

**PILOT COMPARISON OF CLINICAL EFFECTS AND
COMPLIANCE WITH COMMONLY PRESCRIBED
ANTIHYPERTENSIVE DRUGS IN HIV HYPERTENSIVE
PATIENTS AT UNIVERSITY TEACHING HOSPITAL**

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A dissertation submitted to the University of Zambia in partial fulfilment of the
requirements for the degree of Master of Science in Pharmacology

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I, Takondwa Ngulube Chidumayo, at this moment declare that this dissertation is the report of original research work conducted by me, and this dissertation, or any part of it, has not been previously submitted for a degree in this or any other University. All the information from previous studies were appropriately cited in this work.

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CERTIFICATE OF APPROVAL

This dissertation of Dr Takondwa Ngulube Chidumayo (MBChB, BScHB), has been approved as partial fulfilment of the requirements for the award of the Master of Science in Pharmacology by the University of Zambia.

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ABSTRACT

Pilot comparison of clinical effects and compliance with commonly prescribed antihypertensive drugs in HIV hypertensive patients at UTH.

By Dr Takondwa Ngulube Chidumayo

HIV infection and hypertension disproportionately affect sub-Saharan Africa including Zambia. The challenges of effectively treating patients with these co-morbidities include pill burden, drug interactions that may influence the efficacy and side effect profile of antihypertensive and antiretroviral therapies.

This study determined the association between clinical effects regarding blood pressure control, side effect profile and compliance with the commonly used antihypertensive drugs classes in Zambia.

The study was a prospective cohort analysis of randomly selected hypertensive people living with HIV (PLWHIV) on commonly used antihypertensive drug classes. Antihypertensive drug efficacy was assessed using sitting clinic and 24-hour ambulatory blood pressure monitoring (ABPM) for participants on antihypertensive drugs for at least six weeks. The validated anti-retroviral therapy (ART) clinic follow-up questionnaire and 'WHO questionnaire for hypertension in a rapidly ageing population' gathered quantitative data on management, treatment, patient knowledge and complications of HIV and hypertension during the 8-week period at Adult Infectious Disease Centre (AIDC). To determine the most effective, safest antihypertensive therapies acceptable to this population.

Participants on CCB (140.4/98.8 mmHg) and CCB with Enalapril (147.9/92.7 mmHg) had higher median daytime blood pressure than Moduretic (136.8/84.2 mmHg, $p=0.186$ and 0.168 respectively) and Moduretic with Enalapril (140.5/84 mmHg, $p=0.003$). The attributable risk for good daytime systolic and diastolic BP control was at least 20 % and 32 % for Moduretic and Enalapril (50 % and 67 %, $p=0.046$ and 0.0143 respectively) and Moduretic (50 % and 62%, $p=0.691$ and 0.425 respectively). The circadian systolic and diastolic BP decrease was less than 10 % for Moduretic and Enalapril (8.25 % and 10.25 %, $p=0.005$ and 0.003 , respectively). The difference in the median clinic systolic and diastolic BP (170/106 mmHg) was greater than 22.62 mmHg and 11.20 mm Hg than daytime ABPM (142/95.5 mmHg, $p=0.0001$ and 0.001 respectively). Moduretic had the highest side effect proportion (62.5 %), mainly related to hypokalemia in patients on Tenofovir ($p=0.25$). The highest occurrence of non-compliance was in CCBs with Enalapril (50 %) and CCBs (40 %) with $p=0.048$. CCBs with Enalapril (100 %) and Moduretic with Enalapril (100 %) had the highest proportion of awareness of the importance of compliance and BP control ($p=0.02$). This finding mitigated the effects of increased antihypertensive pill burden which did not affect compliance, especially in the latter group.

The study supported the alternative hypothesis. Moduretic with Enalapril had the highest ration of BP, with fewer side effects and better compliance. The use of Nifedipine ® in PLWHIV on NNRTIs should be carefully monitored as combinations with and Enalapril alone is less efficacious in hypertensive PLWHIV of African origin. Antihypertensive drug compliance improved by patient knowledge of hypertension treatment rather than reduced pill burden. A more rigorous study

long-term with larger samples sizes is required to determine the BP control rates using more diverse combinations of antihypertensive drugs, Nifedipine XR formulations, hypertension in PLWHIV.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reactions
AIDC	Adult Infectious Disease Center
AKI	Acute Kidney Injury
ARB	Angiotensin Receptor Blockers
ART	Antiretroviral Therapy
ATT	Anti Tuberculosis Treatment
BP	Blood Pressure
CCB	Calcium Channel Blocker
CKD	Chronic Kidney Disease
C VA	Cardiovascular Accident
CVD	Cardiovascular Disease
CYP3A4	Cytochrome Isoenzyme 3A4
DDI	Drug-Drug Interactions
DM	Diabetes Mellitus
CART	Combined Antiretroviral Therapy
HHD	Hypertensive Heart Disease
HIV	Human Immune Deficiency Virus

MI	Myocardial Infarction
NCD	Non-Communicable Diseases
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
PI	Protease Inhibitor
PLWHIV	People Living with HIV
SE	Side effects
TB	Tuberculosis

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 Global picture of HIV and Hypertension

People living with HIV (PLWHIV) are experiencing improved quality of life and increased life expectancy globally. Increased access to combined antiretroviral therapy (cART) is responsible for this benefit (Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection, 2016). However, this windfall has brought about an increased incidence of non-communicable diseases (NCDs) including hypertension in this population (Medina-Torne et al., 2012). Development of hypertension is not associated with ART (Medina-Torne et al., 2012) but the duration of HIV infection and increased body mass index (BMI). In addition to obesity and age (Medina-Torne et al., 2012).

Hypertension is defined as persistent blood pressure above 140/90 mmHg or average daytime readings higher than 135/85 mmHg using ambulatory blood pressure monitoring (ABPM) (O'Brien et al., 2003). The prevalence of hypertension among PLWHIV ranges between 13 to 45 percent in PLWHIV (Guaraldi et al., 2011, Bergersen et al., 2003, Baekken et al., 2008, Mateen et al., 2013, De Socio et al., 2014, Njelekela et al., 2016).

Hypertension in the black population is more likely to cause stroke, renal failure, and mortality than in the non-black population regardless of their geographical location (Ojji et al., 2015). It is, therefore, more pertinent to ensure treatment and control of blood pressure in the African population. Antihypertensive drug coverage in PLWHIV reported in most global studies is low due to an emphasis on HIV

treatment than CVDs (Bloomfield et al., 2014). Less than two-thirds PLWHIV suffering from hypertension are aware of their affliction (Manner et al., 2012, De Socio et al., 2014, Bauer, 2016). Less than two-thirds of those on pharmacological intervention achieve clinic BP target less than 140/90 (De Socio et al., 2014, Reinsch et al., 2012). These studies were in a predominantly white population of PLWHIV reported the use of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) monotherapy (De Socio et al., 2014).

Pharmacological treatment of hypertension is a challenge in PLWHIV due to concurrent use of cART and requires individualised treatment (Feldman et al., 2015, Langan and Jones, 2015, Mallat et al., 2013). The goal of antihypertensive therapy is clinic BP below 140/90 mmHg or 130/80 mmHg and 120/70 mmHg for renal and diabetic patients. The target blood pressure for ambulatory BP monitoring (ABPM) is a day BP less than 135/85 mmHg and circadian BP decrease higher than ten percent. Although some antihypertensive drugs are readily available and affordable, many PLWHIV on cART with hypertension are not on antihypertensive medications due to the decentralised treatment of HIV and CVDs (De Socio et al., 2014, Antonello et al., 2015).

The classes of available antihypertensive drugs include diuretics, beta-blockers, ACE inhibitors, ARBs and calcium channel blockers (CCBs). The American Association of Hypertension (AAH) guidelines recommend the use of thiazide diuretics and CCBs for African Americans (James et al., 2014) as the most effective first-line treatment. Combined antihypertensive drug regimen is usually favoured in severe hypertension to reduce adverse drug reactions (ADRs) by reducing the single drug dosage required to achieve BP control (James et al., 2014, Langan and Jones, 2015).

The first line drugs for reducing blood pressure in Caucasians include angiotensin-converting enzyme (ACE) inhibitors that are known to lower blood pressure and left ventricular hypertrophy. ARBs have the same benefit for those who are not able to tolerate ACE inhibitors (James et al., 2014). These drug classes are less efficacious in hypertensive patients of African origin as it is postulated that essential hypertension in this population is low renin in nature (Brewster and Seedat, 2013, James et al., 2014). It is related to increased salt intake and salt sensitivity resulting in increased blood volume. Hence thiazide diuretics are the preferred first-line drugs in hypertensive patients of African origin as they initially reduce fluid volume but later improve vascular compliance.

The studies above describe the high prevalence of hypertension, increased mortality in PLWHIV with hypertension and lack of blood pressure control in hypertensive patients on treatment. No specific details are comparing the efficacy of antihypertensive drug classes, their interactions with CART or adherence to antihypertensive drugs.

1.1.2 HIV and Hypertension in Africa

The disproportionate burden of HIV in sub-Saharan Africa coincides with the burden of hypertension in a recent study showing one in three people with hypertension in developing countries (Angkurawaranon et al., 2016). There is controversy as to whether the prevalence of hypertension in HIV is similar to HIV negative population (Okpa et al., 2017, Okello et al., 2015).). The mean age of hypertensive PLWHIV in Nigerian study and Uganda was less than that of the developed countries in less than 40 years. However, like the Western studies, increasing age and life expectancy in PLWHIV (Divala et al., 2016), BMI and smoking were associated with the risk of hypertension in PLWHIV. The other unique feature of hypertension in PLWHIV is

predominantly diastolic hypertension (Okpa et al., 2017). The consensus in southern African studies is that control of blood pressure in PLWHIV is inadequate.

Initiatives to ensure antihypertensive drugs and linking HIV clinics with preexisting hypertension clinics are underway in sub-Saharan Africa (Divala et al., 2016).

African studies support the finding of low treatment coverage in developed countries and frequent use of antihypertensive drug monotherapy (Adigun et al., 2003).

Adigun et al. showed 11.5 percent on diuretics, 4.7 percent on CCBs and 3.5 percent on ACE inhibitors with Diuretics achieved BP control in Nigeria regardless of HIV status. 11 percent of participants reported side effects from these drug classes.

Another study in sub-Saharan Africa found the most commonly used antihypertensive drugs were thiazide diuretics, CCBs and ACE inhibitors mostly as two or three combinations per patient (Olanrewaju et al., 2010). The reasons for inadequate blood pressure control among hypertensive PLWHIV on antihypertensive drugs remains elusive. There is speculation that interaction of antiretroviral drugs with some antihypertensive drug classes or poor compliance with high pill burden are contributing factors. The non-reverse transcriptase inhibitors and (NNRTIs) and protease inhibitors (PIs) interfere with calcium channel blocker bioavailability through CYP3A4 liver enzyme induction and inhibition respectively. The former may reduce BP control while the latter may increase adverse drug reactions of CCBs. Thiazide diuretics and beta blockers are not affected by antiretroviral drugs, but they may have additive metabolic derangements when used with PIs.

These reports do not state whether blood pressure control is affected by the ART regimen or the choice of antihypertensive drugs. There are no recommendations on the best antihypertensive drug management for control of hypertension in PLWHIV.

1.1.3 HIV and Hypertension in Zambia

Prevalence of HIV among adults in Zambia is 12.3 to 14.9 percent, approximately 980,000 people living with HIV (PLWHIV) between 15 to 59 years (ZAMPHIA, 2016). Increased access to antiretroviral therapy (ART) has led to increased life expectancy among PLWHIV (Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection, 2016). The current guidelines recommend Highly Active Antiretroviral Therapy (cART) regimen to include a minimum of three drugs from at least two antiretroviral drug classes to minimise the emergence of HIV resistance and treatment failure. Commonly used NNRTIs are Efavirenz and Nevirapine and PIs ritonavir-boosted lopinavir or Atazanavir. Tenofovir, Abacavir, and Emtricitabine are the commonly used NRTIs (Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection, 2016). There is no particular recommendation for the treatment of hypertension in HIV depending on antiretroviral therapy. The current clinical practice has not fully integrated the treatment of hypertension with HIV. There are possible increased drug-drug interactions that have not been well researched, nor clinicians sensitised to them.

Kabwe, (2014) reported a 35 percent prevalence of hypertension among PLWHIV at AIDC, Lusaka. Better Health Outcomes through Mentoring and Assessment (BHOMA) stated less than 18 percent antihypertensive drug coverage among patients with hypertension from three health centres in rural Zambia. Only two percent of treated patients achieved clinic BP control less than 140/90 (Yan et al., 2015). This study did not stratify patients by HIV status to compare the proportion of BP control in PLWHIV with that of the general population. Bauer et al. (2015) found low rates of pharmacological treatment and awareness of hypertension and its control in PLWHIV with hepatitis B. Electronic records at AIDC do not adequately

capture non-HIV related conditions such as hypertension and many co-administered drugs.

All the studies in Zambia showed frequent use of CCBs and monotherapy for the treatment of hypertension in Zambia. Whether the use of CCBs and lack of combination therapy in the treatment of hypertension in PLWHIV was responsible for such low-rated of blood pressure control in Zambia is undetermined. All the studies are in agreement that further studies are required to determine the best antihypertensive drugs in different subpopulations such as PLWHIV and other comorbidities.

This study compared blood pressure control, side effect profile and compliance in hypertensive PLWHIV on CCBs and other commonly used antihypertensive drug classes. The efficacy of these treatment regimens was measured using clinic BP and 24-hour ABPM to measure 24-hour BP, daytime BP, nocturnal BP, circadian rhythm, and heart rate. As well as the variation in nocturnal diastolic BP and blood pressure load (percentage of readings above abnormal BP threshold). These parameters have value in predicting adverse CVD outcomes (Abdalla, 2017, de la Sierra et al., 2010, Hermida et al., 2013, Mallion et al., 1999). The side effects and compliance of antihypertensive drugs were observed over an eight-week treatment period. Using the ART follow-up forms and 'WHO questionnaire for hypertension in rapidly ageing populations.' The resting sitting clinic blood pressure was measured at each contact to determine the relationship between clinic BP and mean daytime BP PLWHIV (Giles et al., 2011).

1.2 Statement of The Problem

The growing incidence of Hypertension and other CVD risk factors in PLWHIV is undisputed (Divala et al., 2016, Muhammad et al., 2013, Nduka, 2016, Antonello et al., 2015). The need to integrate treatment of HIV and hypertension is underway globally. Many patients with HIV are on either NNRTIs or PIs that are known to interfere with CCB drug bioavailability and side effect profile. There are over 5000 patients followed up at Adult Infectious Disease Center (AIDC), Lusaka. Majority of patients are on NNRTIs, 1101 on PIs, 197 of whom are on third line regimen. On the other hand, thiazide diuretics and diuretics may potentiate metabolic side effects of CCBs and some nucleoside reverse transcriptase inhibitors (NRTIs). The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to be less efficacious in hypertensive patients of African descent. This fact necessitates investigating the clinical significance of the concurrent treatment of HIV and hypertension.

Hypertension is an easily detectable and treatable cause of CVD that increases mortality in PLWHIV (Reinsch et al., 2012, Nuesch et al., 2013). Trends show poor BP control in hypertensive PLWHIV on antihypertensive drugs (Manner et al., 2012, De Socio et al., 2014, Bauer, 2016). Little information is available to recommend the best antihypertensive drugs for PLWHIV on CART (Olanrewaju et al., 2010, Rochlani et al., 2017).

This study aimed to compare the clinical effects of commonly antihypertensive drugs in PLWHIV with clinic BP measurement and ABPM methods (Giles et al., 2011). To determine the proportion of participants that achieved mean daytime BP less than 140/90 mmHg and 135/85 mmHg respectively in PLWHIV. The side effects and

antihypertensive drug compliance in the four treatment groups were investigated as these parameters were not assessed in most of the studies cited in this paper.

A prospective cohort analysis of hypertensive PLWHIV at AIDC in Lusaka, Zambia, was conducted over a two-month period to support evidence-based recommendations that foster efficient use of current resources to control hypertension in PLWHIV with the intention of reducing morbidity and mortality from cardiovascular events in hypertensive PLWHIV (Bloomfield et al., 2014)

1.3 Study Rationale

The life expectancy of PLWHIV on CART is increasing as their survival improves with better access to ART (WHO, 2016). However, this has led to increased risk of age-related non-communicable diseases such as hypertension (Bloomfield et al., 2014, Divala et al., 2016, Muhammad et al., 2013). Treatment of both hypertension in HIV is crucial in hypertensive PLWHIV despite the increased risk of disease-drug and drug-drug interactions. CCBs and thiazide diuretics are the first-line antihypertensive drugs in people of African descent just as HIV negative patients. However, CCBs in hypertensive PLWHIV on CART may have reduced drug bioavailability resulting in poor BP control from CYP3A4 enzyme induction by NNRTIs. PIs may increase the occurrence of CCB side effects from CYP3A4 enzyme inhibition causing increased serum CCB levels. In vitro studies of the interaction between PIs and Nifedipine for 30 days had no clinical effect on blood pressure in HIV negative normotensive Chinese individuals (Wang et al., 2015). How these factors affect the clinical outcome in a predominantly African population of hypertensive PLWHIV in Zambia is unknown. Taking these drugs for blood pressure control over a longer duration. Thiazide diuretics and Beta-blockers increase the risk of CVD by adding to the potential for deranged lipid and glucose

metabolism caused by PIs. CYP3A4 enzyme inducers and inhibitors do not affect the metabolism of the latter. ACE inhibitors and ARB serum drug levels are not influenced by ART and are more efficacious in nonblack hypertensive patients. ACE inhibitors' efficacy is lower in the African population, but its use in reducing progression of renal dysfunction and cardiomyopathy in hypertensive heart disease (HHD) make them useful in this population.

This comparison of commonly used anti-hypertensive drugs in a clinical setting will add practicality to the data from clinical trials that usually consider one drug against a placebo or compare effects of these medications in HIV-negative population.

Comparing its efficacy, side effect profiles, and compliance when combined with these drugs will add to the body of knowledge on the treatment of hypertension in PLWHIV on cART. Providing information on which drug classes work best with CART. Regarding the ability to achieve mean day-time blood pressure less than 135/85, clinic BP less than 140/90 and circadian rhythm above ten percent.

Also, their ability to reduce 24-hour and nocturnal BP loads less than 50 percent and daytime BP load less than 40 percent. Twenty-four-hour BP load is as the percentage of BP above 140/90 mmHg. Daytime BP load is the proportion of BP above 135/85 mmHg and nocturnal BP load as the percentage of blood pressure above 120/75 mmHg (Mallion et al., 1999, James et al., 2014). The study also compared the occurrence of side effects and compliance over an eight-week follow-up period of hypertensive PLWHIV on the commonly prescribed drug classes.

1.4 Hypothesis

There are no differences in efficacy, compliance and side effect profile of commonly used antihypertensive drugs.

Alternative hypothesis: There are differences in the efficacy, compliance, and adverse drug reactions in patients on of commonly used antihypertensive drugs.

1.5 Objectives

1.5.1 General Objective

To compare the blood pressure control of commonly prescribed antihypertensive drug classes in hypertensive PLWHIV on cART.

1.5.2 Specific Objectives

1. Compare the effects on blood pressure of commonly prescribed antihypertensive drug classes on blood pressure using sitting clinic BP and ABPM after to eight-week period of antihypertensive treatment in hypertensive PLWHIV.
2. To compare the effects ART on the blood pressure control of commonly prescribed antihypertensive drug classes in PLWHIV.
3. To determine the occurrence of antihypertensive related side effects in hypertensive PLWHIV on commonly prescribed antihypertensive drug classes at each contact and by phone interviews over an eight-week period.
4. To determine the compliance of commonly antihypertensive drugs by participant reports using the WHO questionnaire and pill counts.

1.6 Significance of The Study

Hypertension is a treatable cause of cardiovascular disease and mortality, yet there is limited information on the most useful class of antihypertensive drugs for treating hypertension in PLWHIV on cART. The reports of growing incidence of Hypertension necessitate considering the clinical significance of concurrent treatment of HIV and hypertension. This study compared the difference in clinical

effects of commonly prescribed anti-hypertensive drug classes; the clinical outcomes considered being blood pressure control, side effect profile and antihypertensive drug compliance in hypertensive PLWHIV. By Identifying adverse drug reactions resulting from possible disease-drug and drug-drug interactions of the commonly prescribed antihypertensive drugs and ART. For the determination of the antihypertensive drug class combinations that are most efficacious and least harmful.

Recommendations based on the results of this study will be disseminated to effect treatment guidelines for hypertension in PLWHIV. Sensitize health care providers on the importance of pharmacological intervention that provides the best BP control in hypertensive PLWHIV. With the hope of reducing morbidity and mortality from hypertension-related cardiovascular events in this population.

1.7 Conceptual Framework

ART affects the bioavailability of CCBs modifying their efficacy and side effect profile (Fig 1.1). The clinical implications of these interactions are indistinct in PLWHIV although this is undisputed in both in vivo and in-vitro studies.

Conversely, other antihypertensive drugs like thiazide diuretics and ACE inhibitors may have predictable serum drug levels and constant control of the blood pressure with fewer side effects when given with CART (Fig 1.1).

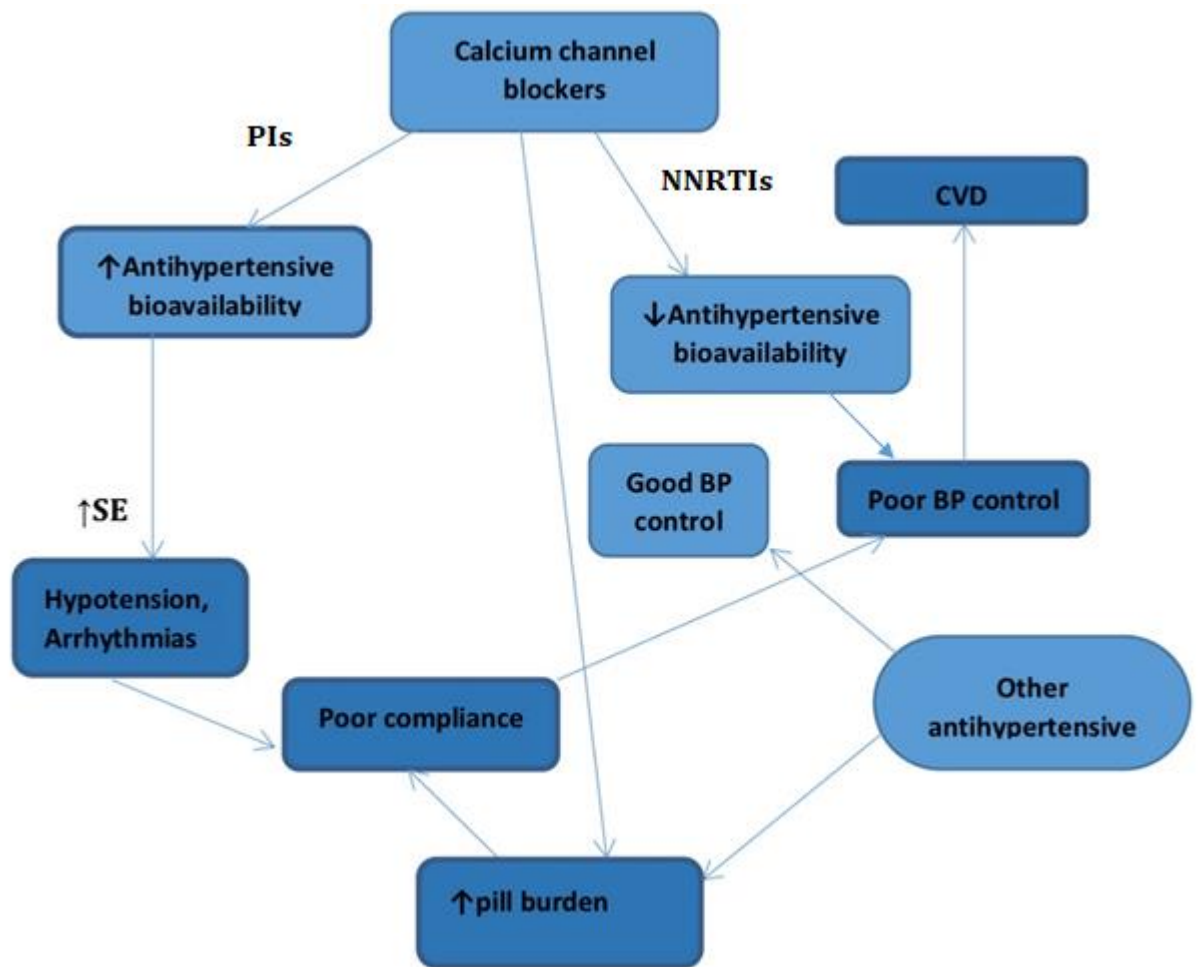


Figure 1.1. The theoretical framework of antihypertensive drug class efficacy, compliance, and side effects in hypertensive PLWHIV.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview

Hypertension is a growing concern among PLWHIV across Europe, Asia and the United States of America (Guaraldi et al., 2011, Medina-Torne et al., 2012). Access to ART is more readily available to PLWHIV regardless of the CD4 count (WHO, 2016). Better immune function implies improved survival and longer lifespans for people infected with HIV. NRTIs and PIs for the treatment of HIV may cause derangements of lipid and glucose metabolism. Which in turn increases the likelihood of developing metabolic syndrome (Bergersen et al., 2003, Wu et al., 2012, Muhammad et al., 2013, Dimala et al., 2016, Dimala and Blencowe, 2017). The burden of hypertension and HIV disproportionately affects developing countries in sub-Saharan Africa (Olanrewaju et al., 2010, Dalas et al., 2011, Syed and Sani, 2013, Bloomfield et al., 2014, Ojji et al., 2015, Okello et al., 2015).

Hypertension affects roughly one in three people in sub-Saharan Africa (Angkurawaranon et al., 2016) including PLWHIV. The findings in Africa are higher those in the rest of the world regarding the high incidence of hypertension among PLWHIV. Possibly due to the black race being an additional risk factor for developing hypertension regardless of HIV status. Hypertension in PLWHIV of African origin affects individuals under 50 years (Okpa et al., 2017, Muhammad et al., 2013). There is no clarification as to whether this discrepancy is due to the choice of antihypertensive drugs used to treat hypertension or from racial differences in antihypertensive drug response in predominantly black populations.

Zambia like the rest of sub-Saharan Africa has not been spared from the scourge of either hypertension or HIV. There is an increasing concern of hypertension among

Zambians in general (Goma et al., 2011) and low rates of BP control (Yan et al., 2015). The rates of blood pressure control in PLWHIV in Zambia was lower than the developed countries and the rest of Sub-Saharan Africa at 2.9 percent of patients on antihypertensive drugs (Bauer 2016). Closer scrutiny of the possible causes of these discrepancies is required to prevent CVD-related morbidity and mortality in PLWHIV. Metabolic syndrome is a risk for the development of CVD complications (Dimala and Blencowe, 2017).

Treatment and control of hypertension are necessary to prevent CVD complications such as stroke, MI, and renal dysfunction as well as increased mortality in PLWHIV (Staessen et al., 2003, Lackland, 2016, Taddei et al., 2003). The challenge of treating hypertension in PLWHIV is providing adequate BP control in patients on drugs known to affect the bioavailability of the antihypertensive drugs above. It is necessary to reduce CVD-related mortality and morbidity in PLWHIV (Vecchiet et al., 2011, Reinsch et al., 2012, Rossi et al., 2011, Manner et al., 2012, Sander et al., 2015). None of these investigators considered whether the lack of blood pressure control was related to the antihypertensive drugs used to treat hypertension or their interaction with ART regimen. The study populations were predominantly non-African and may not be representative of the Zambian patients with hypertension and HIV.

The studies cited above are in agreement of the pandemic of hypertension and HIV. The need to control both conditions to improve life expectancy and quality of life of PLWHIV. None of these studies determined whether the antihypertensive drugs for treating these patients affected blood pressure control or the lack thereof. There was little mentioned by way of the side effect profile of antihypertensive drugs in PLWHIV also on cART. Lastly, the studies both locally and globally did not

determine whether compliance with antihypertensive medications is affected by increased pill burden with cART or antihypertensive drug class.

This study attempted to determine if different commonly prescribed antihypertensive treatment will influence the proportion of blood pressure control, compliance and side effect profile in PLWHIV. To add to findings from in vitro studies (Gandhi et al., 2012), drug trials in healthy individuals (Wang et al., 2015) predominantly of Caucasian or Asian origin (Lamba et al., 2002).

2.2 Prevalence of Hypertension in HIV

Increase in life expectancy has resulted in increased risk of Non-Communicable Diseases (NCDs) including hypertension sub-Saharan Africa and the rest of the world (Antonello et al., 2015, Bloomfield et al., 2014, Guaraldi et al., 2011). The prevalence of hypertension internationally is currently between 10-45 percent (Antonello et al., 2015, De Socio et al., 2014, Reinsch et al., 2012, Syed and Sani, 2013, Baekken et al., 2008). In sub-Saharan Africa hypertension is estimated to affect 28 – 38 percent in individuals including PLWHIV (Dimala et al., 2016, Angkurawaranon et al., 2016, Mateen et al., 2013).

Kabwe, (2014) reported a prevalence of hypertension in PLWHIV was 35 percent at the UTH. So far, studies have centred on determining whether hypertension was due to HIV or ART. Risks of hypertension in PLHWHIV are similar to the general population. The risks included increasing age, smoking, obesity, black race (Guaraldi et al., 2011, Maher et al., 2011) and the duration of use of cART. These factors are related to increasing age rather than antiretroviral drug therapy (Wu et al., 2012). Hypertension is associated with complications like stroke, kidney disease, CVD and increased mortality (Bloomfield et al., 2014). PLWHIV experience CVD

complications at an earlier age than the general population due to premature ageing from HIV Infection (Guaraldi et al., 2011). None of these studies considered compliance with antihypertensive drugs and its effects on the outcomes.

2.3 Pharmacology of Commonly Used Antihypertensive Drugs

The classes of antihypertensive drugs include thiazide diuretics, beta-blockers, Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs). The American Association of Hypertension (AAH) guidelines recommend the use of thiazide diuretics and CCBs for African Americans (James et al., 2014) as the most effective first-line treatment. Combined antihypertensive drug regimen is usually favoured in severe hypertension to reduce ADRs by reducing the single drug dosage required to achieve BP control (James et al., 2014, Langan and Jones, 2015).

Calcium channel blockers (CCBs) cause arteriole dilatation by blocking L-calcium channels hence inhibiting calcium entry into the endothelial cells (James et al., 2014). They suppress coronary artery vasoconstriction and cause vasodilation of peripheral vessels. CCBs do not cause metabolic derangements. CYP3A4 comprises approximately 30 percent of all the cytochrome enzymes; it is responsible for the metabolism of about 60 percent of xenobiotics (Vesell, 1991). PIs inhibit liver isoenzyme CYP3A4 increasing serum drug levels up to 100 percent for Nifedipine (Vourvahis and Kashuba, 2007, Gandhi et al., 2013).

Thiazide Diuretics inhibit renal reabsorption of sodium and chloride from the distal convoluted tubule by blocking the sodium/chloride cotransporter (Musini et al., 2014). The ALLHAT study showed thiazide diuretics are cardioprotective and are the first-line recommendation for treatment of hypertension in JNC8 (Gandhi et al.,

2013, James et al., 2014). Thiazide diuretic efficacy is compromised by increased salt intake and must be in concert with dietary and lifestyle modifications in patients with hypertension. Thiazide diuretics may cause hypokalemia and derangements in lipid and glucose metabolism (insulin resistance) as is the case with PIs (Wu et al., 2012). Thiazide diuretics are excreted unchanged in urine and not prone to changes in drug levels from enzyme inducers and inhibitors. In Zambia, Hydrochlorothiazide 50 mg is usually combined with Amiloride 5 mg as Moduretic or with angiotensin receptor blocker (ARBs in TelmaH). Both combinations are available as a single tablet. Amiloride is a potassium-sparing diuretic that reduces the risk of developing hypokalemia. Recommendations suggest the use of thiazide diuretic without a potassium-sparing diuretics unless a patient is in danger of developing hypokalemia (James et al., 2014). The eighth Joint National Committee for hypertension (JNC8) recommends combining a thiazide diuretic with an ACE inhibitor rather than amiloride for enhanced their efficacy (James et al., 2014).

Beta-blockers act on Beta receptors of the heart and kidneys reducing heart rate and renin releases in the juxtaglomerular area of the kidneys respectively (Wong et al., 2016). The resulting reduction in heart rate and myocardial contractility lowers the cardiac output and blood pressure. They also decrease nodal conduction and inhibit renin release in the kidneys but are less efficacious in the elderly. As a result of the blunted response of adrenergic receptors in the elderly patients. Beta-blockers may increase the risk of stroke in smokers and insulin resistance (Feldman et al., 2015). They may cause lipid and glucose metabolism disorders. Beta-blocker serum levels are affected by CYP3A4 isoenzyme inhibitors and inducers to a smaller extent than CCBs. Beta-blockers require gradual tapering off to avoid rebound hypertension, angina, MI, or arrhythmia. The adverse effects include bradycardia, hypotension,

fatigue, and sexual dysfunction (James et al., 2014). Beta-blockers are not part of first-line treatment for hypertension in any race. They reduce blood pressure in hypertensive patients under 60 years of age as is the case with hypertensive PLWHIV (Okpa et al., 2017). The JNC 8 suggests adding beta blockers or aldosterone receptor blockers as a third drug after CCBs, thiazide diuretics, ACE inhibitors, and ARBs have failed to control blood pressure (James et al., 2014) in HIV negative patients.

ACE inhibitors reduce BP by inhibiting production of angiotensin II and increasing bradykinin levels. The former is a vasoconstrictor and the latter a vasodilator, respectively. ACE inhibitors are Cardio and renal protective, but their adverse effects include angioedema, hyperkalemia, chronic cough, renal insufficiency and sexual dysfunction (James et al., 2014). The ARBs are an alternative to ACE inhibitors by impeding the angiotensin 1 (AT1) receptors in patients who cannot tolerate ACE inhibitors. The benefits and adverse effects are similar to ACE inhibitors (Feldman et al., 2015, James et al., 2014). ACE inhibitors and ARBs delay progression of renal dysfunction and ventricular hypertrophy. However, ACE inhibitors and ARBs are not as effective in hypertensive patients of African origin. Poor BP control by ACE inhibitors and ARBs implies most patients would require a third antihypertensive drug to achieve target blood pressure (Kalra et al., 2010, Taddei, 2012).

The JNC 8 recommend starting with a single drug that should be increased in dosage or addition of a second drug if blood pressure is not controlled after a month (James et al., 2014). The combination therapy to treat hypertension in PLWHIV seems to be the reasonable option in addition to either CCBs or thiazide diuretics in patients of African descent (Rochlani et al., 2017). Combination therapy in the treatment of

hypertension offers the advantage of reducing the occurrence of side effects and providing multiple mechanisms of action for blood pressure control. Combination antihypertensive therapy may negatively impact on the compliance with increasing pill burden and more complicated dosing regimen (Gupta et al., 2017).

2.4 Challenges and Gaps in Blood Pressure Control Hypertensive PLWHIV

Hypertension is defined as a consistent repeatedly elevated blood pressure (BP) reading above 140 mmHg systolic and 90 mmHg diastolic equivalent to mean daytime BP of 135/85 using ABPM (James et al., 2014). Target BP should be less than 140 mmHg systolic and 90 mmHg diastolic non-diabetic patients (Feldman et al., 2015, James et al., 2014). The endpoints using ABPM is a mean daytime BP of 130/80 mmHg and nocturnal BP of 120/70 mmHg. No specific target blood pressure is known to reduce the risk of CVD in PLWHIV. There are no particular pharmacology treatment recommendations for PLWHIV. Most treatment protocols follow those of HIV negative hypertensive patients.

PLWHIV and hypertension suffer from two lifelong diseases requiring lifelong treatment. The medications used to treat either condition affect one another's efficacy and side effect profile. The reports in all these studies are that antihypertensive drug coverage of at least one drug was 53 – 55 percent (De Socio et al., 2014, Reinsch et al., 2012) emphasis was on treatment of HIV and opportunistic infections (Sherer et al., 2014). A small proportion of those on antihypertensive therapy had controlled hypertension 22-33 percent (Manner et al., 2012, De Socio et al., 2014). Most studies mentioned the actual antihypertensive drugs used. (De Socio et al., 2014) Reported use of ACE inhibitors and ARBs as monotherapy or combinations (37 percent) in a mostly Caucasian population. These drugs do not

interact with antiretroviral therapy (ART), so no particular drug interactions were noted.

(Bauer, 2016) Reported 2.7 percent control in PLWHIV of blood pressure in Lusaka, Zambia using mainly CCBs. The evidence supporting aggressive management of cardiovascular risk factors to reduce cardiovascular mortality in HIV patients remains undisputed (Bloomfield et al., 2014, Syed and Sani, 2013). However, the best pharmacological intervention that will achieve blood pressure control or the ideal blood pressure target in PLWHIV is still unknown.

The studies above did not investigate any associations between antihypertensive drug classes BP control. There was no detailed report on compliance and side effect profiles of the antihypertensive drugs used with or without cART. If the interaction of antihypertensive drugs with cART or lack of drug compliance is responsible for inadequate BP control is unknown. There is a lack of knowledge of the acceptable antihypertensive treatment that will produce the best blood pressure control and side effect profile in PLWHIV on cART. There is currently a knowledge gap in which antihypertensive drug class is most efficacious in controlling blood pressure in PLWHIV and whether combination therapy should be used from the outset (Schwartz and Turner, 2004) or gradual addition of antihypertensive drugs in cases of uncontrolled hypertension (James et al., 2014).

NNRTIs' enzyme induction leads to more rapid drug metabolism and reduction in drug bioavailability of Nifedipine by 45 -70 percent, but only 20 percent for extended release formulation. The formulations of CCBs commonly used in Zambia are the intermediate release Nifedipine ® and Amlodipine. (Yan et al., 2015) Found only two percent of hypertensive patients achieved BP control, most of whom were

on Nifedipine a CCB. Similar to the findings by (Bauer, 2016) who found 2.9 percent BP control among treated hypertensive PLWHIV. Whether the CCBs are the cause of the low rate of blood pressure control is debatable.

There is no consensus on whether changes in serum CCB drug levels caused by ART affect clinical outcomes in human beings as the therapeutic and toxic dose ranges of most antihypertensive drugs are not well documented. A study in China found no impact on blood pressure when PIs and Nifedipine were co-administered to healthy participants after 30 days (Wang et al., 2015). The study participants had neither hypertension nor HIV. It is unclear whether this will hold true for Zambian hypertensive PLWHIV taking these drugs for prolonged periods. Whether these changes in CCB bioavailability are clinically significant in hypertensive PLWHIV on CCBs and CART is unknown. The usefulness of CCBs and other antihypertensive drugs is undetermined in hypertensive PLWHIV in the studies reviewed.

Nifedipine ® formulation, Atenolol, Moduretic, and Enalapril are readily available recommendations in the national drug formulary of Zambia. The above drugs belong to are a CCB, beta-blocker, thiazide diuretic/ Amiloride combination and ACE inhibitor respectively. Hence, a comparison of the effectiveness and tolerability of commonly prescribed drugs classes in hypertensive PLWHIV is necessary. This study aims at determining the association between the class of antihypertensive drugs on BP control, side effects and compliance in hypertensive PLWHIV on cART.

2.4.1 Limitations of Clinic Blood Pressure Measurement method

Clinic blood pressure (CBP) measurements were used to determine the prevalence and control rates of hypertension in most of the studies cited above, more so, in Africa and Zambia. The shortfalls of CBP measurements are the reduced accuracy at predicting the likelihood of cardiovascular disease in hypertension (Nobre and Mion Junior, 2016, Baguet, 2012). Clinic BP measured within four to six hours of waking coincides with the sharp physiological rise in blood pressure that overestimates the patients true BP reading (Giles, 2005). White coat effect may compound this phenomenon by the producing raised clinic BPs readings. White coat effect refers to persistently elevated blood pressure reading during clinic visits in patients whose BP is controlled for the rest of the day (Manner et al., 2010). Aggressive treatment of hypertensive patients with exaggerated clinic BPs could cause increased ADRs. PLWHIV are more prone to white coat effect than HIV negative patients, perhaps due to psychological stress related to HIV and autonomic dysregulation (Manner et al., 2010). White coat hypertension may also occur in these patients. White coat hypertension occurs when the clinic BP is above 140/90 in an otherwise normotensive or pre-hypertensive patient who does not need antihypertensive treatment (Chrysant, 2000).

Clinic BP measurements are unable to detect masked hypertension (Abdalla, 2017, Giles et al., 2011). In masked hypertension blood pressure at the clinic visit is normal but remains raised for the rest of the day (Hanninen et al., 2010, Nobre and Mion Junior, 2016). Masked hypertension and nocturnal hypertension are associated with risk of CVD complications and are more prevalent in African Americans with metabolic syndrome (Bromfield et al., 2016, Thomas et al., 2017, Colantonio et al.,

2017). PLWHIV are known to have nocturnal hypertension and abnormal circadian rhythm that may persist after ART treatment (Borkum et al., 2014).

Ambulatory blood pressure provides additional information that is associated with increased CVD risk (Bromfield et al., 2016, Abdalla, 2017, Nobre and Mion Junior, 2016). Such as mean 24-hour, daytime and nocturnal blood pressures. As well as the standard deviation of the nocturnal blood pressure (Ozawa et al., 2009). Circadian rhythm, daytime, nocturnal and 24-hour BP load are also determined by ABPM (Qiu et al., 2004, Sera et al., 2015). Antihypertensive drugs that control clinic BP (CBP) are associated with higher CVD if they do not control nocturnal blood pressure and restore the circadian rhythm (Staessen et al., 1999, Esayag-Tendler and White, 1993).

Ambulatory blood pressure monitoring is encouraged in clinical practice for diagnosis, assessment of BP control and determining the effects of antihypertensive drug clinical trials (Tseng, 2006). Using ambulatory BP is necessary to determine a more accurate picture of blood pressure control in PLWHIV (Kent et al., 2016, Abdalla, 2017). The blood pressure cuff is left in-situ to automatically take multiple blood pressure readings at pre-set times which are stored for upload into a computer after a predetermined period. There are more than 60 BP reading per individual depending on the frequency of the measurements. The multiple measurements mitigate confounders caused by white coat effects, physiological BP surges, and masked hypertension.

BP is controlled at less than 140/80 mmHg, 135/85 mmHg and 120/75 mmHg during the 24-hour, daytime and nighttime periods (Lefebvre et al., 2002, James et al., 2014). The circadian rhythm associated with increased CVD risk is less than a ten

percent decrease (De la Sierra et al., 2010, Hermida et al., 2013, Kent et al., 2016, Sun et al., 2016). The circadian rhythm is the difference between the daytime and nighttime blood pressure divided by the daytime blood pressure (expressed as a percentage). Normal dipping refers to a circadian rhythm between 10-15 percent, whereas, non-dippers have a decrease of less than ten percent. The non-dippers have a higher incidence of CVD (Fagard et al., 2009).

The twenty-four-hour blood pressure load represents the percentage of the day during which blood pressure lies above 140/90 mmHg. A 24-hour BP load higher than 50 percent is the cutoff point for the diagnosis of hypertension using ABPM (James et al., 2014). The daytime and nighttime blood pressure load are the proportion of the daytime and nocturnal BP that is greater than 135/85 mmHg and 120/75 mmHg, respectively. The normal BP load for the day and night times are less than 40 percent and 50 percent, respectively (James et al., 2014). Comparisons of the above parameters were made for commonly prescribed antihypertensive drugs in PLWHIV at UTH.

CHAPTER 3: RESEARCH DESIGN AND METHODS

3.1 Study Design

This study was a quantitative observational comparative prospective study using in a cohort of hypertensive PLWHIV on antihypertensive drugs over a six to eight-week treatment period at the Adult Infectious Disease Centre of the University Teaching Hospital, Lusaka, Zambia. During this time the maximal effect of both cART and Antihypertensive drugs should have occurred for determination of short-term clinical effects and drug interactions. The study was prospective to avoid missing data and dependence on blood pressure readings that may not have been taken using standardised methods with tools that may not have been calibrated in a retrospective study. An observational approach was selected to reduce costs of participant insurance required for interventional research which was beyond the budget of the principal investigator. The comparative approach of this study aided in balancing the effects of other factors in hypertensive PLWHIV such as ART regimen in each antihypertensive treatment group. The epidemiological cohort analysis would determine whether efficacy, side effect profile and compliance of CCBs were compromised in these participants and if any alternative treatments were equally ineffective or more efficacious. Hence this study provided more information to make more generalizable actionable recommendations in the time and resources available.

3.2 Study Population and Setting

Target population: All outpatient PLWHIV with hypertension on any commonly antihypertensive drugs regardless of ART regimen.

Study population: A cohort of outpatient PLWHIV with hypertension on any commonly prescribed antihypertensive drugs actively followed up at AIDC during the 12 weeks of data collection.

3.2.1 Inclusion Criteria

- I. Ages > 18 years of patients reviewed at AIDC and less likelihood of secondary hypertension in keeping with trends of previous studies in this area.
- II. PLWHIV with three or more BP > 140/90 mmHg or any blood pressure if already on antihypertensive drug treatment during the study period.

3.2.2 Exclusion Criteria

- I. Patients with congestive cardiac failure and documented ejection fraction less than 40 percent
- II. Pregnant women
- III. Patients with diagnosed kidney disease or Diabetes Mellitus before study commencement
- IV. In patients likely to be treated for conditions or with drugs that could confound the study.
- V. Patients currently on strong non-ART CYP3A4 inducers or inhibitors to avoid confounding effects of NNRTIs and PIs on CCBs (Azoles, Rifampicin, and Erythromycin)
- VI. Third-line ART treatment
- VII. Patients with sickle cell disease or vaso-occlusive disorders
- VIII. Patients with ulcers on the upper arms
- IX. Patients with atrial fibrillation or irregular heart rhythm
- X. Patients who require constant use of crutches on the arm used for BP measurements.

3.3 Sample Size Calculation

Using STATA 13 at 80 percent power and study significance level of 0.05. The sample size estimation of two-sample comparison of proportions for a two-tailed test. However, three treatment arms were compared in the study. $p_1 = 0.33$ from literature review estimation of 1/3 with BP Control (De Socio et al., 2014) proportion in the developed countries with assumed better antihypertensive drug choices. $p_2 = 0.029$ as the estimated proportion of BP control in Zambian studies due to hypothesised use of CCBs to treat hypertension in HIV (Bauer, 2016). $n_2/n_1 = 1.00$, $n_1=25$, $n_2=25$, $n_1+n_2 = 50$ plus possibility of ten percent loss to follow-up = 55 participants. There are less than 1000 PLWHIV diagnosed with hypertension on treatment; the sample size corrected for small sample size calculation. The number of estimated patients on antihypertensive treatment seen during the three months of the study is approximately 60 based on a preliminary assessment of the feasibility of the study.

Total sample size = $N / (1 + N/n)$

$$n_1+n_2 = 60 / (1 + 60/55) = 28.7 \sim 29$$

$$n_1 = 14, n_2 = 15$$

Where N is the number of PLWHIV on CART and antihypertensive drugs estimated to attend AIDC in the three months allocated for patient recruitment.

3.4 Sampling Method

Participants on antihypertensive drugs regardless of blood pressure readings were randomly selected as they come for ART clinic visit by stratified random sampling.

Informal interviews at the pharmacy and with clinicians revealed Nifedipine ®

formulation were commonly prescribed at UTH. Therefore, efforts were made to ensure that patients on other antihypertensive drugs were selected to make the study more generalizable. Additionally determining whether study findings were isolated to CCB; Nifedipine ® or affected alternative antihypertensive regimens. The stratum ensured an equal number of patients on CCBs and other drug classes to avoid bias associated with enrolling patients as they came into the clinic (convenience sampling). Participant selection in each treatment arm was by the flip of a coin to choose a study population as representative of the target population as possible for the research findings to be generalizable. Hypertensive PLWHIV unknown before the study as cases of hypertension in PLWHIV is not recorded in the ART records system. A simple random sampling of participants from each stratum was chosen rather than the computer-generated selection (Suresh, 2011).

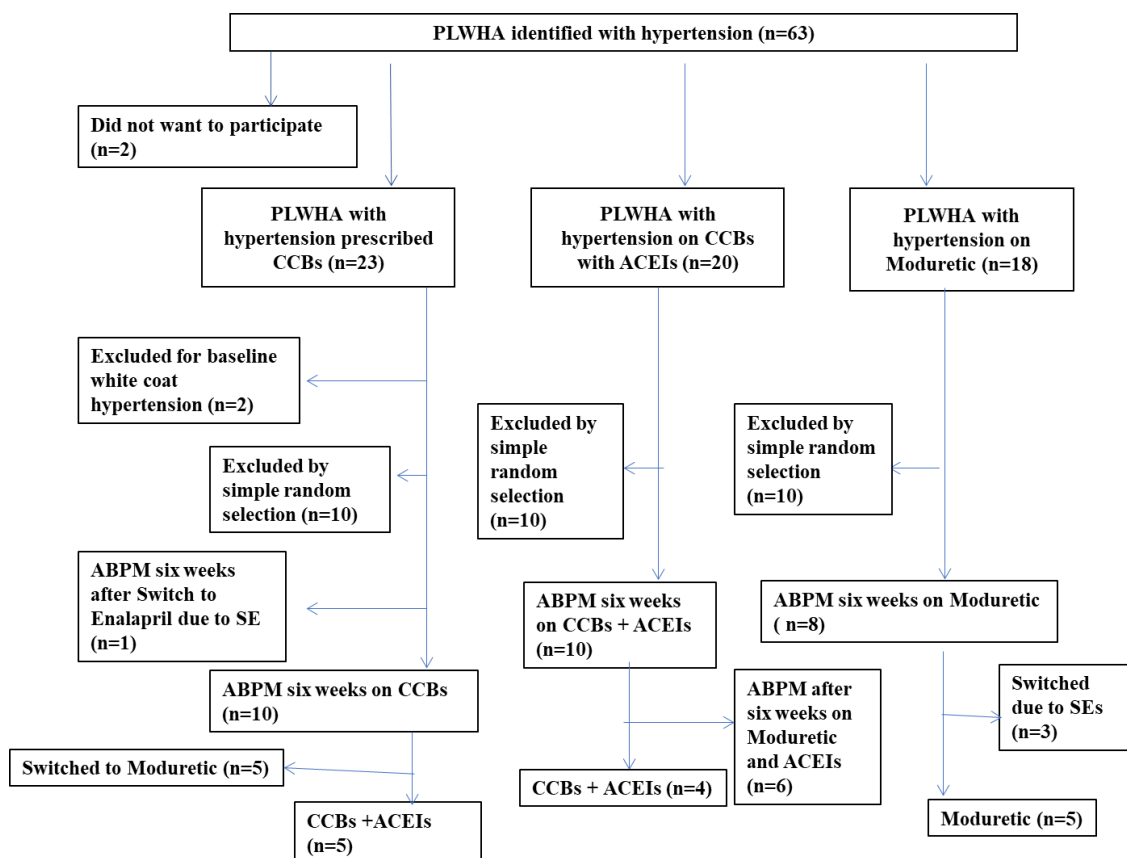


Figure 3.1 Flowchart of participant sampling and ABPM timing for the duration of the study.

The patients were selected from each group with simple random sampling by the flip of a coin as the study aimed to compare the clinical effects of each of the antihypertensive drug classes in PLWHIV (Fig 3.1). Only the patients corresponding to the heads face after a one Kwacha coin toss were enrolled after they gave consent. If the patient declined, the next patient corresponding to the heads face of the coin was selected. ABPM was conducted on participants at baseline if previously noncompliant for over four weeks and after six to eight weeks of treatment.

3.4.1 Study Procedure

The Standard Operating Protocols (SOPs) for measuring static blood pressure using automated oscillatory blood pressure machines by nurses who were not aware of the

participants' antihypertensive regimens to eliminate observer errors. FDA approved CONTEC ABPM-50 machines measured the ambulatory BPs that used oscillatory blood pressure measuring method.

ABPM required no special patient preparation, the BP cuff was attached during the clinic visit after obtaining consent. The daytime ABPM readings were automatically performed every 15 minutes during the day. The BP cuff was kept in-situ throughout a 24-hour period to which the patient was prepared to do. The participants were encouraged to perform regular daily activities during the measurement process but were advised to avoid excessive movement and during automated measurements to prevent unusable readings. During nighttime, the blood pressure was automatically recorded every 30 minutes. The automated measurements were pre-programmed in the ABPM equipment based on the participants' regular bedtime. The BP cuff was removed after a minimum of 24-hours from the time of BP cuff application when participants returned to the clinic and data was uploaded onto a personal computer for analysis. Analysis of nocturnal BP readings of participants consisted their actual bedtime rather than the pre-set 22.00 hours. The participants waking up time was used to determine the waking BP rather than the pre-set 06.00 hours. Any changes in participants' bedtime were collected and considered during analysis of ABPM readings. These precautions accurately assessed the daytime and nocturnal BP averages and the circadian blood pressure decrease. To avoid the shortfall mentioned in studies that considered pre-set bedtime and waking times of 22:00 hours and 06:00 hours respectively. Only ABPM results with greater than 80 percent good readings were analysed. The process was repeated after three days if less than 80 percent of the recordings were available for analysis. The same calibrated clinic and

ABPM machines were used at each visit to ensure the change in BP was not due to change in the equipment.

The principal investigator (PI) conducted participant selection using the method described above dividing them into commonly used antihypertensive drugs. Stratified sampling was performed to minimise selection bias and maintaining the internal validity of the different groups. These measures were taken to fulfil the assumptions required for statistical tests that need a randomly selected population and to make the results valid and generalizable.

3.4.2 Study Precautions

The validity of the study was assured by using an FDA approved ABPM equipment that was calibrated against mercury BP machines (gold standard). Using ABPM to supplement clinic blood pressure improved the accuracy of determining the antihypertensive drug efficacy. The use of validated ART follow-up questionnaires and 'WHO hypertension questionnaire for a rapidly ageing population.' The WHO questionnaire collected quantitative information on hypertension diagnosis, management, patient knowledge, and complications as well as participant biodata. The principal investigator (PI) carried out verbal translations of WHO hypertension questionnaire to the appropriate local language (Bauer, 2016) that ensured that the data obtained was accurate.

Patients brought all their drugs during the reviews for documentation and confirmation of drug history from prescriptions and clinic files. At least one antihypertensive drug dose was ingested in the presence of the PI before ambulatory BP monitoring to confirm immediate drug compliance. Compliance was measured by patient reporting using the WHO questionnaire that collected quantitative data

including the number and reasons for missed doses and reasons for poor compliance.

Pill counting was performed at every contact with participants. The WHO questionnaire was also used to assess the knowledge on hypertension, its complications, and importance of antihypertensive treatment, quantitatively.

Participants who were not compliant on antihypertensive drugs for over a month had a pretreatment baseline ABPM and after at least six weeks on correct drug doses.

This timing of the 24- hour ABPM represented results of antihypertensive drugs at full efficacy. Participants with antihypertensive prescription changes had repeat ABPM taken a month after the switching of treatment. This time was adequate for the previous drugs to wash out and current drugs to reach full efficacy. Participants on antihypertensive therapy before commencing ART had ambulatory BP monitoring before and at least six weeks after initiating cART to determine a relationship, if any, on blood pressure control and side effect due to drug interactions between ART and antihypertensive drugs.

Participants reported any subjective complaints to the PI during the study over the phone as and when they occurred to avoid recall bias. These claims were considered related to the side effects of the antihypertensive drugs if they occurred after the commencement of antihypertensive drugs and within known side effect profile for each drug class given. Clinicians confirmed their occurrence through investigations or by excluding other causes. Additionally, the symptoms should not have persisted after clinicians switched the drugs or treated the side effects. Weekly calls were made by the PI to all the participants to check patient compliance and side effect reports to reduce responder bias. ABPM detected the occurrence of side effects such as bradycardia, tachycardia or hypotension during automated recordings.

Blood pressure was measured using the SOPs that were consistent throughout the study followed by the principal investigator and study nurses. Clinic BP measurements were in duplicates at least three minutes apart, and the average of the last two readings was used in the analysis.

3.5 Ethical Considerations

Good research practices followed during data collection, included not transmitting or emailing participants' information and maintaining the integrity of the research findings. Approval from UNZABREC and permission from the University Teaching Hospital Director and the Head of Department of Internal Medicine were obtained. This study observed the ethics principles prescribed by the Helsinki declaration which included participants' autonomy, beneficence, non-maleficence, confidentiality, and justice. Participant autonomy was ensured by obtaining written informed consent and assurances of the quality of care for Hypertensive PLWHIV not wishing to participate in the study. Transport cost was compensated for scheduled follow-up visits. The amounts reimbursed were per current expenses of the services to avoid coercing the participants into taking part in the study.

Participant non-maleficence was practised by not using experimental drugs or treatments outside hypertension and ART treatment protocols. The attending physicians oversaw the overall management of the participants to ensure participant safety and maintenance of a participants' minimum standard of care. Beneficence included guaranteeing the Participants with non-resolving hypertension or complications received timely appropriate specialists care for treatment and further investigations or management. Participants with severe or worrying side effects were encouraged to make clinic visits with compensation for transport costs. The participants directly benefited from conducting the study by referring them to their

attending physicians for adjustments or changes of the BP-lowering drug doses in cases of uncontrolled hypertension. Patient counselling on hypertension was provided to all hypertensive and pre-hypertensive patients in the ART clinic for the duration of the study. The advice included a healthy diet, weight reduction, exercise and dietary salt intake reduction.

Participant confidentiality was maintained by coding and anonymising Patient ID numbers and names. All data collected was stored in locked cardboard or a password-protected private computer. The patient records will be shredded and data deleted once the permission for the study expires. There was some discomfort from the BP cuff on the upper arm, but no painful procedures were performed. Participant justice was maintained by randomly selecting participants who were representative of the target population. This ensured lack of bias in participant selection and each patient had an equal chance of being chosen for the study. Pregnant women and children less than 18 were excluded from the study as some of the drugs used are contraindicated in the former. Pregnancy-induced hypertension would also have confounded the outcomes. Children were excluded from the study as they were not part of the target population in this study in keeping with the trends of the previous investigator in this area.

Community service and relevance of this study were ensured by researching two pathologies have high prevalence and substantial impact on many communities in Zambia. Free ABPM was performed at the request of some attending physicians for patients with doubtful hypertension diagnosis or poor tolerance of antihypertensive medications. ART clinic staff was reminded of the hypertension treatment protocols to increase antihypertensive coverage among hypertensive PLWHIV Awareness.

3.6 Independent Variables

Age, educational level, BMI, ART regimen, duration of cART, class of Antihypertensive drug, the number of antihypertensive drugs, duration of antihypertensive treatment, smoking, sex, alcohol use.

3.7 Dependent Variables

Blood pressure, compliance with antihypertensive drugs, hypertension-related admission, complications of hypertension, pulse/heart rate

3.8 Data Management

WHO and ART review questionnaire sheets were used to enter the data from interviews with the participant. All the forms were checked for missing data and inaccuracies before the end of the study. The information was entered into Microsoft Excel for data coding, data cleaning, and export into Statistix version 9. The recordings of the ambulatory blood pressure monitoring were downloaded onto the password protected personal computer. The principal investigator performed data validation, cleaning, and de-identification using Microsoft Excel 2016.

3.9 Data Analysis

The data was entered, verified and cleaned in Microsoft Excel 2016 spreadsheet. The hard copies of the collected data were stored in a locked trunk. Statistix version 9 was used to enter the frequency of each code nominal data. The data was converted into proportions and percentages for calculations of risk ratios and attributable risks. The Fisher's exact test was used to determine associations between categorical variables for frequencies of less than 1 or less than 80 percent of rates were less than 5. The modified Freeman-Halton extension of the Fisher's exact probability test

allowed analysis of data with more than two comparison groups using the 2×4 and 3×4 to accommodate the four arms of the antihypertensive drug regimens. Chi-squared test was used to determine the difference in proportions of the four antihypertensive treatment arms (CCBs, CCBs with Enalapril, Moduretic, Moduretic with Enalapril) for nominal variables with minimum frequencies greater than one and 80 percent of entries were greater than five.

Continuous variables were tested for normality in Statistix version 9 using Shapiro-Wilk Normality test. All the data did not follow normal distribution necessitating the use of non-parametric tests to determine the significance of the differences of the medians of the results rather than means using Kruskal-Wallis One-Way Nonparametric analysis of variance. The Wilcoxon Signed-Rank test analysed paired data. The p-value for the two-tailed test was selected whenever an alternative one-tailed p-value was calculated. The differences in the variables of the three antihypertensive drug regimens were determined at 95 percent confidence interval and considered significant at p-values were less than 0.05.

CHAPTER 4: RESULTS

4.1 Participant Characteristics

ART clinic nursing staff identified hypertensive patients with blood pressure greater than 140/90 on at least three different visits or BP less than 140/90 with a history of the antihypertensive drug on each day. Sixty-two patients with hypertension on antihypertensive treatment were identified (23 on CCBs, 20 on CCBs and Enalapril and 18 on Moduretic). Two patients declined participation due to inability to return for ABPM removal. Two patients had white coat hypertension (170/ 100 mmHg) with normal ambulatory BP when not on treatment.

After stratified sampling 29 participants were selected with a median age of 48 years and comprised 69 percent (n=20) females. Twenty-one percent (n=6) had access to home BP measurements, and sixty-six percent only had blood pressure checks at the ART clinic. Sixty- two percent (n=18) had free access to antihypertensive drugs, and twenty-eight percent (n=8) purchased their medication. Thirty-five percent (n=10) of participants were on CCBs and CCBs + Enalapril, 28 percent (n=8) on Moduretic and three percent (n=1) on Enalapril. Six participants were switched from CCBs with Enalapril to Moduretic with Enalapril during the study.

All twenty-nine participants had predominantly diastolic hypertension. Forty-one percent (n=12) of participant had a history of complications of hypertension mostly cerebral vascular accidents (CVA) or and transient ischemic attacks (TIA). Fifty-two percent (n=15) had at least one hypertension related admission in the past year.

Except for the two most recently recruited, all the participants had complete viral load suppression of HIV and all the participants received education about non-pharmacological interventions for blood pressure control. Thirty-one percent (n= 9)

and sixty-two percent (n=18) of the participants had hypertension for less and longer than five years respectively. Only fifteen percent (n=3) of participants on CCBs were concurrently on PIs as most participants were on NNRTIs. The median BMI was 25.4 Kg/m², and seventy-six percent (n=22) and eighty-three percent (n= 25) of the participants had no history of consuming alcohol or smoking respectively.

Characteristics of participants on the Moduretic, Enalapril with CCB and CCB only were comparable. Hence the internal validity of the findings exists (Table 4.1).

Table 4.1. Study population characteristics among the first three antihypertensive treatment arms.

Variable	Moduretic (n=8)	IQR	CCB + Enalapril (n=10)	IQR	CCB only (n=10)	IQR	p- value
Median age (years)	49.5	45.5- 52.3	51.5	41-55	47	42-51	0.8007
Sex: Females	50% (n=4)		80% (n=8)		66.7% (n=6)		0.461
Median BMI	24.9	22-29	27.2	25-30	23.9	22-25	0.4686
Median duration of cART (years)	6.5	3-11	4.5	2-10	5.0	3-7	0.7200
Duration of hypertension: New diagnosis < 5 years > 5 years	22.2 % (n=2) 22.2 % (n=2) 55.6 % (n=5)		0 30 % (n=3) 70 % (n=7)		0 40% (n=4) 60 % (n=6)		0.441
ART regimen: NNRTI PI TDF	100 % (n=8) 0 100 % (n=8)		90 % (n=9) 10 % (n=1) 100 % (n=10)		80 % (n=8) 20 % (n=2) 100 % (n=10)		0.492
Alcohol use: Never Stopped Yes	75 % (n=6) 12.5 % (n=1) 12.5 % (n=1)		80 % (n=8) 0 20 % (n=2)		80% (n=8) 20% (n=2) 0		0.362
Smoking Never Stopped	87.5 % (n=7) 12.5 % (n=1)		100 % (n=10) 0		80 % (n=8) 20 % (n=2)		0.3711
Herbal drug use:	0		10 % (n=1)		20 % (n=2)		1.0000
Relative with hypertension	87.5 % (n=7)		70 % (n=7)		70 % (n=7)		1.0000
Hypertension complication awareness	87.5 % (n=7)		100 % (n=10)		90 % (n=9)		0.5320

Variable	Moduretic (n=8)	IQR	CCB + Enalapril (n=10)	IQR	CCB only (n=10)	IQR	p- value
Median CD4 count/L	473	419.5- 714	600	296- 857	364.5	241- 364.5	0.2327
Viral load Suppressed	100 % (n=8)		90 %(n=9)		90 % (n=9)		1.0
Serum creatinine (umol/L)	71.6	60-89	58.8	53-72	70	58-82	0.4452
Median clinic blood pressure (mmHg): Systolic	161.5	154- 166.5	169.0	162- 175	170	160- 195	0.3940
Diastolic	101	96-106.5	101.5	96-127	110	103- 117	0.3030

4.2 Blood Pressure Control Assessment Using ABPM

All (n=29) the patients had white coat effect and no cases of masked hypertension.

ABPM detected 7 percent (n=2) had white coat hypertension and did not require pharmacological intervention. The daytime blood pressure remained high (clinic BP 170/120 mmHg) after five months for the patient on Enalapril. The difference in median systolic and diastolic, 24-hour blood pressure (p=0.13 and p=0.18), circadian BP decrease (p=0.08 and p=0.23) of CCBs, CCBs with Enalapril and Moduretic were not significant. As well as the BP load and incidence of hypotension (p=0.25 and p=0.08 systolic and diastolic BP respectively), bradycardia (p=0.91), and tachycardia (p= 0.97, Table 4.2). The three antihypertensive regimens produced a circadian decrease of greater than ten percent (Table 4.2).

Table 4.2. Median ABPM parameters in Moduretic, CCBs with Enalapril and CCBs only.

Variable	Moduretic	IQR	CCB + Enalapril	IQR	CCB only	IQR	p-value
Median 24-hour BP (mmHg):							
Systolic	135.0	128-142	152.9	128-157	139.0	127-156	0.1273
Diastolic	81.0	80-94	90.6	79-108	97.6	82-102	0.1827
Median daytime BP (mmHg):							
Systolic	136.8	131-147	147.9	130-159	140.4	131-163	0.1864
Diastolic	84.2	83-96	92.7	81-108	98.8	86-104	0.1683
Median nighttime BP (mmHg):							
Systolic	123.1	114-127	130.8	124-149	128.4	110-133	0.2028
Diastolic	73.6	69-83	79.4	71-92	79.6	71-85	0.6067
Circadian BP decrease %							
Systolic	11.5	7-14	10.6	7-12	15.8	12-18	0.0824
Diastolic	12.2	9-18	12.3	10-17	17.7	17-23	0.2293
Median 24-hour BP load % (>140/90)							
Systolic	32.9	15-51	74.8	23-85	35.1	17-73	0.1236
Diastolic	35.1	14-63	35.8	18-85	68.1	25-73	0.1453
Median day BP load % (>135/85)							
Systolic	62.1	40-82	91.2	39-96	66.1	46-99	0.2179
Diastolic	58.8	51-81	69.1	41-96	90.6	61-95	0.1646
median night BP load % (>120/75)							
systolic	58.0	16-77	93.0	57-99	63.2	7-93	0.3753
diastolic	17.1	11-64	51.3	17-97	47.4	12-81	0.5203
Hypotension % in 24 hours							
Systolic	1.2	0-7	0	0-1	0	0-2	0.2475
Diastolic	5.35	1-8	1.35	0.3-1	0	0-3	0.0819
Median heart rate	82.6	79-89	86	81-91	87.6	79-96	0.5826
Tachycardia % in 24 hours	10.5	6-22	11.7	4-18	11	2-22	0.9704
Bradycardia % in 24 hours	0.65	0-2.4	0	0-2	0	0-2	0.9055
Median nighttime BP variability	8.15	6-10	6.7	6-7	10.2	8-15	0.3202

Participants on CCB containing regimens had higher median blood pressure than the equivalent Moduretic containing regimen. The differences between daytime systolic and diastolic BP in CCBs (140.4/98.8 mmHg), CCBs with Enalapril (147.9/92.7 mmHg) and Moduretic (136.8/84.2 mmHg) were not statistically significant (p=0.19 and 0.17 respectively, Table 4.2). Only the difference between daytime systolic and diastolic blood pressures for Moduretic with Enalapril (140.5/84 mmHg) and CCBs with Enalapril (147.9/92.7 mmHg) was significant (p=0.003, Fig 4.1).

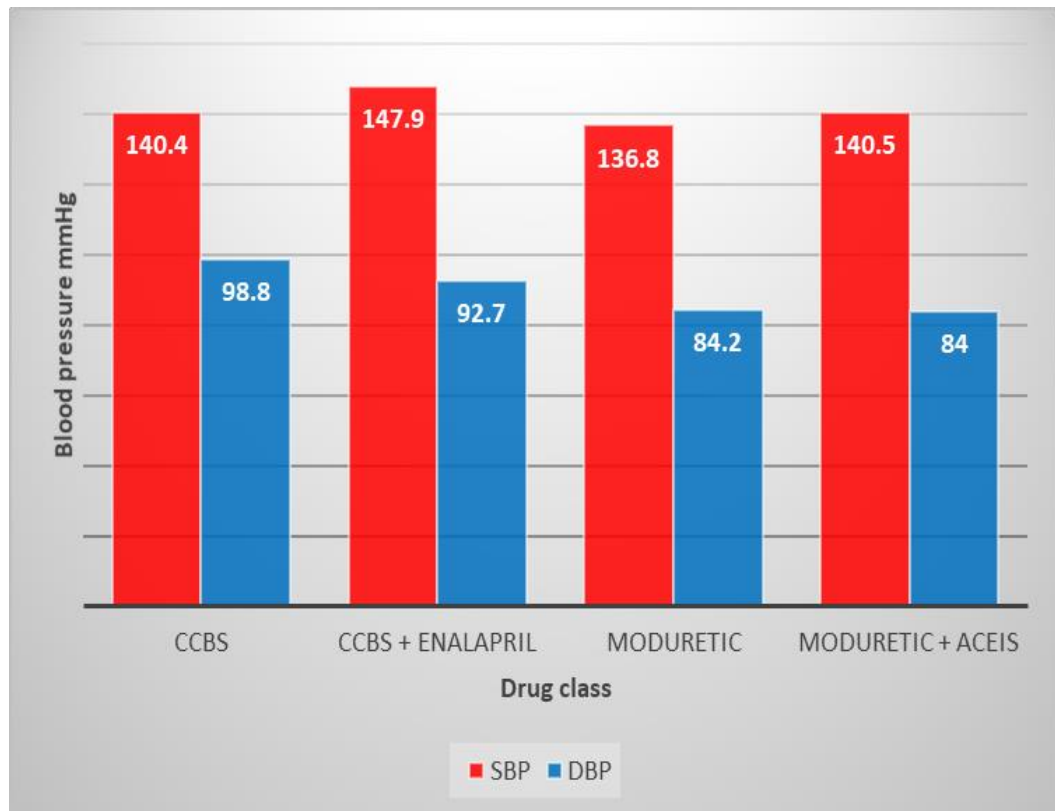


Fig 4.1. Median daytime systolic (SBP) and diastolic blood pressure (DBP) of commonly prescribed antihypertensive drugs.

All the differences in median ABPM parameters between CCBs with Enalapril and Moduretic with Enalapril were statistically significant except for the occurrence hypotension (2.1 percent, $p=0.46$ and 4.9 percent, $p=0.84$, systolic and diastolic, respectively). As well as bradycardia (2.6 percent, $p=0.67$) and 24-hour systolic BP load (-22.5 percent, $p=0.46$). The systolic circadian decrease was less than ten percent for both regimens, although it was higher by -1.5 percent in the CCB with Enalapril group (8.25 percent, $p=0.005$, Table 4.2).

Table 4.3. Median ABPM parameters in the crossover from CCB + Enalapril to Moduretic with Enalapril.

Variable	Moduretic + Enalapril	IQR	CCB + Enalapril	IQR	difference	p- value
Median 24-hour BP (mmHg):						
Systolic	139.3	130-143	161.8	158-170	-22.5	0.0025
Diastolic	82.1	80-96	106.5	102-113	-24.2	0.0025
Median day BP (mmHg):						
Systolic	140.5	133-146	171.2	163-175	-30.7	0.0025
Diastolic	84.0	81-100	109.8	107-116	-25.9	0.0025
Median night BP (mmHg):						
Systolic	127.8	120-136	152.2	138-159	-24.4	0.0025
Diastolic	79.9	74-83	93.2	91-101	-13.3	0.0025
Circadian BP decrease %:						
Systolic	8.25	5.2-13.4	9.8	7.0-15.1	-1.5	0.0054
Diastolic	10.25	7.2-20.3	10.9	9.5-20.1	-0.6	0.0033
24-hour BP Load %:						
Systolic	46.6	20-57	88.8	78-92	-42.2	0.4561
Diastolic	20.1	15-61	83.9	77-89	-63.9	0.0025
Day BP Load %:						
Systolic	79.85	52-81	99.1	93-100	-19.2	0.0025
Diastolic	65.9	51-75	96.8	94-100	-31.0	0.0025
Night BP Load %:						
Systolic	74.7	33-93	97.1	93-100	-22.5	0.0025
Diastolic	59.4	14-69	94.1	85-100	-52.1	0.0025
Hypotension % in 24 hours:						
Systolic	2.1	0.3-6.0	0.0	0-0	2.1	0.4561
Diastolic	4.85	1.2-7.6	0.0	0-0.8	4.9	0.8445
Median heart rate (beats/min)	82.0	17.0	91.7	13.4	-9.7	0.0025
Tachycardia % in 24 hours:	10.85	2-25	18.9	7-20	-8.1	0.0108
Bradycardia% in 24 hours:	2.6	2-7	0	0-0	2.6	0.6661
Night diastolic BP SD	7.0	6-14	13.6	9-17	-6.6	0.0059

4.2.1 Proportion of Blood Pressure Control Using ABPM

Moduretic had higher proportions of daytime systolic and diastolic BP control (50 and 62 percent) than CCB only and CCB with Enalapril (attributable risk of getting better 20 percent, $p = 0.69$. and 32 percent $p = 0.42$ respectively). The proportion of daytime systolic and diastolic blood pressure control was higher in the participants on Moduretic with Enalapril (50 percent and 67 percent) than CCBs with Enalapril

combination (attributable risk of getting better 20 percent, $p = 0.046$ and 37 percent, $p = 0.014$ respectively, Fig 4.2). Neither Moduretic + Enalapril nor CCB + Enalapril controlled nocturnal systolic BP in this subgroup, but Moduretic had 33 percent attributable risk of controlling nocturnal diastolic BP ($p = 0.12$).

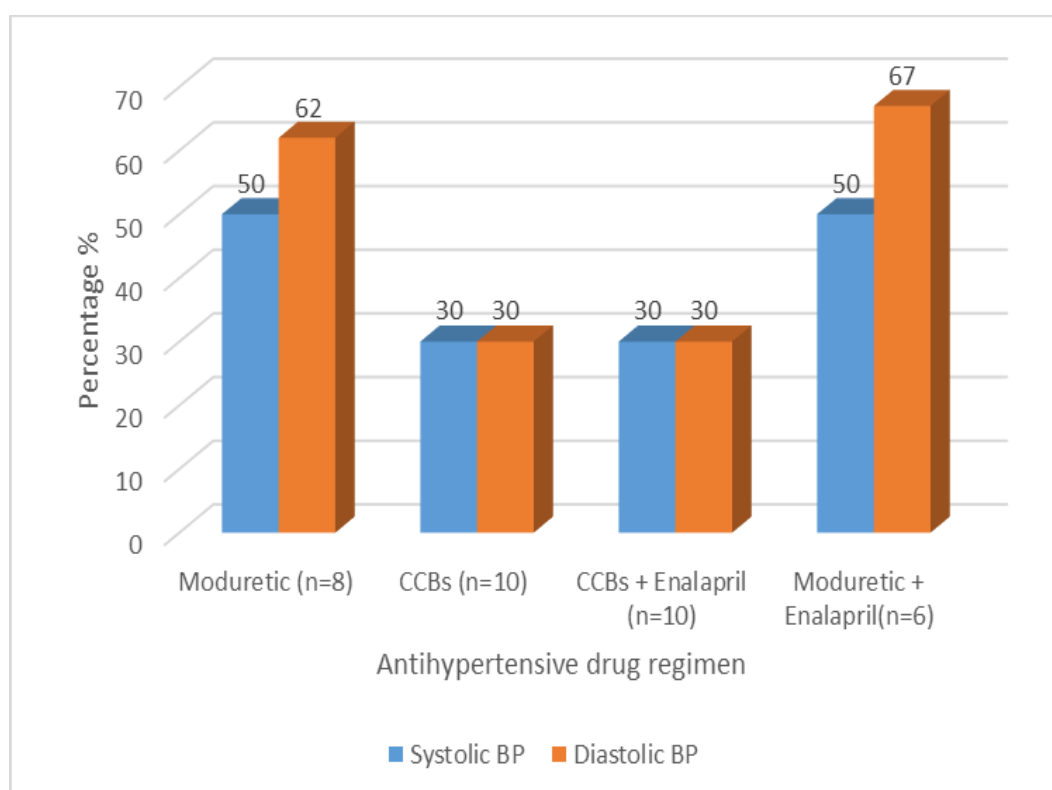


Figure 4.2. The proportion of mean daytime BP control (< 135/85 mm Hg) by antihypertensive drug class. Moduretic regimens had a better proportion of BP control than the CCB regimens.

Overall proportion of nighttime diastolic (44 percent) BP control was higher by 11.11 percent compared to nighttime systolic (33 percent) BP ($p = 0.34$, Fig 4.3). Overall, non-dippers comprised of 38.9 percent ($n=14$) for systolic BP and 27.8 percent ($n=10$) for diastolic BP. Dippers comprised of 38.9 percent ($n=14$) for systolic BP and 27.8 percent ($n=10$) for diastolic BP of the 36 independent ABPM recordings.

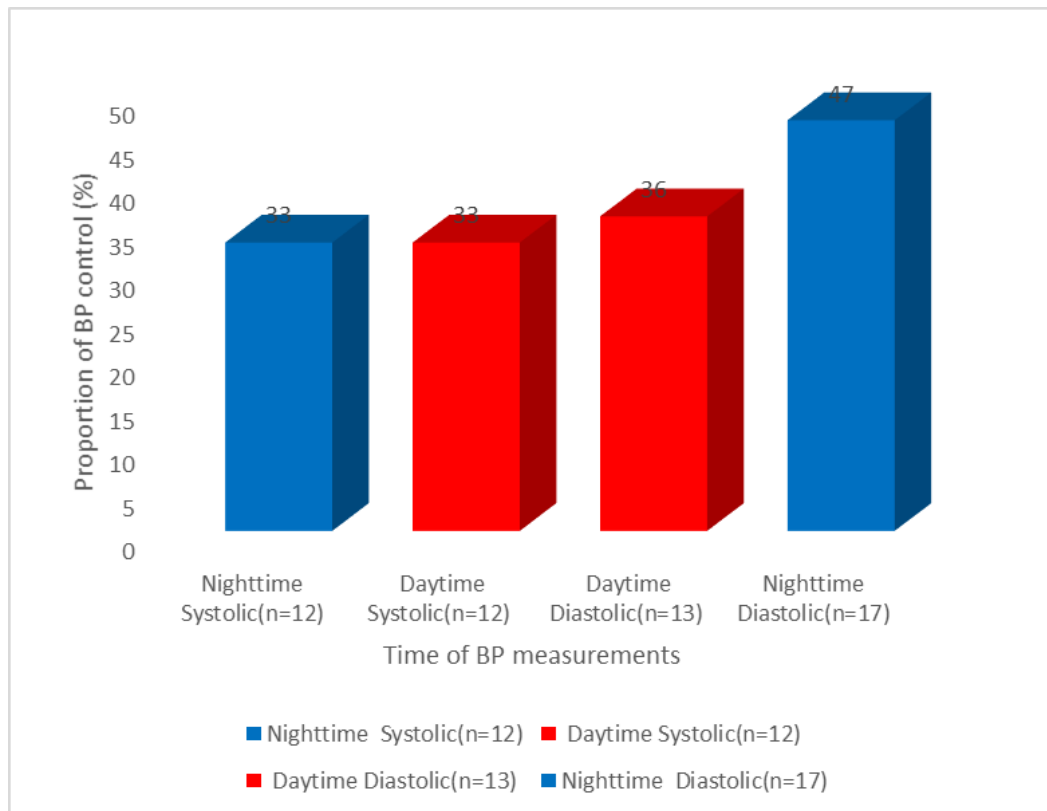


Figure 4.3. Overall Proportion of BP control in PLWHIV on commonly prescribed antihypertensive drugs.

4.2.2 Detection of Blood Pressure Control Using Clinic and ABPM Methods

The median clinic BP (170/106 mmHg) was higher than median daytime (142/95.5 mmHg) by 22.62 mmHg and 11.20 mmHg for the systolic and diastolic BPs ($p=0.0001$ and 0.001 respectively). Ambulatory blood pressure monitoring is a more sensitive method of detecting proportions of antihypertensive drug control (daytime BP $<135/85$ mmHg and clinic BP $<140/90$ mmHg) than sitting clinic blood pressure measurements. Clinic BP was able to detect a higher efficacy for diastolic blood pressure than systolic BP as with ABPM. However the clinic BP measurement

method underestimated systolic (11 percent) and diastolic (14 percent) blood pressure control by 19.4 percent ($p=0.047$ and 0.030 respectively, Fig.4.4).

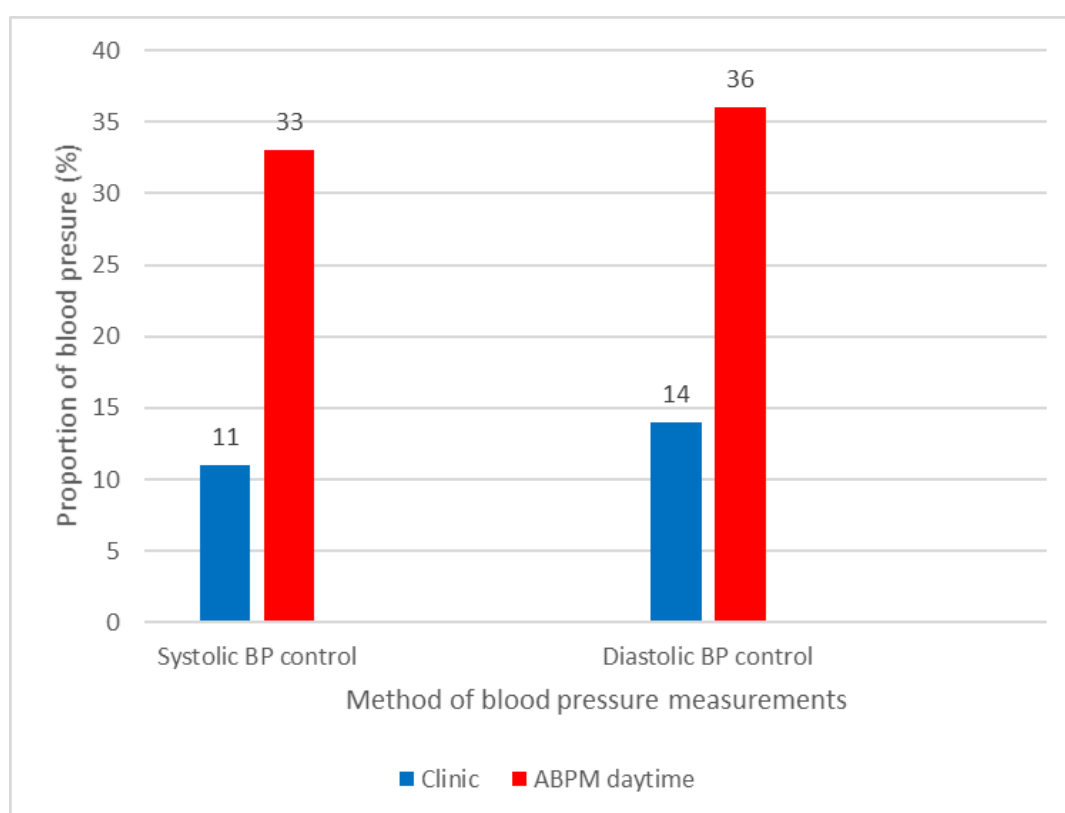


Figure 4.4. The difference in the proportion of detection of BP control using clinic BP measurement and daytime BP from ABPM method.

4.3 Effects of Coadministration of cART with CCBs

All three participants with pre and post CCB ABPM or pre and post NNRTI treatment on CCBs had poor blood pressure control after six weeks of coadministration. The mean blood pressure parameters including circadian rhythm were worse after coadministration of the two drug classes. Except for nighttime systolic BP with a mean reduction of 7.05 mmHg for two participants commenced on CCBs already on NNRTIs (Table 4.3); the CCB was Nifedipine ®. However, the sample size of participants is too small for statistical analysis.

Table 4.4 ABPM parameters for CCBs in pre-CART and post- CART with baseline pre-CCB and one month after baseline ABPM.

VARIABLE	CCB PRE- ART	CCB PRE-ART	DIFFERENCE	MEAN PRE- CCB	MEAN POST- CCB	DIFFERENCE
24 HR SYS BP	122.4	151.2	28.8	143.0	144.2	12.0
24 HR DI BP	79.7	98.0	98	98.35	99.9	1.55
DAY SYS BP	126.2	158.5	158.5	146.05	149.65	3.6
DAY DI BP	83.1	103.1	20.0	98.85	104.45	5.6
NIG SYS BP	109.9	131.9	22.0	131.25	124.2	-7.05
NIG DI BP	68.4	84.5	16.1	75.45	82.95	7.5
CIR SYS DEC	12.1	16.8	4.7	10.3	16.9	6.6
CIR DI DEC	17.7	18	0.3	23.7	20.35	-3.35
24 SYS LOAD	11.5	61.6	50.1	51.2	56.45	5.25
24 DI LOAD	0	69.9	69.9	58.85	69.6	10.75
SYS HYPOT	0	0	0	1.9	0.65	-1.25
DI HYPOT	0	1.4	1.4	3.85	0	-3.85
24 HEART RT	78.41	87.6	1.19	93.5	88.45	-5.05
NIG DI SD	11.1	10.3	-0.8	8.9	9.25	0.35
% TACHY	1.5	11.0	9.5	18.7	15.95	0.35
% BRADY	1.0	0	-1.0	0	0.65	0.65

SYS = systolic, DI= diastolic, NIG= night, CIR= circadian, DEC= decrease, HYPOT= hypotension, RT= rate, SD= standard deviation, TACHY= tachycardia, BRADY= bradycardia

4.4 Side Effect Profile of Commonly Used Antihypertensive Drugs

Only seven percent (n= 2) of the participants had symptoms of hypertension (headache), and 34 percent (n= 10) had side effects from antihypertensive drugs during the study. 25 percent (n=2) of participants switched from the Moduretic due urinary frequency that interfered with responsibilities at work. Thirty-eight percent (n=3) participants prescribed Moduretic had serum levels between 3.1 – 3.3 umol/L.

Only ten percent (n=3) of the participants had baseline serum potassium measurement (3.4 – 3.6 umol/L). One participant required potassium supplements, while the rest of the participants were on Enalapril to improve BP control and ameliorate hypokalemia. No participants on Enalapril and Moduretic developed hypokalemia or hyperkalemia.

The one participant on Enalapril was switched from Nifedipine due to history of nose bleeds while on Nifedipine. Fifteen percent (n=3) of participants on high dose CCBs developed persistent headaches and dizziness were investigated for causes of a headache in HIV with ENT referrals. Two of the participants were switched from EFV to NVP which was suspected to have caused the central nervous system (CNS) symptoms. The symptoms resolved with the withdrawal of Nifedipine and commencement of Moduretic. The proportion of side effects was highest for Moduretic 62.5 percent (n=5), but the differences with the other regimens were not significant (p= 0.25, Fig 4.5).

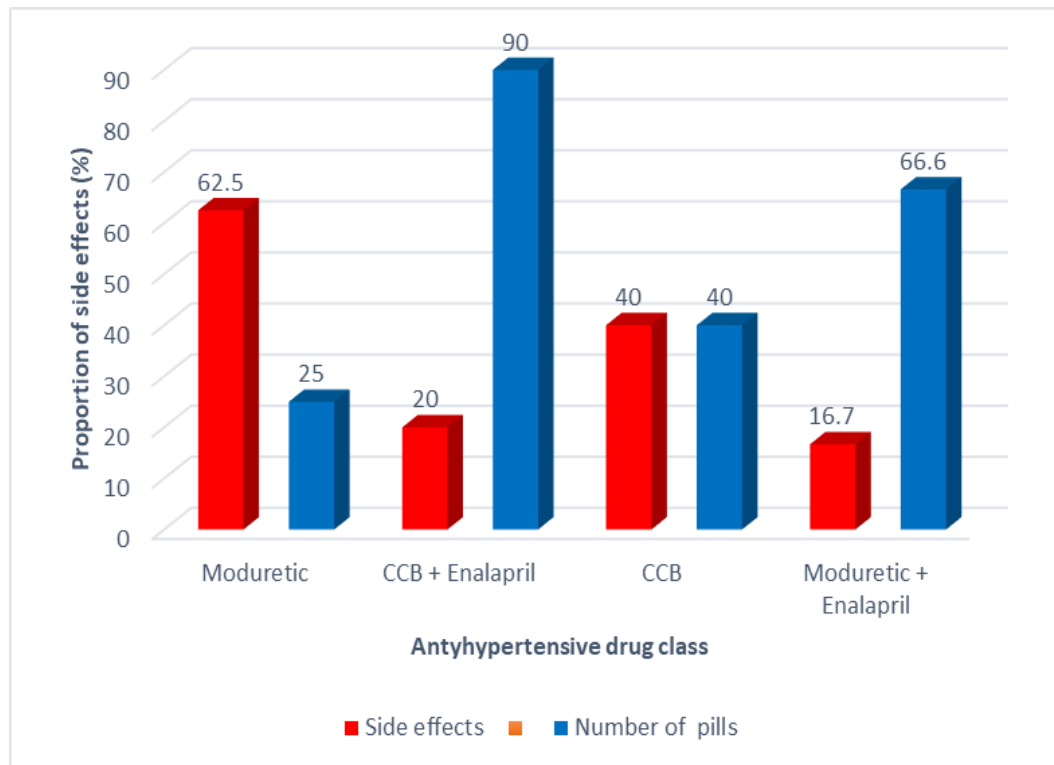


Figure 4.5. Side effect profile of the different drug classes and the relationship with pill burden.

The highest pill burden was in CCBs with Enalapril (90 percent, n=9) and Moduretic with Enalapril (67 percent, n=4, p=0.025). The pill burden had no association with side effects as these two regimens had the lowest proportion of side effects (Fig 4.5). The one participant on Enalapril reported no side effects.

4.5 Compliance with Antihypertensive Drugs in PLWHIV

Thirty-three percent (n=3) of participants on Enalapril with CCB were not aware of omitting Enalapril from the regimen. Non-compliance was commonest in participants on CCB with Enalapril (40 percent, n=4) and CCBs (50 percent, n=5, p=0.048). The main reasons for noncompliance side effects and under-frequency for Nifedipine but not Amlodipine. The CCB with Enalapril had reports of drug omissions. The differences in reasons for non-compliance were not significant (p=0.12, Fig 4.6).

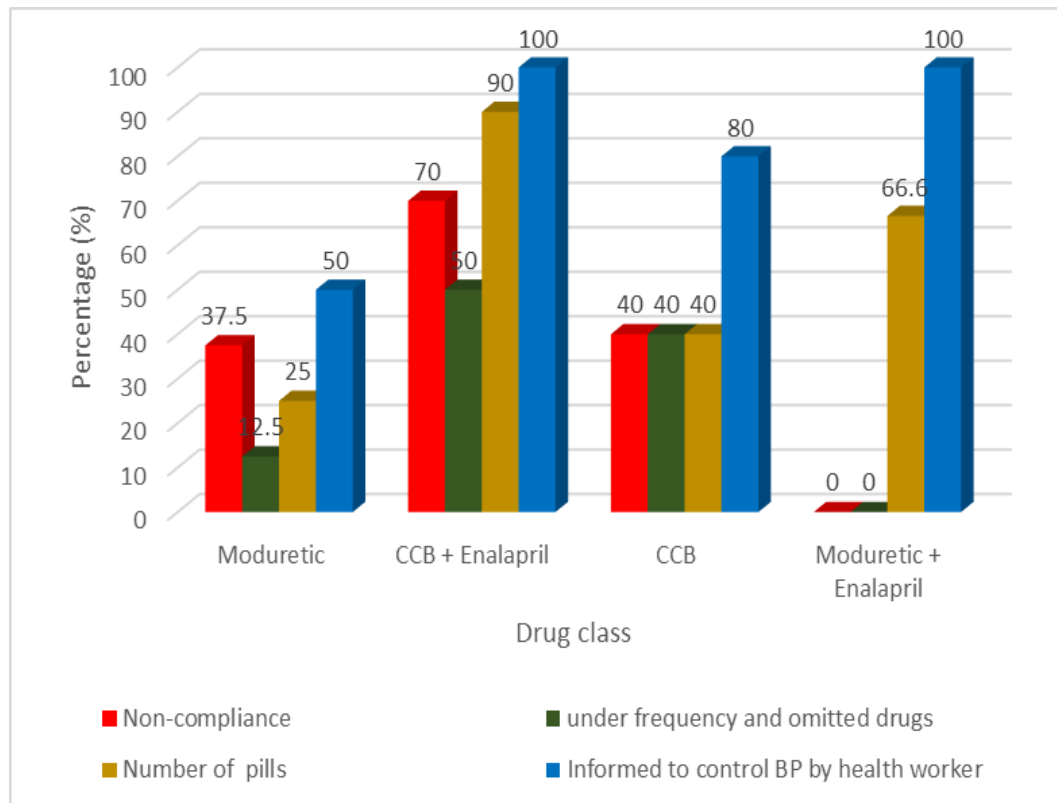


Figure 4.6. The relationship between noncompliance, pill burden, side effects, and knowledge of the importance of BP control by drug classes.

Increased pill burden did not increase noncompliance for CCB + Enalapril and Moduretic with Enalapril. The two groups had the highest proportion (100 percent) of knowing the importance of control of hypertension ($p=0.02$). The participant on Enalapril had no problems with compliance to treatment despite lack of BP control.

CHAPTER 5: DISCUSSION

5.1 Participant Characteristics

The population characteristics of the four groups compared groups were not statistically significant giving this study internal validity. All the data did not follow a normal distribution, and analysis was with non- parametric methods. The commonly prescribed antihypertensive drug classes included CCBs (Nifedipine and Amlodipine), ACE inhibitors (Enalapril) and thiazide diuretics (Hydrochlorothiazide/ Amiloride or Moduretic). The different antihypertensive treatment regimens where CCBs alone, Moduretic alone and combinations of the two with Enalapril. Only one patient was on Enalapril only. They were all African in origin which may have affected the findings of the drug efficacy especially poor response to Enalapril due to higher rates of low-renin hypertension in this population (Brewster and Seedat, 2013). All the participants had predominantly diastolic hypertension and the median age of 48 years and mostly female participants. These finding reported in Nigeria by (Okpa et al., 2017) to which the results of this study may be applicable.

Diastolic hypertension is more common in patients younger than 60 years (Yan Li et al., 2014). However, this phenomenon was present in all the participants including those over 60 may suggest that the HIV infection itself or some other factor may be responsible for this finding. Age has not been shown to affect the efficacy of CCBs or Moduretic. Predominate female may have contributed to lower rates of BP control in this study considering the interaction between NNRTIs and CCBs. Previous reports state that serum levels of NNRTI especially Efavirenz are elevated in the female due to differences in drug metabolism (Burger et al., 2006). Predominant

diastolic hypertension may have affected the differences in control rates for systolic and diastolic BPs by Moduretic. Previous reports stated that Moduretic and CCBs more significant effect on lowering the systolic than diastolic BP, whereas beta blockers had a more substantial impact on diastolic BP (Wu et al., 2005).

There was low use of herbal medication ten percent (n=3), possibly due to counselling received but patients on dangers of herb-drug interactions. These findings contradict other studies that report significant herbal use in hypertension regardless of HIV status (Tabassum and Ahmad, 2011, Liwa et al., 2014). Therefore, herbal medicinal consumption was assumed to not be a confounder in BP control, side effect profile and compliance with convention drugs in this study. The same argument applied to the low rates smoking and alcohol consumption in this study not affecting CCB efficacy. Smoking and alcohol consumption are known to cause CYP3A4 enzyme induction or inhibition (Barry and Feely, 1990). The median BMI of the participants was within the normal range hence it may not have played a factor in the BP control rates and absence of masked hypertension in this group. Obesity may be associated with hypertension with metabolic syndrome and occurrence of masked hypertension (Colantonio et al., 2017).

5.2 Blood Pressure Control Using ABPM

Clinicians at UTH were more likely to prescribe CCBs and rarely prescribed thiazide diuretics. At the time of the study, all antihypertensive drugs were only available at the central hospital pharmacy for half the duration of the study. This practice is still in compliance with treatment guideline for pharmacologic intervention in hypertensive patients of African descent (James et al., 2014). Studies that reported higher rates of BP control rates in general African populations reported more varied

prescribing pattern with more use of thiazide diuretics and combination therapy regardless of HIV status (Olanrewaju et al., 2010).

All in all, CCB containing combinations are less efficacious in controlling blood pressure than the Moduretic containing combinations in patients on NNRTI-based regimens. The absolute risk difference of good systolic and diastolic BP Control was 20 percent and 37 percent respectively ($p= 0.046$ and $p= 0.014$ respectively) for Moduretic and Enalapril (50 percent and 67 percent). Possibly due to interactions between the CCBs and NNRTIs, however, inter-individual variations in metabolism of both CCBs and NNRTIs may exist so that some participants (30 percent, $n= 3$) were responsive to CCBs and CCBs + Enalapril, despite co-administration of these drug classes. Addition of Enalapril to Moduretic added a third drug to the hydrochlorothiazide/Amiloride (Moduretic) combination. Expected to yield better BP control theoretically. Amiloride is a weaker antihypertensive drug than Enalapril whose primary purpose is to prevent hypokalemia by reducing sodium-potassium exchange at the distal tubule of the kidneys. Enalapril function at a site separate from the distal tubule at the renin-angiotensin-aldosterone system (RAAS). Enalapril has a different mechanism of action is more efficacious by overcoming the ceiling limit of hydrochlorothiazide with Amiloride. Hence JNC 8 recommends the use of thiazide diuretics with ACE inhibitors for enhancement of blood pressure control (James et al., 2014). Why this phenomenon did not occur for CCBs with enalapril in the same patients is uncertain. It is possible that since ACE inhibitors reduce vasoconstriction by inhibiting the conversion of angiotensinogen from angiotensin and CCBs also cause vasodilation, they have different mechanisms of action but similar sites of action. Which probably is not the area of pathology in hypertensive PLWHIV.

The study did not attribute lower CCB efficacy entirely to NNRTIs as there was an inadequate efficacy of CCBs in two of three participants on PIs. This study did not have an HIV negative control group to determine if this finding was restricted to PLWHIV or Zambians in general. The general blood pressure (33 percent systolic, 36 percent daytime diastolic and 47 percent nighttime diastolic BPs) control rates in this study slightly exceeded the range previously reported in PLWHIV (22 -33 percent) in other studies (De Socio et al., 2014, Manner et al., 2012). The BP control rates were better possibly due to the use of thiazide diuretics in this study predominantly occasionally combined with Enalapril in an African population. ABPM method is more sensitive in detecting BP control may have contributed to these findings especially the nighttime readings.

There was no statistical difference in the proportion of systolic and diastolic blood pressure control between CCBS, CCBs with Enalapril and Moduretic ($p= 0.69$. and $p= 0.42$, respectively). The median 24-hour, daytime and nocturnal decrease were greater than 20 mmHg and 10 mmHg, respectively, after six weeks of the latter combination for systolic and diastolic blood pressures. Although the reduction in blood pressure was not statistically significant, previous studies show that such a reduction is enough to reduce the risk of MI and stroke (Law et al., 2009). Therefore, the findings in this study may still be clinically relevant in Zambian PLWHIV with the need to explore this possibility on a more extended study.

Moduretic with Enalapril combination was significantly different in systolic and diastolic BP control compared to the CCB with Enalapril ($p= 0.046$ and $p= 0.014$ respectively). Moduretic as a thiazide diuretic had better efficacy as the participants were of African origin thought to have salt sensitivity hypertension resulting in

volume overload rather than vasoconstriction. Hence diuretics cause natriuresis and diuresis with additional increased vascular compliance (Brewster and Seedat, 2013).

Improved Moduretic with ACE inhibitors efficacy agrees with the JNC 8 recommendations that thiazide diuretics are more potent when combined with ACE inhibitors (James et al., 2014) as the first line in hypertensive patients of African origin with Moderate to severe hypertension. Addition of Enalapril was unable to affect blood pressure control when combined with failing CCBs or Moduretic regimens. ACE inhibitors are known to have less efficacy in lowering blood pressure in hypertension patients of African descent (James et al., 2014). This lack of effectiveness is because essential hypertension in people of African origin is most likely low renin in nature (Brewster and Seedat, 2013). Hence ACE inhibitors and ARBs with mechanisms of action in the renin angiotensin aldosterone system (RAAS) have little effect in modulating blood pressure in this group of patients.

Prescribing the combination of ACE inhibitors with thiazide diuretic without amiloride has less risk of causing hypokalemia and useful to a broader range of patients (Olanrewaju et al., 2010, Rochlani et al., 2017, Kalra et al., 2010, Mallat et al., 2013, Taddei, 2012). More than half the participants on Moduretic and Enalapril, ten percent (n=3) and 20 percent (n=6) of total participants had uncontrolled daytime and nighttime blood pressure respectively. Patients who do not reach their target BP on three drugs including a diuretic have resistant hypertension (Freeman et al., 2017).

Moduretic with Enalapril did not significantly control nighttime blood pressure over CCBs with Enalapril ($p=0.12$). This inadequacy was possibly due to disturbed sleep from nocturia caused by Moduretic (Hermida et al., 2010).

Non-dippers comprised of 38.9 percent (n=14) for systolic BP and 27.8 percent (n=10) for diastolic BP. This proportion of nondippers could have been due to use of Nifedipine ® as well as Moduretic. This study found participants on both CCB with Enalapril and Moduretic with Enalapril with abnormal circadian rhythm. The results contradict previous reports of higher prevalence of nondippers on long-acting CCBs such as Nifedipine XR and less in diuretics and ACE inhibitors (Qiu et al., 2004). Nifedipine XR 30 mg OD is superior to Nifedipine R 20 mg BD regarding consistency of serum levels (Snider et al., 2008). The HIV status of the patients may also have played a role in this discrepancy through other poorly understood mechanisms. There are more frequent reports of abnormal circadian rhythm than in HIV negative populations (Borkum et al., 2014). The other possibility is that patients with HIV, of relatively younger age group, predominant diastolic hypertension, and poor BP control may have secondary hypertension rather than essential hypertension. Hyperaldosteronism with hypertension may mimic low renin essential hypertension. ACE inhibitors would not be effective against secondary hypertension from hyperaldosteronism (Aronova et al., 2014, Mosso et al., 2003, Acelajado and Calhoun, 2011). Further studies to rule out this condition in this population would assist in the management of hypertension in PLWHIV at UTH.

The results of this study suggest that more than two drugs may be required to effectively control the blood pressure in almost 90 percent (n=26) as only three participants had controlled BP on CCBs only. These results were consistent with other investigators suggesting more than three drugs were required to reach target blood pressures in moderate and severe (Schillaci and Vaudo, 2001, Olanrewaju et al., 2010, Rochlani et al., 2017). This consideration during routine hypertension treatment could be considered.

Further studies are required to determine if other Enalapril with CCBs are less effective in HIV negative hypertensive patients due to low renin essential hypertension (Brewster and Seedat, 2013). These studies need to elucidate the characteristics of PLWHIV with resistant hypertension and the best treatment combinations in these patients (Persu et al., 2014, Yaxley and Thambar, 2015, Rossi et al., 2011). Hypertensive PLWHIV on cART at UTH had better BP control on Moduretic containing regimens, especially with combination therapy. A more extended study would determine whether surrogate blood pressure findings correlate with actual cardiovascular outcomes in Zambian PLWHIV.

5.2.1 Blood Pressure Control Using Sitting Clinic BP

This study utilised ABPM to identify hemodynamic factors that affect CV outcomes that cannot be measured by clinic BP measurements. The results confirmed the deficits of determining antihypertensive drug efficacy by clinic blood pressure alone. All participants in this study had white coat effect. Consistent with findings of markedly elevated clinic BP in PLWHIV possibly psychological stress associated with HIV infection and autonomic dysregulation (Manner et al., 2010).

The proportion of detection of systolic and diastolic BP control using the ABPM 19.4 percent higher than that detected by clinic BP measurements ($p=0.047$ and 0.03 respectively). ABPM was more sensitive in detecting antihypertensive drug effects than sitting clinic blood pressure (CBP) due to multiple BP measurements throughout the day and night. ABPM may have moderated the white coat effect and a physiological surge in morning blood pressure in the four to six hours of waking up (White, 2007). Mean daytime blood pressure compensates for the overestimated BP measurements at the clinic hence giving lower mean BPs (Persu et al., 2014). The absence of these confounders at night may also explain better nighttime than

daytime blood pressure control as the nighttime readings exclude the readings taken at the clinic and the BP surge upon waking up. This study recorded the time of sleeping and waking up of the participants to ensure these phenomena did not mar the nighttime readings.

This study showed that routine use of ABPM in hypertensive patients would improve the sensitivity and specificity of diagnosing cases of hypertension and identify patients with resistant hypertension. Consistent with finding by (Ayala et al., 2013, Yaxley and Thambar, 2015, Persu et al., 2014). Correct identification of resistant hypertension that requires more aggressive antihypertensive drugs from white coat hypertension would reduce unnecessary antihypertensive treatment in the latter. ABPM in this study helped minimise inertia among clinicians to escalate therapy of participants switched to Moduretic to Enalapril after six weeks on CCBs with Enalapril. Inertia in hypertension treatment was identified as one of the reasons for poor BP control in other studies (Patel et al., 2016, Manner et al., 2010).

The routine uses of ABPM method in hypertensive patients on and off treatment will add a wealth of information we can use to determine the effects of cART and antihypertensive therapy. It would aid in the individualised treatment of hypertension by titration antihypertensive therapy against blood pressure response in Zambian PLWHIV in the long term.

5.3 Effects of cART on CCBS

Ambulatory BP readings in participants on PIs (ten percent, n=3) had less variability in blood pressure profile during the 24-hour period than those on NNRTIs. The sample size was too small to make any conclusions or carry out any statistical analysis. One participant on Nifedipine with PI had controlled blood pressure, but

the other two did not. However, this shows that poor BP control with CCBs cannot be entirely attributable to NNRTI interaction in PLWHIV. Most of the participants had moderate and severe hypertension that requires more than one antihypertensive drug for successful treatment.

There is no dispute in previous studies that serum CCB levels increase with concomitant use of PIs (Singh et al., 2014). This study showed no evidence of clinical significance regarding BP control and side effect profile in PLWHIV on CCBs and PIs. This finding is consistent with results by (Wang et al., 2015) in healthy Chinese participants. However, the sample size was inadequate to make any conclusions as other studies have reported considerable interindividual variations in drug metabolism (Lamba et al., 2002). Use of CCBs and PIs warrants caution as CCBs may have a wide therapeutic index, but ADRs are probably likely in older patients (Gandhi et al., 2013). The participants of this study and in the Chinese study were relatively young which may have contributed to the lack of adverse effects reporting in PI and CCB coadministration.

One participant with good BP control before commencing NNRTI-based CART regimen developed poor BP control after six weeks on cART. Supporting the interaction between CCBs and NNRTIs may interfere with BP control in some patients. The mean ABPM parameters showed worsening BP parameters in two participants after a month on Nifedipine. One of the participants had an increase from baseline blood pressure. With the associated increase in heart rate after Nifedipine was commenced. Adverse changes in blood pressure and pulse rate could be a result of increased reflex sympathetic activation from the CCBs with catecholamine release postulated by (De Champlain et al., 1998). Nifedipine ®

formulation and Amlodipine are long-acting CCBs that should provide sustained BP control during drug peak and trough level (Ueng et al., 2011).

However, the increased CYP3A4 enzyme metabolism by NNRTIs (inducer) may have shortened CCB half-life for their actions to be similar to shorter-acting CCBs in this patients. Shorter-acting CCBs are associated with reflex sympathetic nervous system activation and increased serum norepinephrine levels (De Champlain et al., 1998). Similar to reports of rebound hypertension occurring after sudden CCB drug withdrawal (Reidenberg, 2011). In this patient, sympathetic activation may occur during the Nifedipine ® serum trough levels as a result of its shortened half-life.

The use of Moduretic in Zambian patients on Tenofovir (TDF) was likely to cause hypokalaemia in despite containing Amiloride. The hypokalaemia was ameliorated by the addition of Enalapril to the treatment. This finding must be explored on a more substantial number of patients to encourage change on policy in treatment and monitoring hypertensive patients on Moduretic and TDF.

5.4 Side Effect Profiles of Antihypertensive Drugs in PLWHIV

Moduretic had the highest proportion of side effects (62.5 percent, n=5, p= 0.25).

Mainly urinary frequency and hypokalemia. Routine supplementation of thiazide with a potassium-sparing drug like Amiloride is not recommended by JNC 8 (James et al., 2014) unless a patient is at risk of hypokalemia. Amiloride did not prevent the occurrence of hypokalemia in this population. Enalapril reduces aldosterone secretion via the RAAS preventing the absorption of sodium in the renal collecting duct at the expense of potassium. The combination of a thiazide diuretic, amiloride and Enalapril was required to improve hypokalaemia without increasing the risk of hyperkalemia after a month of treatment. Perhaps two potassium-sparing drugs are

required to prevent continued hypokalemia from Tenofovir. Alternatively, there might be an element of hyperaldosteronism that could be responsible for both the hypokalemia and hypertension that may present with predominantly raised diastolic blood pressure (Aronova et al., 2014, Mosso et al., 2003, Acelajado and Calhoun, 2011). Aldosterone: renin ratios would aid in understanding this phenomenon and characterisation of hypertension in this population. These participants required closer monitoring to avoid hyperkalemia. This drug regimen is an example of “thinking outside the box” and individualised treatment of hypertension in patients with suspected TDF-related hypokalemia. Caution should be used in such patients as patients on tenofovir may also develop hyperkalemia as reported by (Cirino and Kan, 2006, Eluwa et al., 2012).

The main reason for the noncompliance was due to side effects of Nifedipine but not Amlodipine. CCBs (40 percent) had higher side effect proportion than CCBs with Enalapril (20 percent $P = 0.65$). The difference was due to increasing doses of CCBs to the maximum dose before adding Enalapril to control blood pressure. This approach increased side effects without further improving BP control in the CCB group. This occurrence in side effects concurs with findings in previous studies that increasing doses of a single drug increased chances of SEs (Taddei, 2012). There is evidence of better efficacy and fewer side effects when appropriate combination therapy is used to treat hypertension (Chen et al., 2010, da Silva, 2010, Kalra et al., 2010, Taddei, 2012, Digne-Malcolm et al., 2016, Rochlani et al., 2017).

The side effects of CCBs were no different from HIV negative patients. However, there may have been an increase in proportion due to NNRTIs by reducing CCBs half-life which led clinicians to increase CCB doses to achieve control during serum trough levels results in increased side effects during the peak levels. Supported by

finding by (Grundy and Foster, 1996). This postulation cannot be stated with certainty as there was no HIV negative control group on CCBs.

The three participants on concurrent CCBs and PIs did not report any side effects on Nifedipine. Hypertension and its treatment cannot be independent of treatment of HIV in PLWHIV. In three cases, the symptoms of hypertension and side effects from antihypertensive drug treatment overlapped with symptoms of HIV-related opportunistic infections and antiretroviral drug side effects. The clinicians may treat PLWHIV without awareness of the hypertension diagnosis overlooking treatment side effects of antihypertensive drugs. The side effects of the drugs led to expensive investigations and unnecessary changes in ART regimen that did not resolve the symptoms. The symptoms were alleviated on withdrawal of high doses of CCBs and controlling blood pressure with Moduretic and Enalapril.

5.5 Compliance with Antihypertensive Drugs

Increasing number of antihypertensive drugs did not negatively impact on drug compliance in this study. These findings contradicting (Gupta et al., 2017) who reported an association between increased pill count and poor compliance with antihypertensive drugs. The reason for the discrepancy may lie in patient education on the importance of antihypertensive compliance in controlling hypertension. There was more awareness of BP control among participants on CCB with Enalapril and Moduretic with Enalapril (100 percent, $p=0.02$). Probably due to repeated contact with healthcare workers during previous hospital admission and drug escalations from monotherapy. Participants whose health care providers added a second antihypertensive drug to the treatment to control hypertension were more likely to be told about the importance of BP control and antihypertensive medication compliance.

All the Participants in this study received education on drug compliance, dietary and lifestyle changes that prevent progression of CVDs as part of the ethical obligation of this study. The emphasis on adherence to antihypertensive drugs alongside adherence counselling to ART may further improve antihypertensive drug compliance. Timely identification and treatment of side effects may also have enhanced compliance as was the case with Moduretic and hypokalemia.

Non-compliance was commonest in CCB with Enalapril (40 percent, n=4) and CCBs (50 percent, n=5, p=0.048). This finding is contradictory to findings by (Gupta et al., 2017) who reported the use of diuretics as a risk factor for noncompliance. Patient education and different side effect profiles of CCB from Moduretic may have affected this finding in this study. The main reasons for noncompliance were side effects and under-frequency for Nifedipine but not Amlodipine. The under frequency was a result of both prescriber and patient error daily with Nifedipine ® that was taken once daily like Amlodipine rather than twice daily. The CCB with Enalapril had reports of drug omissions especially for recent changes in prescriptions or when the second drug, usually Enalapril was out of stock. The differences in reasons for non-compliance in CCBs were not significant (p=0.12). Health care providers at UTH should be encouraged to countercheck prescriptions for correct dosage and frequency of antihypertensive drugs and inform patients of prescription changes at every contact. To reduce non-compliance by under frequency and drug omission.

The information from this study provides guidance on the more useful antihypertensive drug combinations that are more acceptable and easier to comply with by hypertensive PLWHIV at UTH. The types of side effects of different antihypertensive combinations in this study are no different from those reported in other populations. However, they may occur at higher frequencies (34 percent, n=10)

than HIV negative patients (11 percent, Adigun, 2003). Addressing side effects would improve antihypertensive drug compliance and save time and money on expensive investigations in this setting. Continued patient education on hypertension and its control during ART adherence counselling would improve compliance rates and BP control in PLWHIV at UTH. There is considerable intra-individual and inter-individual variability in response to antihypertensive drugs, which requires each patient's treatment to be individualised to their needs and expected exposure to other medicines and patient preferences (Jingi et al., 2016). This goal may be aided by the use of ABPM to complement clinic BP measurements. The objectives of this study were met supporting the alternative hypothesis of this study.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Hypertension is common in sub-Saharan Africa which coincides with the high burden of HIV. Hypertension is more likely to progress to CVD in patients of African origin as well as HIV patients. It is necessary to co-administer antihypertensive drugs with cART to ensure the continued survival of hypertensive PLWHIV. Therefore, the comparison of commonly used anti-hypertensive drug classes in a clinical setting added practicality to the reports from clinical trials that compare effects of these medications in HIV-negative population predominantly of non-African origin. Comparing the efficacy, side effect profiles, and compliance in patients on commonly used antihypertensive drugs filled some gaps preventing the effective control of hypertension in PLWHIV on cART.

The use of Moduretic with Enalapril produced the highest ratio of blood pressure control with the least Side effects and good compliance. The study demonstrated that blood pressure control rates might be improved with careful consideration of drug interactions in PLWHIV. Routine use of ABPM in clinical practice had a role to play incorrect diagnosis, characterisation, and management of hypertension. Its regular use would aid in achieving higher BP control rates in hypertensive PLWHIV.

The findings provided information that may assist drug companies to develop single pill combinations that relevant in PLWHIV to aid in patient compliance. Not just for antihypertensive drugs but combinations with cART as hypertension continues to affect this population. The challenges of treating hypertension in PLWHIV of African will require further research into novel combinations of antihypertensive drugs that produce better BP control. These combinations must not increase CVD complications by causing metabolic derangements in a population already at risk for metabolic disorders.

6.1 Limitations

The sample size was small, and the duration of the study was short. However, it remains within the duration antihypertensive drug efficacy studies trends in literature, but the study could not make significant generalizable conclusions. The pill count and participants' word of mouth were used to determine compliance with antihypertensive drugs during this study. Inability to reliably confirm compliance may have underestimated treatment efficiency of drugs such as Amlodipine and thiazide diuretics with long half-lives are sensitive to noncompliance as they take longer to reach steady state and full efficacy. Serum drug levels of CART and antihypertensives were not measured to verify assumption of drug interactions between CCBs with PIs and NNRTIs.

The findings of this study may not be generalizable to hypertensive PLWHIV on longer acting CCBs such as Nifedipine XR, those with diabetes, renal dysfunction, and secondary hypertension. As well as patients with PI-based CART regimen or mild to moderate hypertension in PLWHIV and non-African origin. The study did not determine long-term cardiovascular outcomes such as ADRs, development of CVD and mortality. However, ABPM increased the accuracy and reliability of this study by measuring several parameters that are known to determine the risk of developing CVD independently. The parameters were interpreted using recommendations in HIV negative patients. Drug efficacy is best calculated by the area under the curve of the peak and trough BP by ABPM before and after antihypertensive treatment.

6.2 Recommendations

Harmonizing the health care system to include hypertension treatment in the ART clinic by including antihypertensive drugs available in the ART clinic pharmacy for patient convenience is necessary. Prescribers should double check antihypertensive

drug prescriptions. Where possible avoid the use of single or dual antihypertensive regimens that contain Nifedipine® formulations in PLWHIV on NNRTI-based ART. Clinicians should be sensitised to the increased risk of hypokalemia in patients on TDF and thiazide diuretics. Hypertension should be treated with combination therapy for moderate and severe hypertension. Routine use of ABPM in PLWHIV with hypertension is necessary.

There is a need for the Ministry of Health to revisit the preferred hydrochlorothiazide/ Amiloride combination recommended by the Zambia drug formulary in PLWHIV. Adherence to antihypertensive drugs should be integrated into ART adherence counselling sessions to emphasise the importance of treating both conditions.

A more rigorous study of longer duration with longer acting CCBs and control for drug brands would add to the information gathered by this study. Further investigations to characterise the effects of antihypertensive treatment on actual cardiovascular outcomes rather than blood pressure which is a surrogate marker. To determine the end point blood pressure that prevents CVD in PLWHIV as current trends recommend treatment outcomes similar to HIV negative populations. A similar study of African and non-African participants on more diverse combinations of antihypertensive drug classes with HIV negative controls for longer duration is required. The question of whether PLWHIV have blunted responses to antihypertensive drugs independent of ART perhaps to the inflammatory process, autonomic dysfunction, secondary hypertension or oxidative stress could be explored.

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APPENDICES

Appendix A: Information Sheet

(TO BE RETAINED BY THE PARTICIPANT)

Description of the Study Procedures

My name is Dr Takondwa Ngulube Chidumayo, a Master of Pharmacology student at the University of Zambia. I am doing this research as a requirement to graduate in this program while adding knowledge that will be helpful in finding out if certain medicines will work better in patients with high blood pressure and HIV.

I would also like to invite you to participate in this study designed to see how the different medication used to treat high blood pressure in people with HIV taking ARVs affect the blood pressure. To find out whether there is a difference in the side effects compared to other patients taking different medicines for high BP. The results of this study will help us to make suggestions on how best to treat your conditions in future based on the findings of this study. Please ask any questions that you might have.

The study nurse, medical student or I will measure your blood pressure to include attaching a BP machine to you for 24 hours and ask you some questions. The questions will be about the medicines you are taking, your lifestyle and food habits. We will also examine you as part of your review during your ART clinic visit. You will be able to carry out your normal activities once the BP machine is attached to your arm or in a pouch. If any problem is found, you may be referred for special treatment to a specialist. You will be recruited once you accept to join this study.

All this will be done before you are reviewed by your doctor to minimise the time we take. You will be required to take the medication under observation and return

the following day to return the BP machine. Transport cost to and from this visit will be provided to you upon arrival.

What are the possible advantages to me?

Taking part in this study will provide you with health information about your BP and medicine you are taking. This study may in the future help others who suffer from the HIV infection and high blood pressure. The readings of your blood pressure will be shared with you and if you wish the overall results of this study.

What are the possible disadvantages to me?

The medicine you are taking has no added risk to your usual treatment, as this study will just be observing how you respond to your usual treatment. There will be no painful procedures although you may experience some discomfort from the BP cuff as we check your blood pressure. We will be taking up some of your time during your return visit, and we are thankful for your participation in this study.

The study is voluntary

You do not have to participate in this study if you do not want to, if you refuse to take part in this study, you will receive your usual care from this ART clinic. If you do agree, you are also free to change your mind later. The Biomedical Research Ethics Committee of the University of Zambia has approved this research study, and their contact details are given below.

Contact details of the study Principal Investigator: Dr Takondwa Ngulube
Chidumayo, Department of Pharmacology, University of Zambia, School of
Medicine. (Phone 0968306061).

Contact details of Biomedical Research Ethics Committee: The Chairperson,
UNZABREC office, Department of Anatomy, Ridgeway Campus, Nationalist Rd,
Lusaka (phone 0211 256067).

Appendix B: Consent Form

24th January 2017 – Version 2.2

Consent record sheet (TO BE KEPT BY THE STUDY TEAM)

Comparing the effects of calcium channel blockers and other antihypertensive drug classes in Hypertensive HIV patients on cART at Adult Infectious Disease Centre, Lusaka, Zambia: a prospective comparative cohort analysis.

I confirm that I have understood the information I have been given about the study. I agree to participate in answering the additional questionnaires and have my blood pressure measured. I confirm that I am joining the study of my free will and that I can withdraw at any time without affecting the care available to me. I understand what will be required of me.

I agree to participate in the above mentioned study:

Participant's Name (print) Participant's Signature/thumbprint Date

I have observed the participant sign or make his/her mark above and I believe he/she has understood and knowingly gives consent for participation.

Witness' Name (print) Witness' Signature Date

I have explained the purpose of continuing in this study to the participant. He/she had the form read to him/her, was given a chance to ask questions, accepted the answers, and signed to enrol in the study.

_____	_____	_____
Study Staff's Signature	Study Staff's Name (print)	Date

Note: This consent form with original signatures must be retained on file by the principal investigator. A copy must be offered to the volunteer.

7.31 WHO Questionnaire for Hypertensive patients



World Health Organization
Developing Integrated Response of Health Care Systems to Rapid
Population Ageing

PATIENT QUESTIONNAIRE
 Questionnaire for **Hypertensive patients**

DIAGNOSIS OF HYPERTENSION: Q 1-4, 6,7

1. How did you come to know about your hypertension?	1. in a routine medical control 2. screening programme 3. emergency service 4. other (specify: _____) 5. I do not know
2. When were you diagnosed?	1. First time 2. < 5 years 3. > 5 years
3. Where were you first diagnosed as having hypertension?	1. This primary health centre 2. Other primary care clinic/physician 3. Secondary care hospital* 4. Tertiary care hospital* 5. at a pharmacy/drugstore 6. other (specify) 7. I do not know * manual explains what it is meant
4. Was the clinic or hospital where you were first diagnosed run by the government, a charitable organization or was it privately run? (Please mark only one option)	1. Public 2. Private 3. Non-governmental Organization/Charity organization
6. Where do you regularly go for routine follow up to check your blood pressure?	1. Diagnosis on this visit 2. This health centre 3. Nearby primary health care clinic 4. Nearby hospital (secondary facility) 5. Tertiary hospital 6. I do not do any routine follow up → Why? _____
7. Do you have to pay fees for consultation and/or drugs at the facility that you regularly go to for the treatment of your hypertension ? (Please mark only one option)	1. Paid nothing 2. Paid part 3. Paid fully 4. Paid (I do not know if part or fully) 5. I do not know

Management. Q 5, 8, 9, 11

5. Have you been told by a doctor or nurse or someone by this health centre to control your blood pressure?	<ul style="list-style-type: none"> 1. Yes 2. No
8. When do you go for your routine blood pressure check?	<ul style="list-style-type: none"> 1. Diagnosis on this visit 2. As advised by the doctor 3. When I do not feel well 4. Both 5. Other (specify) _____
9. Beside a primary health centre, how else do you get your blood pressure measured (checked)?	<ul style="list-style-type: none"> 1. Secondary care hospital* 2. Tertiary care hospital* 3. Neighbour/family member 4. Myself 5. Check in a nearby pharmacy/ market place 6. Other (specify) _____ 7. I only check my blood pressure in the primary health centre
11. Compared to 12 months ago, is your blood pressure:	<ul style="list-style-type: none"> 1. better 2. same 3. worse 4. I do not know 5. I didn't get my blood pressure measurement 12 months ago

COMPLICATIONS AND HOSPITALIZATION: Q 12-15; 20

10. Do you have blood relatives with history of hypertension?	1. Yes 2. No 3. I do not know
12. Over the last year have you been admitted to the hospital?	1. Yes 2. No → Go to Q16
13. Do you know why?	1. No 2. Yes (specify) _____ _____ _____
14. Was it related to hypertension?	1. Yes 2. No 3. I do not know
15. Was your blood pressure controlled at your admission to the hospital?	4. Yes 5. No 6. I do not know
20. Have you had any complications from your hypertension?	1. No 2. renal disease 3. stroke 4. retinopathy 5. cardiovascular 6. other _____ 7. I do not know

MEDICATIONS AND ADHREENCE: Q16-19

16. Have you been prescribed any medication to lower your blood pressure?	1. Yes 2. No 3. I do not know
17. Do you take all your prescribed medications?	1. Yes 2. No
18. How many different medicines a day are you taking (approximate number)?	[] []
19. If you don't take your medication regularly, why don't you take them as directed?	1. I cannot afford the cost 2. medication are not easily available 3. I do not like to take medications 4. I only take them when I feel that I need them. 5. I do not like the side effects of the medication. 6. I prefer alternative medicine 7. I forget 8. I do not know 9. Other_____

KNOWLEDGE AND SELF CARE: Q 21,22,23

21. Are you aware of any complication of hypertension?	8.
22. If you are aware, have you been informed by the doctor or nurses or someone by the health centre about these complications?	1. Yes 2. No → Go to Q23
23. Have been told that stroke is related to hypertension?	1. Yes 2. No