect of HIV infection on high incidence of heart diseases in Kinshasa (Zaire). Echocardiographic study]. *Ann Cardiol Angeiol (Paris),* 46, 81-7.

Longo-Mbenza, B., Seghers, K. V., Phuati, M., Bikangi, F. N. & Mubagwa, K. 1998. Heart involvement and HIV infection in African patients: determinants of survival. *Int J Cardiol,* 64, 63-73.

Lucas, R. M. & McMichael, A. J. 2005. Association or causation: evaluating links between "environment and disease". *Bull World Health Organ,* 83, 792-5.

Maartens, G., Celum, C. & Lewin, S. R. 2014. HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet,* 384, 258-71.

Malaza, A., Mossong, J., Barnighausen, T. & Newell, M. L. 2012. Hypertension and obesity in adults living in a high HIV prevalence rural area in South Africa. *PLoS One,* 7, e47761.

Malvestutto, C. D. & Aberg, J. A. 2010. Coronary heart disease in people infected with HIV. *Cleve Clin J Med,* 77, 547-56.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Bohm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D. E., Jaarsma, T., Kirchhof, P., Kjeldsen, S. E., Laurent, S., Manolis, A. J., Nilsson, P. M., Ruilope, L. M., Schmieder, R. E., Sirnes, P. A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F., Burnier, M., Ambrosioni, E., Caufield, M., Coca, A., Olsen, M. H., Tsioufis, C., van de Borne, P., Zamorano, J. L., Achenbach, S., Baumgartner, H., Bax, J. J., Bueno, H., Dean, V., Deaton, C., Erol, C., Ferrari, R., Hasdai, D., Hoes, A. W., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M. F., Ponikowski, P., Tamargo, J. L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Clement, D. L., Gillebert, T. C., Rosei, E. A., Anker, S. D., Bauersachs, J., Hitij, J. B., Caulfield, M., De Buyzere, M., De Geest, S., Derumeaux, G. A., Erdine, S., Farsang, C., Funck-Brentano, C., Gerc, V., Germano, G., Gielen, S., Haller, H., Jordan, J., Kahan, T., Komajda, M., Lovic, D., Mahrholdt, H., Ostergren, J., Parati, G., Perk, J., Polonia, J., Popescu, B. A., Reiner, Z., Ryden, L., Sirenko, Y., Stanton, A., Struijker-Boudier, H., Vlachopoulos, C., Volpe, M. & Wood, D. A. 2013. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J,* 34, 2159-219.

Manner, I. W., Baekken, M., Kvale, D., Oektedalen, O., Pedersen, M., Nielsen, S. D., Nowak, P., Os, I. & Troseid, M. 2013a. Markers of microbial translocation predict hypertension in HIV-infected individuals. *HIV Med,* 14, 354-61.

Manner, I. W., Troseid, M., Oektedalen, O., Baekken, M. & Os, I. 2013b. Low nadir CD4 cell count predicts sustained hypertension in HIV-infected individuals. *J Clin Hypertens (Greenwich),* 15, 101-6.

Markowitz 2007. *Environmental and occupational medicine* Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins.

Mary-Krause, M., Cotte, L., Simon, A., Partisani, M. & Costagliola, D. 2003. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS,* 17, 2479-86.

Mashinya, F., Alberts, M., Colebunders, R. & Geetruyden, J.-P. V. 2014. Cardiovascular risk factors in treatment-naive, human immunodeficiency virus-infected rural population in Dikgale, South Africa. *South African Family Practice,* 56, 190-195.

Mashinya, F., Alberts, M., Van Geertruyden, J. P. & Colebunders, R. 2015. Assessment of cardiovascular risk factors in people with HIV infection treated with ART in rural South Africa: a cross sectional study. *AIDS Res Ther,* 12, 42.

Masur, H., Michelis, M. A., Wormser, G. P., Lewin, S., Gold, J., Tapper, M. L., Giron, J., Lerner, C. W., Armstrong, D., Setia, U., Sender, J. A., Siebken, R. S., Nicholas, P., Arlen, Z., Maayan, S., Ernst, J. A., Siegal, F. P. & Cunningham-Rundles, S. 1982. Opportunistic infection in previously healthy women. Initial manifestations of a community-acquired cellular immunodeficiency. *Ann Intern Med,* 97, 533-9.

Mateen, F. J., Kanters, S., Kalyesubula, R., Mukasa, B., Kawuma, E., Kengne, A. P. & Mills, E. J. 2013. Hypertension prevalence and Framingham risk score stratification in a large HIV-positive cohort in Uganda. *J Hypertens,* 31, 1372-8; discussion 1378.

Mathers, C. D. & Loncar, D. 2006. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med,* 3, e442.

Mayne, E. S. & George, J. A. 2017. Mortal allies: human immunodeficiency virus and noncommunicable diseases. *Curr Opin HIV AIDS,* 12, 148-156.

Mayosi, B. M., Flisher, A. J., Lalloo, U. G., Sitas, F., Tollman, S. M. & Bradshaw, D. 2009. The burden of non-communicable diseases in South Africa. *Lancet,* 374, 934-47.

McCormack, T., Krause, T. & O'Flynn, N. 2012. Management of hypertension in adults in primary care: NICE guideline. *Br J Gen Pract,* 62, 163-4.

Medina-Torne, S., Ganesan, A., Barahona, I. & Crum-Cianflone, N. F. 2012. Hypertension is common among HIV-infected persons, but not associated with HAART. *J Int Assoc Physicians AIDS Care,* 11, 20-5.

Meguid El Nahas, A. & Bello, A. K. 2005. Chronic kidney disease: the global challenge. *Lancet,* 365, 331-40.

Mehta, N. & Reilly, M. 2005. Atherosclerotic cardiovascular disease risk in the HAART-treated HIV-1 population. *HIV Clin Trials,* 6, 5-24.

Mendis, S., Lindholm, L. H., Mancia, G., Whitworth, J., Alderman, M., Lim, S. & Heagerty, T. 2007. World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. *J Hypertens,* 25, 1578-82.

Mermin, J., Were, W., Ekwaru, J. P., Moore, D., Downing, R., Behumbiize, P., Lule, J. R., Coutinho, A., Tappero, J. & Bunnell, R. 2008. Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study. *Lancet,* 371, 752-9.

Mills, A. M., Nelson, M., Jayaweera, D., Ruxrungtham, K., Cassetti, I., Girard, P. M., Workman, C., Dierynck, I., Sekar, V., Abeele, C. V. & Lavreys, L. 2009. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS,* 23, 1679-88.

Mills, E. J., Bakanda, C., Birungi, J., Chan, K., Ford, N., Cooper, C. L., Nachega, J. B., Dybul, M. & Hogg, R. S. 2011. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Ann Intern Med,* 155, 209-16.

Mirtz, T. A., Morgan, L., Wyatt, L. H. & Greene, L. 2009. An epidemiological examination of the subluxation construct using Hill's criteria of causation. *Chiropr Osteopat,* 17, 13.

Mochan, A., Modi, M. & Modi, G. 2003. Stroke in black South African HIV-positive patients: a prospective analysis. *Stroke,* 34, 10-5.

Ministry of Health (MOH) 2005. The Ghana health sector 2006 programmme of work. Accra: Ministry of Health.

Ministry of Health (MOH) 2011. 2010 Annual Report. Accra: Ministry of Health.

Moir, S., Chun, T. W. & Fauci, A. S. 2011. Pathogenic mechanisms of HIV disease. *Annu Rev Pathol,* 6, 223-48.

Molina, J. M., Andrade-Villanueva, J., Echevarria, J., Chetchotisakd, P., Corral, J., David, N., Moyle, G., Mancini, M., Percival, L., Yang, R., Wirtz, V., Lataillade, M., Absalon, J. & McGrath, D. 2010. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr,* 53, 323-32.

Monhart, V. 2013. Hypertension and chronic kidney diseases. *Cor et Vasa,* 55, E397-E402.

Moore, D. M., Yiannoutsos, C. T., Musick, B. S., Tappero, J., Degerman, R., Campbell, J., Were, W., Kaharuza, F., Alexander, L. N., Downing, R. & Mermim, J. 2011.

Determinants of early and late mortality among HIV-infected individuals receiving home-based antiretroviral therapy in rural Uganda. *J Acquir Immune Defic Syndr* 58, 289-296.

Morris, A., Gingo, M. R., George, M. P., Lucht, L., Kessinger, C., Singh, V., Hillenbrand, M., Busch, M., McMahon, D., Norris, K. A., Champion, H. C., Gladwin, M. T., Zhang, Y., Steele, C. & Sciurba, F. C. 2012. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. *AIDS,* 26, 731-40.

Mothe, B., Perez, I., Domingo, P., Podzamczer, D., Ribera, E., Curran, A., Vilades, C., Vidal, F., Dalmau, D., Pedrol, E., Negredo, E., Molto, J., Paredes, R., Perez-Alvarez, N., Gatell, J. M. & Clotet, B. 2009. HIV-1 infection in subjects older than 70: a multicenter cross-sectional assessment in Catalonia, Spain. *Curr HIV Res,* 7, 597-600.

Mouton, Y., Alfandari, S., Valette, M., Cartier, F., Dellamonica, P., Humbert, G., Lang, J. M., Massip, P., Mechali, D., Leclercq, P., Modai, J. & Portier, H. 1997. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. Federation National des Centres de Lutte contre le SIDA. *AIDS,* 11, F101-5.

Msango, L., Downs, J. A., Kalluvya, S. E., Kidenya, B. R., Kabangila, R., Johnson, W. D., Jr., Fitzgerald, D. W. & Peck, R. N. 2011. Renal dysfunction among HIV-infected patients starting antiretroviral therapy. *AIDS,* 25, 1421-5.

Muhammad, S., Sani, M. U. & Okeahialam, B. N. 2013. Cardiovascular disease risk factors among HIV-infected Nigerians receiving highly active antiretroviral therapy. *Niger Med J,* 54, 185-90.

Mulazzi, I., Cambou, J. P., Girerd, X., Nicodeme, R., Chamontin, B. & Amar, J. 2009. Six-item self-administered questionnaires in the waiting room: an aid to explain uncontrolled hypertension in high-risk patients seen in general practice. *J Am Soc Hypertens,* 3, 221-7.

Muronya, W., Sanga, E., Talama, G., Kumwenda, J. J. & van Oosterhout, J. J. 2011. Cardiovascular risk factors in adult Malawians on long-term antiretroviral therapy. *Trans R Soc Trop Med Hyg,* 105, 644-9.

Mutede, B. R., Magure, T., Gombe, N. T., Bangure, D., Tshimanga, M. & Mungati, M. 2015. Prevalence and factors associated with hypertension among anti-retroviral therapy patients aged 15 years and above in Makonde Distrct, Zimbabwe, 2012: An analytic cross sectional study. *World Journal of Cardiovascular Diseases,* 5, 266-277.

Mutevedzi, P. C., Rodger, A. J., Kowal, P., Nyirenda, M. & Newell, M. L. 2013. Decreased chronic morbidity but elevated HIV associated cytokine levels in HIV-infected older adults receiving HIV treatment: benefit of enhanced access to care? *PLoS One,* 8, e77379.

Mutimura, E., Crowther, N. J., Stewart, A. & Cade, W. T. 2008. The human immunodeficiency virus and the cardiometabolic syndrome in the developing world: an African perspective. *J Cardiometab Syndr,* 3, 106-10.

National AIDS Control Programme (NACP) 2008. 2007 HIV Sentinel Survey Report. Accra: Ghana Health Service, Ghana AIDS Commission, World Health Organisation, Department of International Development.

National AIDS Control Programme (NACP) 2009. 2008 HIV Sentinel Survey Report. *Ghana Health Service, Ministry of Health, Accra.* Accra: Ghana Health Service, Ministry of Health, Accra.

National AIDS Control Programme (NACP) 2010. 2009 HIV Sentinel Survey Report. Accra: National AIDS/STI Control Programme, Ghana Health Service, Ministry of Health, Accra Ghana.

National AIDS Control Programme (NACP), Ghana Health Service (GHS) & Mnistry of Health (MOH) 2014. Guidelines for Antiretrovral Therapy in Ghana. 5th ed.

National AIDS Control Programme (NACP) 2014. 2013 HIV Sentinel Survey Report. Accra: Ministry of Health.

National AIDS Control Programme (NACP) 2015. 2014 HIV Sentinel Survey Report. Accra: Ministry of Health.

National AIDS Control Programme (NACP) 2016. 2015 HIV Sentinel Survey Report. Accra: Ministry of Health.

National AIDS Control Programme (NACP). 2016 HIV Sentinel Survey Report. Accra: Ministry of Health.

Naish, J. & Syndercombe Court, D. 2014. *Medical Sciences,* London, Saunders Ltd.

National Cholesterol Education Program (NCEP) 2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation,* 106, 3143-421.

Nduka, C. U., Stranges, S., Sarki, A. M., Kimani, P. K. & Uthman, O. A. 2016a. Evidence of increased blood pressure and hypertension risk among people living with HIV on antiretroviral therapy: a systematic review with meta-analysis. *J Hum Hypertens,* 30, 355-62.

Nduka, C. U., Stranges, S., Bloomfield, G. S., Kimani, P. K., Achinge, G., Malu, A. O. & Uthman, O. A. 2016b. A plausible causal link between antiretroviral therapy and increased blood pressure in a sub-Saharan African setting: A propensity score-matched analysis. *Int J Cardiol,* 220, 400-7.

Nduka, C. U., Uthman, O. A., Kimani, P. K., Malu, A. O. & Stranges, S. 2016c. Impact of body fat changes in mediating the effects of antiretroviral therapy on blood pressure in HIV-infected persons in a sub-Saharan African setting. *Infect Dis Poverty,* 5, 55.

Negredo, E., Bonjoch, A. & Clotet, B. 2006. Benefits and concerns of simplification strategies in HIV-infected patients. *J Antimicrob Chemother,* 58, 235-42.

Nery, M. W., Martelli, C. M., Silveira, E. A., de Sousa, C. A., Falco Mde, O., de Castro Ade, C., Esper, J. T., Souza, L. C. & Turchi, M. D. 2013. Cardiovascular risk assessment: a comparison of the Framingham, PROCAM, and DAD equations in HIV-infected persons. *ScientificWorldJournal,* 2013, 969281.

Ngala, R. A. & Fianko, K. 2014. Effects of HIV infection and Antiretroviral Therapy on Cardiovascular Diseases. *Trends Mol. Sci.,* 6, 1-12.

Ngatchou, W., Lemogoum, D., Ndobo, P., Yagnigni, E., Tiogou, E., Nga, E., Kouanfack, C., van de Borne, P. & Hermans, M. P. 2013. Increased burden and severity of metabolic syndrome and arterial stiffness in treatment-naive HIV+ patients from Cameroon. *Vasc Health Risk Manag,* 9, 509-16.

Nguyen, K. A., Peer, N., Mills, E. J. & Kengne, A. P. 2016. A Meta-Analysis of the Metabolic Syndrome Prevalence in the Global HIV-Infected Population. *PLoS One,* 11, e0150970.

Niakara, A., Drabo, Y. J., Kambire, Y., Nebie, L. V., Kabore, N. J. & Simon, F. 2002. [Cardiovascular diseases and HIV infection: study of 79 cases at the National Hospital of Ouagadougou (Burkina Faso)]. *Bull Soc Pathol Exot,* 95, 23-6.

National Institute for Health and Care Excellence (NICE) 2011. *Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18, 34 and 127.* London.

Nigatu, T., Setswe, G., Elliott, J. & Oldenburg, B. 2012. Developing a Public Health Framework for the Epidemiological Linkages between HIV/AIDS and NCDs: A Thematic Research Synthesis. *International Journal of Prevention and Treatment,* 1, 53-60.

Njelekela, M., Muhihi, A., Aveika, A., Spiegelman, D., Hawkins, C., Armstrong, C., Liu, E., Okuma, J., Chalamila, G., Kaaya, S., Mugusi, F. & Fawzi, W. 2016. Prevalence of Hypertension and Its Associated Risk Factors among 34,111 HAART Naive HIV-Infected Adults in Dar es Salaam, Tanzania. *Int J Hypertens,* 2016, 5958382.

Nofer, J. R., Kehrel, B., Fobker, M., Levkau, B., Assmann, G. & von Eckardstein, A. 2002. HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis,* 161, 1-16.

Normand, S. T., Landrum, M. B., Guadagnoli, E., Ayanian, J. Z., Ryan, T. J., Cleary, P. D. & McNeil, B. J. 2001. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol,* 54, 387-98.

Norrving, B. & Kissela, B. 2013. The global burden of stroke and need for a continuum of care. *Neurology,* 80, S5-12.

Nsagha, D. S., Assob, J. C., Njunda, A. L., Tanue, E. A., Kibu, O. D., Ayima, C. W. & Ngowe, M. N. 2015. Risk Factors of Cardiovascular Diseases in HIV/AIDS Patients on HAART. *Open AIDS J,* 9, 51-9.

Ntsekhe, M. & Hakim, J. 2005. Impact of human immunodeficiency virus infection on cardiovascular disease in Africa. *Circulation,* 112, 3602-7.

Nuesch, R., Wang, Q., Elzi, L., Bernasconi, E., Weber, R., Cavassini, M., Vernazza, P., Thurnheer, M. C., Calmy, A., Battegay, M. & Bucher, H. C. 2013. Risk of cardiovascular events and blood pressure control in hypertensive HIV-infected patients: Swiss HIV Cohort Study (SHCS). *J Acquir Immune Defic Syndr,* 62, 396-404.

Nunez-Cordoba, J. M., Martinez-Gonzalez, M. A., Bes-Rastrollo, M., Toledo, E., Beunza, J. J. & Alonso, A. 2009. Alcohol consumption and the incidence of hypertension in a Mediterranean cohort: the SUN study. *Rev Esp Cardiol,* 62, 633-41.

Nyabera, R. A., Yonga, G., Mwangemi, F. & Bukachi, F. 2011. Evaluation of a project integrating cardiovascular care into HIV programmes. *Cardiovascular Journal of Africa,* 22, S17.

Nyirenda, M., Chatterji, S., Falkingham, J., Mutevedzi, P., Hosegood, V., Evandrou, M., Kowal, P. & Newell, M. L. 2012. An investigation of factors associated with the health and well-being of HIV-infected or HIV-affected older people in rural South Africa. *BMC Public Health,* 12, 259.

Nzuobontane, D., Blackett, K. N. & Kuaban, C. 2002. Cardiac involvement in HIV infected people in Yaounde, Cameroon. *Postgrad Med J,* 78, 678-81.

O'Rourke, M. F., Hayward, C. S. & Lehmann, E. D. 2000. Arterial stiffness. *In:* OPARAL, S. & WEBER, M. A. (eds.) *Hypertension: A Companion to Brenner and Rector's The Kidney.* Philadelphia: WB Saunders.

Ogah, O. S. & Rayner, B. L. 2013. Recent advances in hypertension in sub-Saharan Africa. *Heart,* 99, 1390-7.

Ogunmola, O. J., Oladosu, O. Y. & Olamoyegun, A. M. 2014. Association of hypertension and obesity with HIV and antiretroviral therapy in a rural tertiary health center in Nigeria: a cross-sectional cohort study. *Vasc Health Risk Manag,* 10, 129-37.

Okello, S., Kanyesigye, M., Muyindike, W. R., Annex, B. H., Hunt, P. W., Haneuse, S. & Siedner, M. J. 2015. Incidence and predictors of hypertension in adults with HIV-initiating antiretroviral therapy in South-western Uganda. *J Hypertens,* 33, 2039-45.

Oliviero, U., Bonadies, G., Apuzzi, V., Foggia, M., Bosso, G., Nappa, S., Valvano, A., Leonardi, E., Borgia, G., Castello, G., Napoli, R. & Sacca, L. 2009. Human immunodeficiency virus per se exerts atherogenic effects. *Atherosclerosis,* 204, 586-9.

Oni, T., McGrath, N., BeLue, R., Roderick, P., Colagiuri, S., May, C. R. & Levitt, N. S. 2014. Chronic diseases and multi-morbidity--a conceptual modification to the WHO ICCC model for countries in health transition. *BMC Public Health,* 14, 575.

Oni, T., Youngblood, E., Boulle, A., McGrath, N., Wilkinson, R. J. & Levitt, N. S. 2015. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa- a cross sectional study. *BMC Infect Dis,* 15, 20.

Oparil, S., Zaman, M. A. & Calhoun, D. A. 2003. Pathogenesis of hypertension. *Ann Intern Med,* 139, 761-76.

Opie, L. H. & Seedat, Y. K. 2005. Hypertension in sub-Saharan African populations. *Circulation,* 112, 3562-8.

Ortblad, K. F., Lozano, R. & Murray, C. J. 2013. The burden of HIV: insights from the Global Burden of Disease Study 2010. *AIDS,* 27, 2003-17.

Ortegon, M., Lim, S., Chisholm, D. & Mendis, S. 2012. Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study. *BMJ,* 344, e607.

Ovbiagele, B. & Nath, A. 2011. Increasing incidence of ischemic stroke in patients with HIV infection. *Neurology,* 76, 444-50.

Owusu-Sekyere, E., Bonyah, E. & Ossei, L. 2013. Spatial modeling of hypertension disease in the Kumasi Metropolitan area of Ghana. *International Journal of Statistics and Applications,* 3, 132-140.

Palacios, R., Santos, J., Garcia, A., Castells, E., Gonzalez, M., Ruiz, J. & Marquez, M. 2006. Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naive patients. *HIV Med,* 7, 10-5.

Palella, F. J., Jr., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman, D. J. & Holmberg, S. D. 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med,* 338, 853-60.

Palella, F. J., Jr. & Phair, J. P. 2011. Cardiovascular disease in HIV infection. *Curr Opin HIV AIDS,* 6, 266-71.

Parati, G., Kilama, M. O., Faini, A., Facelli, E., Ochen, K., Opira, C., Mendis, S., Wang, J., Atkins, N. & O'Brien, E. 2010. A new solar-powered blood pressure measuring device for low-resource settings. *Hypertension,* 56, 1047-53.

Patel, V. B., Sacoor, Z., Francis, P., Bill, P. L., Bhigjee, A. I. & Connolly, C. 2005. Ischemic stroke in young HIV-positive patients in Kwazulu-Natal, South Africa. *Neurology,* 65, 759-61.

Pattman, R. 2010. *Oxford handbook of genitourinary medicine, HIV, and sexual health,* Oxford, Oxford University Press.

Peck, R. N., Shedafa, R., Kalluvya, S., Downs, J. A., Todd, J., Suthanthiran, M., Fitzgerald, D. W. & Kataraihya, J. B. 2014. Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study. *BMC Med,* 12, 125.

Pier, G. B. 2004. *Immunology, infection, and immunity.* , Washington, D.C, ASM Press.

Pirs, M., Jug, B., Erzen, B., Sabovic, M., Karner, P., Poljak, M. & Tomazic, J. 2014. Cardiovascular risk assessment in HIV-infected male patients: a comparison of Framingham, SCORE, PROCAM and DAD risk equations. *Acta Dermatovenerol Alp Pannonica Adriat,* 23, 43-7.

Pobee, J. O., Larbi, E. B., Dodu, S. R., Pisa, Z. & Strasser, T. 1979. Is systemic hypertension a problem in Ghana? *Trop Doct,* 9, 89-92.

Post, W. S. 2011. Predicting and preventing cardiovascular disease in HIV-infected patients. *Top Antivir Med,* 19, 169-73.

Poulter, N. R., Prabhakaran, D. & Caulfield, M. 2015. Hypertension. *Lancet,* 386, 801-12.

Prendergast, A., Prado, J. G., Kang, Y. H., Chen, F., Riddell, L. A., Luzzi, G., Goulder, P. & Klenerman, P. 2010. HIV-1 infection is characterized by profound depletion of CD161+ Th17 cells and gradual decline in regulatory T cells. *AIDS,* 24, 491-502.

Rahimi, K., Emdin, C. A. & MacMahon, S. 2015. The epidemiology of blood pressure and its worldwide management. *Circ Res,* 116, 925-36.

Rasmussen, L. D., Engsig, F. N., Christensen, H., Gerstoft, J., Kronborg, G., Pedersen, C. & Obel, N. 2011. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. *AIDS,* 25, 1637-46.

Redd, A. D., Gray, R. H. & Quinn, T. C. 2011. Is microbial translocation a cause or consequence of HIV disease progression? *J Infect Dis,* 203, 744-5; author reply 746.

Redman, L. A., Naidoo, P. & Biccard, B. M. 2014. HIV, vascular surgery and cardiovascular outcomes: a South African cohort study. *Anaesthesia,* 69, 208-13.

Reinsch, N., Neuhaus, K., Esser, S., Potthoff, A., Hower, M., Mostardt, S., Neumann, A., Brockmeyer, N. H., Gelbrich, G., Erbel, R. & Neumann, T. 2012. Are HIV patients undertreated? Cardiovascular risk factors in HIV: results of the HIV-HEART study. *Eur J Prev Cardiol,* 19, 267-74.

Remais, J. V., Zeng, G., Li, G., Tian, L. & Engelgau, M. M. 2013. Convergence of non-communicable and infectious diseases in low- and middle-income countries. *Int J Epidemiol,* 42, 221-7.

Reyskens, M. S. E., Essop, M. F. & CMRG 2014. HIV protease inhibitors and onset of cardiovascular diseases: A central role for oxidative stress and dysregulation of the ubiquitin-proteasome system. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease,* 1842, 256-268.

Ribaudo, H. J., Benson, C. A., Zheng, Y., Koletar, S. L., Collier, A. C., Lok, J. J., Smurzynski, M., Bosch, R. J., Bastow, B. & Schouten, J. T. 2011. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis,* 52, 929-40.

Rodriguez, M. A., Kumar, S. K. & De Caro, M. 2010. Hypertensive crisis. *Cardiol Rev,* 18, 102-7.

Rokx, C., Verbon, A. & Rijnders, B. J. 2015. Short communication: Lipids and cardiovascular risk after switching HIV-1 patients on nevirapine and emtricitabine/tenofovir-DF to rilpivirine/emtricitabine/tenofovir-DF. *AIDS Res Hum Retroviruses,* 31, 363-7.

Rosenbaum, P. A. & Rubin, D. B. 1983a. Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. *Journal of the Royal Statistical Society. Series B,* 45, 212-218.

Rosenbaum, P. R. & Rubin, D. B. 1983b. The central role of the propensity score in observational studies for causal effects. *Biometrica,* 70, 41-55.

Rosenbaum, P. R. & Rubin, D. B. 1984. Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American Statistical Association,* 79, 516-524.

Rosenbaum, P. R. & Rubin, D. B. 1985. Constructing a control group using multivariate matched sampling methods that incoporate the propensity score. *The American Satistician,* 39, 33-38.

Roth, G. A. & Murray, C. J. 2013. The Global Burden of Disease Study 2010 does not show a rise in the age-standardized mortality rate for cardiovascular disease in sub-Saharan Africa. *Prog Cardiovasc Dis,* 56, 278-80.

Rubin, D. B. 1974. Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology,* 66, 688-701.

Rubin, D. B. 2001. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Services and Outcomes Research Methodology,* 2, 169-188.

Rubin, D. B. 2007. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med,* 26, 20-36.

Sabin, C. A., Worm, S. W., Weber, R., Reiss, P., El-Sadr, W., Dabis, F., De Wit, S., Law, M., D'Arminio Monforte, A., Friis-Moller, N., Kirk, O., Pradier, C., Weller, I., Phillips, A. N. & Lundgren, J. D. 2008. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet,* 371, 1417-26.

Safar, M. E. 1999. Hypothesis on isolated systolic hypertension in the elderly. *J Hum Hypertens,* 13, 813-5.

Sakurai, M., Miura, K., Takamura, T., Ota, T., Ishizaki, M., Morikawa, Y., Kido, T., Naruse, Y. & Nakagawa, H. 2006. Gender differences in the association between anthropometric indices of obesity and blood pressure in Japanese. *Hypertens Res,* 29, 75-80.

Salami, A. K., Akande, A. A. & Olokoba, A. B. 2009. Serum lipids and glucose abnormalities in HIV/AIDS patients on antiretroviral therapies. *West Afr J Med,* 28, 10-5.

Sander, L. D., Newell, K., Ssebbowa, P., Serwadda, D., Quinn, T. C., Gray, R. H., Wawer, M. J., Mondo, G. & Reynolds, S. 2015. Hypertension, cardiovascular risk factors and antihypertensive medication utilisation among HIV-infected individuals in Rakai, Uganda. *Trop Med Int Health,* 20, 391-6.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., Coresh, J., Culleton, B., Hamm, L. L., McCullough, P. A., Kasiske, B. L., Kelepouris, E., Klag, M. J., Parfrey, P., Pfeffer, M., Raij, L., Spinosa, D. J. & Wilson, P. W. 2003. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation,* 108, 2154-69.

Saves, M., Chene, G., Ducimetiere, P., Leport, C., Le Moal, G., Amouyel, P., Arveiler, D., Ruidavets, J. B., Reynes, J., Bingham, A. & Raffi, F. 2003. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis,* 37, 292-8.

Schaeffner, E. S., Kurth, T., Curhan, G. C., Glynn, R. J., Rexrode, K. M., Baigent, C., Buring, J. E. & Gaziano, J. M. 2003. Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol,* 14, 2084-91.

Schim van der Loeff, M. F. & Aaby, P. 1999. Towards a better understanding of the epidemiology of HIV-2. *AIDS,* 13 Suppl A, S69-84.

Schoffelen, A. F., de Groot, E., Tempelman, H. A., Visseren, F. L., Hoepelman, A. I. & Barth, R. E. 2015. Carotid Intima Media Thickness in Mainly Female HIV-Infected Subjects in Rural South Africa: Association With Cardiovascular but Not HIV-Related Factors. *Clin Infect Dis,* 61, 1606-14.

Scholten, F., Mugisha, J., Seeley, J., Kinyanda, E., Nakubukwa, S., Kowal, P., Naidoo, N., Boerma, T., Chatterji, S. & Grosskurth, H. 2011. Health and functional status among older people with HIV/AIDS in Uganda. *BMC Public Health,* 11, 886.

Schutte, A. E., Schutte, R., Huisman, H. W., van Rooyen, J. M., Fourie, C. M., Malan, N. T., Malan, L., Mels, C. M., Smith, W., Moss, S. J., Towers, G. W., Kruger, H. S., Wentzel-Viljoen, E., Vorster, H. H. & Kruger, A. 2012. Are behavioural risk factors to be blamed for the conversion from optimal blood pressure to hypertensive status in Black South Africans? A 5-year prospective study. *Int J Epidemiol,* 41, 1114-23.

Schwartz, T., Magdi, G., Steen, T. W. & Sjaastad, I. 2012. HIV as a risk factor for cardiac disease in Botswana: a cross-sectional study. *Int Health,* 4, 30-7.

Seaberg, E. C., Munoz, A., Lu, M., Detels, R., Margolick, J. B., Riddler, S. A., Williams, C. M. & Phair, J. P. 2005. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS,* 19, 953-60.

Seedat, Y. K. 2004. Recommendations for hypertension in sub-Saharan Africa. *Cardiovasc J S Afr,* 15, 157-8.

Seeger, J. D., Kurth, T. & Walker, A. M. 2007. Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care,* 45, S143-8.

Sesso, H. D., Buring, J. E., Chown, M. J., Ridker, P. M. & Gaziano, J. M. 2005. A prospective study of plasma lipid levels and hypertension in women. *Arch Intern Med,* 165, 2420-7.

Shapiro, R. L., Souda, S., Parekh, N., Binda, K., Kayembe, M., Lockman, S., Svab, P., Babitseng, O., Powis, K., Jimbo, W., Creek, T., Makhema, J., Essex, M. & Roberts, D. J. 2012. High prevalence of hypertension and placental insufficiency, but no in utero HIV transmission, among women on HAART with stillbirths in Botswana. *PLoS One,* 7, e31580.

Sharp, P. M. & Hahn, B. H. 2011. Origins of HIV and the AIDS pandemic. *Cold Spring Harb Perspect Med,* 1, a006841.

Sherer, R., Solomon, S., Schechter, M., Nachega, J. B., Rockstroh, J. & Zuniga, J. M. 2014. HIV provider-patient communication regarding cardiovascular risk: results from the AIDS Treatment for Life International Survey. *J Int Assoc Provid AIDS Care,* 13, 342-5.

Shlay, J. C., Bartsch, G., Peng, G., Wang, J., Grunfeld, C., Gibert, C. L., Visnegarwala, F., Raghavan, S. S., Xiang, Y., Farrough, M., Perry, H. E., Kotler, D. & El-Sadr, W. M. 2007. Long-term body composition and metabolic changes in antiretroviral naive persons randomized to protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or protease inhibitor plus nonnucleoside reverse transcriptase inhibitor-based strategy. *J Acquir Immune Defic Syndr,* 44, 506-17.

Siedner, M. J., Kim, J. H., Nakku, R. S., Hemphill, L., Triant, V. A., Haberer, J. E., Martin, J. N., Boum, Y., 2nd, Kwon, D. S., Tsai, A. C., Hunt, P. W., Okello, S. & Bangsberg, D. R. 2016. HIV infection and arterial stiffness among older-adults taking antiretroviral therapy in rural Uganda. *AIDS,* 30, 667-70.

Sigal, A., Kim, J. T., Balazs, A. B., Dekel, E., Mayo, A., Milo, R. & Baltimore, D. 2011. Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy. *Nature,* 477, 95-8.

Silva, E. F., Bassichetto, K. C. & Lewi, D. S. 2009. Lipid profile, cardiovascular risk factors and metabolic syndrome in a group of AIDS patients. *Arq Bras Cardiol,* 93, 113-8.

Singh, R. B., Suh, I. L., Singh, V. P., Chaithiraphan, S., Laothavorn, P., Sy, R. G., Babilonia, N. A., Rahman, A. R., Sheikh, S., Tomlinson, B. & Sarraf-Zadigan, N. 2000. Hypertension and stroke in Asia: prevalence, control and strategies in developing countries for prevention. *J Hum Hypertens,* 14, 749-63.

Singh, S. 2013. Hypertension in chronic kidney disease. *Clinical Queries: Nephrology,* 2, 15-22.

Siontis, G. C., Tzoulaki, I., Siontis, K. C. & Ioannidis, J. P. 2012. Comparisons of established risk prediction models for cardiovascular disease: systematic review. *BMJ,* 344, e3318.

Siu, A. L. 2015. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med,* 163, 778-86.

Sliwa, K., Forster, O., Tibazarwa, K., Libhaber, E., Becker, A., Yip, A. & Hilfiker-Kleiner, D. 2011. Long-term outcome of peripartum cardiomyopathy in a population with high seropositivity for human immunodeficiency virus. *Int J Cardiol,* 147, 202-8.

Sliwa, K., Carrington, M. J., Becker, A., Thienemann, F., Ntsekhe, M. & Stewart, S. 2012. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J,* 33, 866-74.

Smith, J. A. & Daniel, R. 2006. Following the path of the virus: the exploitation of host DNA repair mechanisms by retroviruses. *ACS Chem Biol,* 1, 217-26.

Solages, A., Vita, J. A., Thornton, D. J., Murray, J., Heeren, T., Craven, D. E. & Horsburgh, C. R., Jr. 2006. Endothelial function in HIV-infected persons. *Clin Infect Dis,* 42, 1325-32.

Spence, R. A., Kati, W. M., Anderson, K. S. & Johnson, K. A. 1995. Mechanism of inhibition of HIV-1 reverse transcriptase by nonnucleoside inhibitors. *Science,* 267, 988-93.

Ssinabulya, I., Kayima, J., Longenecker, C., Luwedde, M., Semitala, F., Kambugu, A., Ameda, F., Bugeza, S., McComsey, G., Freers, J. & Nakanjako, D. 2014. Subclinical atherosclerosis among HIV-infected adults attending HIV/AIDS care at two large ambulatory HIV clinics in Uganda. *PLoS One,* 9, e89537.

Stacey, A. R., Norris, P. J., Qin, L., Haygreen, E. A., Taylor, E., Heitman, J., Lebedeva, M., DeCamp, A., Li, D., Grove, D., Self, S. G. & Borrow, P. 2009. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. *J Virol,* 83, 3719-33.

Stevens, V. J., Obarzanek, E., Cook, N. R., Lee, I. M., Appel, L. J., Smith West, D., Milas, N. C., Mattfeldt-Beman, M., Belden, L., Bragg, C., Millstone, M., Raczynski, J., Brewer, A., Singh, B. & Cohen, J. 2001. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med,* 134, 1-11.

Steyn, K., Sliwa, K., Hawken, S., Commerford, P., Onen, C., Damasceno, A., Ounpuu, S. & Yusuf, S. 2005. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. *Circulation,* 112, 3554-61.

Stover, J., Fidzani, B., Molomo, B. C., Moeti, T. & Musuka, G. 2008. Estimated HIV trends and program effects in Botswana. *PLoS One,* 3, e3729.

Stringhini, S., Sinon, F., Didon, J., Gedeon, J., Paccaud, F. & Bovet, P. 2012. Declining stroke and myocardial infarction mortality between 1989 and 2010 in a country of the african region. *Stroke,* 43, 2283-8.

Stuart, E. A., Lee, B. K. & Leacy, F. P. 2013. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. *J Clin Epidemiol,* 66, S84-S90 e1.

Syed, F. F. & Sani, M. U. 2013. Recent advances in HIV-associated cardiovascular diseases in Africa. *Heart,* 99, 1146-53.

Tantchou Tchoumi, J. C., Ambassa, J. C., Kingue, S., Giamberti, A., Cirri, S., Frigiola, A. & Butera, G. 2011. Occurrence, aetiology and challenges in the management of congestive heart failure in sub-Saharan Africa: experience of the Cardiac Centre in Shisong, Cameroon. *Pan Afr Med J,* 8, 11.

Tantillo, C., Ding, J., Jacobo-Molina, A., Nanni, R. G., Boyer, P. L., Hughes, S. H., Pauwels, R., Andries, K., Janssen, P. A. & Arnold, E. 1994. Locations of anti-AIDS drug binding sites and resistance mutations in the three-dimensional structure of HIV-1 reverse transcriptase. Implications for mechanisms of drug inhibition and resistance. *J Mol Biol,* 243, 369-87.

Tanuma, J., Ishizaki, A., Gatanaga, H., Kikuchi, Y., Kimura, S., Hiroe, M. & Oka, S. 2003. Dilated cardiomyopathy in an adult human immunodeficiency virus type 1-positive patient treated with a zidovudine-containing antiretroviral regimen. *Clin Infect Dis,* 37, e109-11.

Tedla, F. M., Brar, A., Browne, R. & Brown, C. 2011. Hypertension in chronic kidney disease: navigating the evidence. *Int J Hypertens,* 2011, 132405.

Teo, K., Chow, C. K., Vaz, M., Rangarajan, S. & Yusuf, S. 2009. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J,* 158, 1-7 e1.

Thawornchaisit, P., de Looze, F., Reid, C. M., Seubsman, S. A. & Sleigh, A. C. 2013. Health risk factors and the incidence of hypertension: 4-year prospective findings from a national cohort of 60 569 Thai Open University students. *BMJ Open,* 3.

Thiebaut, R., El-Sadr, W. M., Friis-Moller, N., Rickenbach, M., Reiss, P., Monforte, A. D., Morfeldt, L., Fontas, E., Kirk, O., De Wit, S., Calvo, G., Law, M. G., Dabis, F., Sabin, C. A. & Lundgren, J. D. 2005. Predictors of hypertension and changes of blood pressure in HIV-infected patients. *Antivir Ther,* 10, 811-23.

Tipping, B., de Villiers, L., Wainwright, H., Candy, S. & Bryer, A. 2007. Stroke in patients with human immunodeficiency virus infection. *J Neurol Neurosurg Psychiatry,* 78, 1320-4.

Torre, D. 2006. Nitric oxide and endothelial dysfunction in HIV type 1 infection. *Clin Infect Dis,* 43, 1086-7.

Torriani, F. J., Komarow, L., Parker, R. A., Cotter, B. R., Currier, J. S., Dube, M. P., Fichtenbaum, C. J., Gerschenson, M., Mitchell, C. K., Murphy, R. L., Squires, K. & Stein, J. H. 2008. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol,* 52, 569-76.

Trautmann, L., Janbazian, L., Chomont, N., Said, E. A., Gimmig, S., Bessette, B., Boulassel, M. R., Delwart, E., Sepulveda, H., Balderas, R. S., Routy, J. P., Haddad, E. K. & Sekaly, R. P. 2006. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. *Nat Med,* 12, 1198-202.

Trevino, A., de Mendoza, C., Caballero, E., Rodriguez, C., Parra, P., Benito, R., Cabezas, T., Roc, L., Aguilera, A. & Soriano, V. 2011. Drug resistance mutations in patients infected with HIV-2 living in Spain. *J Antimicrob Chemother,* 66, 1484-8.

Triant, V. A., Regan, S., Lee, H., Sax, P. E., Meigs, J. B. & Grinspoon, S. K. 2010. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. *J Acquir Immune Defic Syndr,* 55, 615-9.

Twagirumukiza, M., Nkeramihigo, E., Seminega, B., Gasakure, E., Boccara, F. & Barbaro, G. 2007. Prevalence of dilated cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. *Curr HIV Res,* 5, 129-37.

Twagirumukiza, M., De Bacquer, D., Kips, J. G., de Backer, G., Stichele, R. V. & Van Bortel, L. M. 2011. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. *J Hypertens,* 29, 1243-52.

Tzoulaki, I., Liberopoulos, G. & Ioannidis, J. P. 2009. Assessment of claims of improved prediction beyond the Framingham risk score. *JAMA,* 302, 2345-52.

Joint United Nations Program on HIV/AIDS (UNAIDS) 2007. *AIDS epidemic update* [Online]. Switzerland: WHO. [Accessed 20/08/2015 2015].

Joint United Nations Program on HIV/AIDS (UNAIDS) & World Health Organisation (WHO) 2008. Report on the global HIV/AIDS epidemic. Geneva: UNAIDS.

Joint United Nations Program on HIV/AIDS (UNAIDS) 2012. *The quest for an HIV vaccine* [Online].Geneva:UNAIDS.Available:http://www.unaids.org/en/resources/presscentre/featurestories/2012/may/20120518vaccinesday/ [Accessed 31-03-2016 2016].

Joint United Nations Program on HIV/AIDS (UNAIDS) 2015. *2015 Facts Sheet* [Online].Geneva:WHO.Available: http://www.who.int/mediacentre/factsheets/fs360/en/ [Accessed 24th April 2016 2016].

United Nations Development Program (UNDP) 2005. Human development report. New York: UNDP.

United States Renal Data Systems (USRDS) 2010. United States Renal Data Systems 2010 annual data report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *United States Renal Data System.* Bethesda, Md, USA: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

van der Valk, M., Kastelein, J. J., Murphy, R. L., van Leth, F., Katlama, C., Horban, A., Glesby, M., Behrens, G., Clotet, B., Stellato, R. K., Molhuizen, H. O. & Reiss, P. 2001. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS,* 15, 2407-14.

Van Pelt, R. E., Evans, E. M., Schechtman, K. B., Ehsani, A. A. & Kohrt, W. M. 2001. Waist circumference vs body mass index for prediction of disease risk in postmenopausal women. *Int J Obes Relat Metab Disord,* 25, 1183-8.

van Zoest, R. A., Wit, F. W., Kooij, K. W., van der Valk, M., Schouten, J., Kootstra, N. A., Wiersinga, W. J., Prins, M., van den Born, B. J. & Reiss, P. 2016. Higher Prevalence of Hypertension in HIV-1-Infected Patients on Combination Antiretroviral Therapy Is Associated With Changes in Body Composition and Prior Stavudine Exposure. *Clin Infect Dis,* 63, 205-13.

Wang, N. Y., Young, J. H., Meoni, L. A., Ford, D. E., Erlinger, T. P. & Klag, M. J. 2008. Blood pressure change and risk of hypertension associated with parental hypertension: the Johns Hopkins Precursors Study. *Arch Intern Med,* 168, 643-8.

Warburton, D. E., Charlesworth, S., Ivey, A., Nettlefold, L. & Bredin, S. S. 2010. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. *Int J Behav Nutr Phys Act,* 7, 39.

Ward, K. D., Bliss, R. E., Vokonas, P. S. & Garvey, A. J. 1993. Effects of smoking cessation on blood pressure. *Am J Cardiol,* 72, 979-81.

Westphal, S. A. 2008. Obesity, abdominal obesity, and insulin resistance. *Clin Cornerstone,* 9, 23-29; discussion 30-1.

Whaley-Connell, A. T., Sowers, J. R., Stevens, L. A., McFarlane, S. I., Shlipak, M. G., Norris, K. C., Chen, S. C., Qiu, Y., Wang, C., Li, S., Vassalotti, J. A. & Collins,

A. J. 2008. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Am J Kidney Dis,* 51, S13-20.

Whelton, P. K., He, J., Appel, L. J., Cutler, J. A., Havas, S., Kotchen, T. A., Roccella, E. J., Stout, R., Vallbona, C., Winston, M. C. & Karimbakas, J. 2002. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA,* 288, 1882-8.

Whitworth, J. A. 2003. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens,* 21, 1983-92.

World Health Organisation (WHO) 1995. Physical status : The use of and interpretation of anthropometry , report of a WHO expert committee (Report 854). Geneva: World Health Organisation.

World Health Organisation (WHO) 2000. Obesity: Preventing and managing the global epidemic-Report on a WHO Consultation on Obesity. Geneva: World Health Organisation.

World Health Organisation (WHO) & Joint United Nations Program on HIV/AIDS (UNAIDS) 2000. Guidelines for second generation HIV surveillance. Geneva: WHO and UNAIDS. Geneva: WHO

World Health Organisation (WHO) 2003. Affordable Technology : Blood Pressure Measuring Devices for Low Resource Settings. Geneva: World Health Organization.

World Health Organisation (WHO) 2004. The global burden of disease: 2004 update Geneva: WHO.

World Health Organisation (WHO) & African Union (AU) 2006. The health of the people. *The African Regional Health Report.* Geneva: WHO Regional Office for Africa.

World Health Organisation (WHO) 2007. Pocket guidelines for assessment and management of cardiovascular risk:WHO/ISH cardiovascular risk prediction charts for the African Region. Geneva: WHO.

World Health Organisation (WHO) 2008a. The WHO STEPwise Approach to Chronic Disease Risk Factor Surveillance. *Non communicable Diseases and Mental Health Cluster 2008.* Geneva: World Health Organization.

World Health Organisation (WHO) 2008b. Causes of Death. Geneva, Switzerland: World Health Organization.

World Health Organisation (WHO) 2009a. Fast facts about HIV/AIDS. Geneva: World Health Organisation.

World Health Organisation (WHO) 2009b. Global Health Risks: Mortality and Burden of Dosease Attributable to Selected Major Risks. Geneva: World Health Organisation.

World Health Organisation (WHO) 2011a. Global status report on non-communicable diseases 2010 Geneva, Switzerland.

World Health Organisation (WHO) 2011b. Progress Report 2011. *Global HIV/AIDS Response.* Geneva: WHO.

World Health Organisation (WHO) 2012. WHO STEPS Instrument. Geneva, Switzerland: World Health Organisation.

World Health Organisation (WHO) 2013a. A global brief on Hypertension: Silent killer, global public health crisis. *World Health Day 2013.* Geneva, Switzerland: World Health Organisation.

World Health Organisation (WHO) 2013b. Global Health Observatory (GHO) data Geneva, Switzerland: World Health Organisation.

World Health Organisation (WHO) 2013c. Consolidated Guidelines On The Use of Antiretroviral Drugs For Treating And Preventing HIV infection: Recommendations for a Public Health Approach. *WHO Guidelines.* Geneva, Switzerland: World Health Organisation.

World Health Organisation (WHO) 2015. *Questions and Answers on Hypertension* [Online]. Geneva: World Health Organisation. Available: who.int/features/qa/82/en [Accessed 01-Sept-2015 2015].

World Health Organisation (WHO) 2016. *Cardiovascular diseases (CVDs)* [Online]. Geneva:WHO.Available: http://www.who.int/mediacentre/factsheets/fs317/en/ [Accessed 12 October 2016].

Williams, B., Poulter, N. R., Brown, M. J., Davis, M., McInnes, G. T., Potter, J. F., Sever, P. S. & Mc, G. T. S. 2004. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens,* 18, 139-85.

Williams, B. 2015. Essential hypertension-definition, epidemiology, and pathophysiology. *In:* WARREL, D. A., COX, T. M. & FIFTH, J. D. (eds.) *Oxford Textbook of Medicine.* 5th ed. Oxford: Oxford University Press.

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H. & Kannel, W. B. 1998. Prediction of coronary heart disease using risk factor categories. *Circulation,* 97, 1837-47.

Wilson, P. W. F. 2017. *Estimation of cardiovascular risk in an individual patient without known cardiovascular disease* [Online]. UpToDate: Wolters Kluwer Health. Available: www.uptodate.com [Accessed 16th April 2017 2017].

Wilson, S. L., Scullard, G., Fidler, S. J., Weber, J. N. & Poulter, N. R. 2009. Effects of HIV status and antiretroviral therapy on blood pressure. *HIV Med,* 10, 388-94.

Worm, S. W., Sabin, C., Weber, R., Reiss, P., El-Sadr, W., Dabis, F., De Wit, S., Law, M., Monforte, A. D., Friis-Moller, N., Kirk, O., Fontas, E., Weller, I., Phillips, A. & Lundgren, J. 2010. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis,* 201, 318-30.

Xin, X., He, J., Frontini, M. G., Ogden, L. G., Motsamai, O. I. & Whelton, P. K. 2001. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension,* 38, 1112-7.

Yu, M. & Vajdy, M. 2010. Mucosal HIV transmission and vaccination strategies through oral compared with vaginal and rectal routes. *Expert Opin Biol Ther,* 10, 1181-95.

Yusuf, S., Reddy, S., Ounpuu, S. & Anand, S. 2001. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation,* 104, 2746-53.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J. & Lisheng, L. 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet,* 364, 937-52.

Zhang, C., Zhou, S., Groppelli, E., Pellegrino, P., Williams, I., Borrow, P., Chain, B. M. & Jolly, C. 2015. Hybrid spreading mechanisms and T cell activation shape the dynamics of HIV-1 infection. *PLoS Comput Biol,* 11, e1004179.

APPENDICES

APPENDIX I-QUESTIONNAIRE FOR DATA COLLECTION

Hypertension and associated risk factors in patients attending HIV Clinic at the Korle-Bu Teaching Hospital in Accra

Study ID: **Institutional ID:** **Date:**

Part 1: To be administered to study participant

DEMOGRAPHY

Sex Male □ Female □	**Age:** ....yrs	**Educational Level :** Tertiary □ Sec./Voc/Commercial □ JSS/Elementary □ None □

Religion:
Christian □ Moslem □ Traditionalist □ Atheist □

Marital Status:
Married □ Co-habiting □ Single □ Divorced □ Widowed □

Occupation:
Govt/Private employed □ Self-employed □ Unemployed □ Pensioner □

Level of income:
............./month None□

LIFE STYLE FACTORS AND HISTORY

Smoking::
None smoker □ Current smoker □ (No. of years..........) Previous smoker □

Alcohol drinking:
None drinker □ Current drinker □ (No. of years..........) Previous drinker □

How often do you consume fruits?
Daily □ ..../week ..../month Rarely □

How often do you exercise?

Type of Exercise	*Frequency*			
	Daily□	......./week	....../month	Rarely □
	Daily□	......./week	....../month	Rarely □
	Daily□	......./week	....../month	Rarely □

Date HIV status was diagnosed?	**Age at HIV diagnosis:** ....yrs
Are you currently on ARVs: Yes □ No □	

Do you have any of these diseases?		**Is any family member with any of these diseases?**	
Hypertension □	Year of diagnosis	Hypertension □	Relation.............................
Diabetes □	Year of diagnosis	Diabetes □	Relation.............................
Hyperlipidemia □	Year of diagnosis	Hyperlipidemia □	Relation.............................
Other	Year of diagnosis	Others (specify)	
Other	Year of diagnosis		
Other	Year of diagnosis		

How does the presence of this/these co-morbidity (ies) affect you?

ANTHROPOMETRIC MEASUREMENTS

Weight (kg): 1st: 2nd:	
Waist Circumference (m): 1st: 2nd:	**Hip circumference (m):** 1st: 2nd:

BLOOD PRESSURE MEASUREMENTS

1st: 2nd:

Hypertension and associated risk factors in patients attending HIV Clinic at the Korle-Bu Teaching Hospital in Accra

Study ID:	Institutional ID:	Date:

Part 2: To be extracted from clinical folder

HIV-related parameters

Height (m):	Date HIV status was diagnosed:	Age at HIV diagnosis (yrs):
HIV stage at diagnosis: Stage 1☐ Stage 2 ☐ Stage 3 ☐ Stage 4 ☐		Viral load at diagnosis:
HIV type: HIV 1 ☐ HIV 2 ☐ Mixed ☐		CD_4 count at diagnosis (cells/mL):

History of ART administered

ARV administered	Date started	Date stopped	Reason(s) for HAART Modification

Co-morbid conditions

Hypertension ☐	Year of diagnosis................	1. Other	Year of diagnosis............
Diabetes ☐	Year of diagnosis................	2.	Year of diagnosis............
Hyperlipidemia ☐	Year of diagnosis................	3.	Year of diagnosis............
Tuberculosis ☐	Year of diagnosis................	4.	Year of diagnosis............

Concomitant medications

1.
2.
3.
4.
5.

Adverse events (for patients on ARVs)

1.	6.
2.	7.
3.	8.
4.	9.
5.	10.

Parameters (Within the last 1 year)

Parameter	Date	Value
BP		
BP		
BP		
BP		
BP		
Weight		
Weight		
Weight		
Weight		
Weight		
CD4 Count		
CD4 Count		
CD4 Count		

Parameters (Most current)

Parameter	Date	Value
Viral load		
Haemoglobin level		
AST		
ALT		
Urea		
Creatinine		
Fasting Blood glucose		
Nadir CD4 Count		
Others:		
BP at enrolment		
CD4 at enrolment		
Weight at enrolment		

APPENDIX II-PATIENT CONSENT FORM

PATIENT CONSENT FORM

This form is to be read individually and privately to each participant recruited into the study. Following consent to participate in the study, each patient is to be asked to give documented consent

RESEARCH TITLE

Hypertension and associated risk factors in patients attending HIV clinic at the Korle-bu Teaching Hospital in Accra

Principal Investigator: Edmund Tetteh Nartey
Address: Department of Epidemiology, School of Public Health, University of Ghana
Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana

Introduction

This Consent Form contains information about the research named above. In order to be sure that you are informed about being in this research, we are asking you to read (or have read to you) this Consent Form. You will also be asked to sign it (or make your mark in front of a witness). We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

Reason for the Research

You are being asked to take part in research to find out about the number of people with hypertension and whether the medicines being given to you (ARV) are responsible for the hypertension

Research Purpose/General Information about Research

This is a research to find out whether the HIV in persons on ARV (or on care) is resulting in these patients getting hypertension. In addition, whether other factors like age, sex and the drugs (ARVs) they are taking is resulting in hypertension. The development of hypertension and other chronic diseases like diabetes can make the management of the HIV disease challenging. Some people may have higher possibility of developing hypertension and other chronic conditions than others. This research will find out what makes some PLHIV to develop hypertension and look at their liver enzymes, kidney function, blood sugar level as well as their CD4 count.

Your Part in the Research

If you agree to be in the research, you will be asked to answer a few question on your exercises, fruit consumption etc and also asked to give 7ml of your blood sample, taken from your veins, only once, although the project is expected to last over a two-year period. About 310 adults (both males and females) from KBTH HIV clinic will take part in this study.

Possible Risks and Discomforts

Participants may have some discomfort and pain when blood sample is being taken. However, efforts will be made to minimize any risk and reduce discomfort associated with this procedure according to laid down rules in good laboratory practices.

Possible Benefits

The data generated from this research would be useful in monitoring your CD4 count and the presence of other diseases in you including liver and kidney diseases. This will directly benefit participants by informing change in treatment regimens if necessary or advice on health style. The project will also benefit all persons living with HIV by providing information for the better management of the infection.

Alternatives to Participation

You will continue to benefit from the ART programme even if you decline to participate in this research project

Confidentiality

We will protect information about you and your part in this research to the best of our ability. No report generated from this research will name, or be linked to, the persons involved. Where necessary however, the researcher and your doctor may need to discuss your specific results to enable a better management of your condition.

Compensation

You will not be paid for participating in this research

Your rights as a participant

This research project has been reviewed and approved by the EPRC of the College of Health Sciences, University of Ghana. If you have any questions about your rights as a research participant you may contact The Research Office of the School of Medicine and Dentistry, University of Ghana located on the Korle-bu Campus.

If You Have a Problem or Have Other Questions, please call Edmund Nartey (0244 220014)

APPENDIX III-STUDY PARTICPANTS AGREEMENT FORM

The above document describing the benefits, risks and procedures for the research title "Hypertension and associated risk factors in patients attending HIV clinic at the Korle-bu Teaching Hospital" has been read and explained to me. I have been given an opportunity to have any questions about the research answered to my satisfaction. I agree to participate as a volunteer.

____________________ ______________________________

Date Signature or mark of volunteer

If volunteers cannot read the form themselves, a witness must sign here:
I was present while the benefits, risks and procedures were read to the volunteer. All questions were answered and the volunteer has agreed to take part in the research.

____________________ __________________________

Date Signature of Witness

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual.

____________________ ______________________________

Date Signature of Person Who Obtained Consent

APPENDIX IV-ETHICAL CLEARANCE CERTIFICATE

UNIVERSITY OF GHANA
COLLEGE OF HEALTH SCIENCES
ETHICAL AND PROTOCOL REVIEW COMMITTEE

My Ref. No.........

1st December, 2015.

Mr. Edmund Tetteh Nartey,
Department of Epidemiology and Disease Control
School of Public Health
University of Ghana

RE: ETHICAL CLEARANCE

Protocol Identification Number: **MS-Et/M.3 – P 4.4/2015-2016**

The Ethical and Protocol Review Committee of the College of Health Sciences unanimously approved your research proposal.

TITLE OF PROTOCOL: **"Hypertension and Associated Risk Factors in Patients attending HIV Clinic at the Korle-Bu Teaching Hospital in Accra"**

PRINCIPAL INVESTIGATORS: **Mr. Edmund Tetteh Nartey**

This approval requires that you submit six-monthly review reports of the protocol to the Committee and a final full review to the Ethical and Protocol Review Committee at the completion of the study. The Committee may observe, or cause to be observed, procedures and records of the study during and after implementation.

Please note that any significant modification of this project must be submitted to the Committee for review and approval before its implementation.

You are required to report all serious adverse events related to this study to the Ethical and Protocol Review Committee within seven (7) days verbally and fourteen (14) days in writing.

As part of the review process, it is the Committee's duty to review the ethical aspects of any manuscript that may be produced from this study. You will therefore be required to furnish the Committee with any manuscript for publication.

This ethical clearance is valid till 30th September, 2017.

Please always quote the protocol identification number in all future correspondence in relation to this protocol.

Signed: ....
PROFESSOR ANDREW A. ADJEI
CHAIRPERSON, ETHICAL AND PROTOCOL REVIEW COMMITTEE

cc: Provost, CHS
Dean, SPH
Head of Department

File