PREVALENCE AND INCIDENCE OF HYPERTENSION AND DIABETES MELLITUS IN HIV INFECTED PERSONS ON HAART IN CHONGWE DISTRICT IN LUSAKA PROVINCE, ZAMBIA

By

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ABSTRACT

The Zambia National strategic plan (ZNHSP)-2011-2017 highlights the need for risk factor stratification at the community level to form the basis of incidence and prevalence data, which are currently inadequate. This research aims to determine the prevalence and incidence of hypertension and diabetes among HIV infected patients on Highly Active Anti-Retroviral Therapy (HAART) and its association with ARVs use. A retrospective cohort study was used using the SMART CARE electronic database in Chongwe district to assess 2,070 HIV infected persons on HAART. Data was analyzed using SPSS version 20, and analyzed using Chi-square Kruskal-Wallis for analysis of variance, and logistic regression was used to establish the determinants of hypertension and type II diabetes mellitus among HIV infected persons on HAART. 33.8% HIV positive clients on HAART had hypertension, and an incident case fatality rate of 85.7 cases per 1000 PYFU of hypertension. The prevalence of hypertension was significantly higher ($\chi 2$=49.238, df=1; p<0.001) among men (64%) than among women (49%). The prevalence of hypertension also differed significantly ($\chi 2$=11.194, df=2; p=0.004) among different age categories and was highest (57.2%) among the 18-45 years age bracket. This study also found a significant correlation between hypertension and age of client in years (p=0.009). The study also found an incident rate of 37.4 cases per 1000 PYFU of T2DM. This study also established no significant differences in the prevalence of type II diabetes mellitus between women (26%) and men (23%). However, the prevalence of diabetes differed significantly (($\chi 2$=10.043, df=2; p=0.007) among different age categories and was highest (27.5%) among the 56 years and older age bracket. Results of logistical regression analysis for the determinants T2DM and hypertension show that ART combination (p=0.001), age category (p=0.011) and cigarette smoking (p=0.0460) significantly added to the prediction model for T2DM outcome; and that ART combination (p=0.004), sex (p=0.001), family history of hypertension (p=0.007) and cigarette smoking (p=0.001) had significant associations with and significantly added to the prediction model for hypertension outcome. HIV positive clients on HAART had high prevalence and incidence of hypertension and type II diabetes mellitus. HAART combination regimen of two NRTI classes plus either a PI or INSTI were associated with higher incidence of hypertension whilst combination regimens of two NRTIs plus an NNRTI or INSTI and combination therapy of NRTI+NNRTI+INSTI were associated with higher incidence of type II diabetes mellitus in HAART treated clients.

Dedicated to my family and friends, for their support and love.

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ABBREVIATIONS AND ACRONYMS

3TC	:	Lamivudine
ABC	:	Abacavir
ART	:	Antiretroviral Therapy
ARV	:	Anti-retroviral
ATV	:	Atazanavir (ATV-r: boosted with retinovir)
AZT	:	Azydothymidine (also known as zidovudine ZDV)
BP	:	Blood Pressure
CSO	:	Central Statistics Office (now known as ZamStat)
DHIS	:	District Health Information Systems
T2DM		type II diabetes mellitus
DTG	:	Dolutegravir
DRV	:	Darunavir (DRV-r: boosted with retinovir)
EFV	:	Efavirenz
ETR	:	Etravirine
ETV	:	Entecavir
FTC	:	Emtricitabine
HAART	:	Highly Active Anti-retroviral Therapy
HIA	:	Health Information Aggregate
HIV	:	Human Immunodeficiency Virus
INSTIs	:	Integrase Strand Transfer Inhibitors
IRIS	:	Immune reconstitution inflammatory Syndrome
LPV	:	Lopinavir (LPV-r: boosted with retinovir)

NCD	:	Non-Communicable Diseases
NVP	:	Nevirapine
NNRTI	:	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	:	Nucleoside Reverse Transcriptase Inhibitor
PLHIV	:	People living with HIV
PI	:	Protease Inhibitors
PrEP	:	Pre-Exposure Prophylaxis
PY	:	Person Years
RAL	:	Raltegravir
T2D (M)	:	Type II Diabetes (Mellitus)
TAF	:	Tenofovir Alafanamide
TDF	:	Tenofovir Disoproxil Fumarate
XTC	:	Lamivudine or Emtricitabine
Z	:	Pyrazinamide

OPERATIONAL DEFINITION OF TERMS

Diabetes Mellitus	:	A fasting blood glucose of ≥7.0 mmol/l, or random blood sugar of ≥11.1 mmol/l, or HbA1C > 6.5%
Immune reconstitution Inflammatory Syndrome	:	An exaggerated inflammatory reaction from re-invigorated immune system presentation as unmasking of previously sub-clinical opportunistic infections OR clinical deterioration of pre-existing opportunistic infections OR development of autoimmune disease.
Incidence	:	The number of new cases that develop within a given time period.
Incidence Rate	:	Incidence measured over a known time period in a population of known size (number of new cases during study period /duration of study period totaled for all individuals).
Prevalence	:	The proportion of individuals in a population that have a disease or condition at a particular time.
Person-time	:	An estimate of the actual time at risk in years, months, or days that all persons contributed to a study.
Rate	:	The number of new cases of disease/condition during a period of time divided by the person time at risk.

SMART CARE	:	An Electronic Health Record (EHR) system used for management of client health records, generation of reports and auxiliary services such as pharmacy, labs, logistics and user provider management.

CHAPTER ONE: INTRODUCTION

1.0 BACKGROUND OF THE STUDY

Globally, an estimated 37.9 million people are living with HIV with an adult global prevalence of 0.8%. An estimated 770,000 people die of HIV related illnesses. Globally, 78% (23.3 million) of those who know their status are on treatment. The vast majority of people living with HIV live in the sub-Saharan region with an estimated 68% of the total global estimate (UNAIDS, 2019a). In Zambia, there is an estimated 1.2 million people living with HIV with an estimated adult prevalence rate of 11.3%, and estimated 17,000 AIDS related deaths (UNAIDS, 2019b).

Diabetes mellitus is one of the fastest growing health challenges of the 21st century, with the number of adults living with diabetes having more than tripled over the past 20 years (International Diabetes Federation, 2019a). Diabetes mellitus prevalence has been rising more rapidly in the middle and low-income countries (World Health Organisation, 2018). A decade ago, in 2010, the global projection for diabetes in 2025 was 438 million, with over five years still to go, that prediction has already been surpassed by 25 million. In 2019, it was estimated that 9.3 percent of adults aged 20 to 79 years, a staggering 463 million people were living with diabetes according to (International Diabetes Federation, 2019a). Further to that, globally an estimated 374 million (7.5%) of adults aged 20 to 79 years had impaired glucose tolerance. The number of deaths resulting from diabetes and its complications in 2019 was estimated to be 4.2 million. The majority of these cases are in low and middle-income countries with an estimated 79.4% incidence rate (International Diabetes Federation, 2019b). Zambia is one of the countries without in-country data sources for all forms of diabetes and across all age groups. However, the IDF in 2017 estimated 222, 000 cases of diabetes mellitus putting the prevalence rate at 3 percent

(International Diabetes Federation 2019b; Zambia-International Diabetes Federation 2019). In 2019, the International Diabetes Federation projected Zambia's incidence within the range of 4 to 5 percent.

The Global Status Report on NCDs emphasizes that the negative impacts of NCDs are particularly severe in poor and vulnerable populations such as those living in the Sub Saharan A region , where poverty exacerbates many health conditions (World Health Organization, 2014).

Secondary data from a Systematic Analysis of Population-Based Studies from 90 Countries by Mills and colleagues 2016 on global disparities of hypertension prevalence and control found that an estimated 1.39 billion people (31.1%) had hypertension in 2010 and 349 million (28.5%) of these were in high-income countries and 1.04 billion (31.5%) were in low and middle-income countries; the same study in a country specific map put Zambia at less than 20% in 2010. According to Goma and colleagues (2019), in 2017 the prevalence of hypertension was at 25.9% after a population screening of 9,067 adults. The study also reported that the prevalence of hypertension may be as high as 34% in some areas of Zambia. In comparing the two studies, the incidence rate is probably increasing over time. According to World Health Organization Regional Office for Africa, Zambia's health profile shows an observable high disease burden branded by high levels of maternal, neonatal and child mortality, high incidence and impact of communicable diseases, and a rapidly growing burden of non-communicable diseases (NCDs) (World Health Organization Regional Office for Africa, 2018).

Chongwe District is the second largest District under Lusaka province with a catchment population of 182,174 (CSO 2018) and of these 13, 076 were on anti-retroviral treatment. The end of 2018 closed with a reported number of 3,899 incident cases of hypertension and 887

incident cases of Diabetes mellitus in the District Health Information System (DHIS; HIA 2 and HIA1 2018).

Currently, the combination of antiretroviral (ARV) therapy for people living with HIV (PLHIV) has led to a marked reduction in HIV associated morbidity and mortality, since its introduction in the mid-1990s (Pangmekeh et al., 2019a). Much of the disease burden in PLHIV is now due to morbidities found in the general population. HIV itself, and some of the ARVs used to treat it, are associated with an increased risk and premature development of chronic comorbidities, including Type II diabetes mellitus (T2DM). T2DM is reported to be up to four times more prevalent in PLHIV than those without HIV (Monroe et al., 2015).

The risk factors for Type II diabetes mellitus in the general population are well established, such as age, overweight/obesity, smoking, excessive alcohol consumption, physical inactivity etc (American Diabetes Association, 2014) but in HIV there are additional specific risk factors, including duration of HIV infection, degree of immunosuppression, and exposure to those ARVs known to be associated with dysglycaemia (Hadigan and Kattakuzhy, 2014). Specific ARVs, with a variable contribution from HIV infection itself, are associated with an increased risk of metabolic diseases, including redistribution of fat and other manifestations of lipodystrophy, dyslipidemia, and higher rates of comorbidities associated with ageing, including myocardial infarction and Type II diabetes mellitus (Althoff et al., 2015).

Clinical treatment guidelines for PLHIV include prevention and treatment of cardio metabolic risk factors. However, most of the clinical recommendations are based on drug treatments (Atun et al., 2017). Therefore, it is important to explore non-pharmacological treatments. Reducing cardio metabolic risk factors is essential in the treatment of PLHIV in ART, and nutritional interventions have an important role in the management of metabolic abnormalities (Remais et

al., 2013). A randomized controlled study, demonstrated the effectiveness of both nutritional interventions in reducing some cardio metabolic risk factors in PLHIV treated with ART, particularly hypertension, blood glucose, total triglycerides, high Density Lipoproteins, and the primary outcome of low density lipoproteins (Aparecida Silveira et al., 2020).

Despite improvements in ARVs, the prevalence of conventional T2DM risk factors appear to be increasing in HIV patients as the population ages (Guaraldi et al., 2011). It is important to understand the reasons for the increase in hypertension and T2D in PLHIV in order to effectively target early prevention strategies.

This study aimed to determine the prevalence and incidence of hypertension and diabetes mellitus in HIV infected persons on HAART and also assess the association of HAART use to hypertension and diabetes in Chongwe district.

1.1 STATEMENT OF THE PROBLEM

Antiretroviral therapy in the treatment of HIV confers significant benefit by prolonging life through immune reconstitution. However, this immuno competence is at a cost of metabolic function which includes a range of metabolic aberrations that are not limited to hypertension, insulin resistance, glucose intolerance and type II diabetes. This may lead to an increased risk in cardiovascular disease (Pangmekeh et al. 2019; Fahme, Bloomfield, and Peck 2018; Olaiya et al. 2018). A Zambian study on the prevalence of subclinical cardiovascular disease in healthy HIV infected patients at the University Teaching Hospital in Lusaka found that 34.6% of their sample had systolic hypertension and 36.6% had diastolic hypertension, and that diabetes was not common at 3.3%. The study concluded that the prevalence of subclinical cardiovascular diseases in healthy HIV infected patients was high (Kabwe et al., 2016). Another cross-sectional study

carried out in the neighbouring Malawi found that the combined prevalence of hypertension and diabetes mellitus was high among adult Malawian HIV patients in care (Divala et al. 2016). An observational analytical cross-sectional study in Ethiopian and non-Ethiopian HIV infected adults by Korem et al. (2018a) found the prevalence of hypertension significantly higher ($p < 0.001$) in the study population at 53% as compared to the general population at 20%. However, a review summarizing recent evidence on increased cardiovascular risk in patients linking HIV infection to hypertension found the available data as still inconclusive on whether hypertension was prevalent among HIV patients or not (Sanidas et al., 2018). For instance, the Malawian study noted that data from HIV infected populations are limited and hence concluded that more research on CVD risk in HIV infected Africans is urgently needed to generate evidence (Divala et al., 2016).

The Zambia National Health Strategic Plan (ZNHSP) 2017-2021 notes that the burden of NCDs in Zambia is on the rise, and that NCDs have received less attention in the past decade as compared to communicable diseases. The strategic plan further states that there is need for risk factor stratification at the community level so that it forms the basis of incidence and prevalence data, which are currently inadequate (Zambia Ministry of Health, 2017). In response to these problems and gaps in evidence, this study intends to contribute to the knowledge pool and partially answer to the problem by showing a case of Chongwe district by defining the burden and quantifying the risk factors of NCDs among ARV users. Most of the past studies reviewed were cross-sectional in design and had limitations in showing temporal associations. This retrospective cohort study would provide a different set of quantitative evidence to the problem of hypertension and T2DM in people on HAART.

1.2 CONCEPTUAL FRAMEWORK

Possible linkages between HIV/ARVs with hypertension and diabetes

HIV and ARVs provide a direct link to hypertension and diabetes through the metabolic changes that take place in the body. HIV through its inflammatory effects and immune reconstitution increases the risk of having hypertension and or diabetes. Systemic inflammation has been associated with incident diabetes in multiple cohorts in the general population (Pradhan et al., 2001; Spranger et al., 2003; Wang et al., 2013). Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, may induce insulin resistance by binding to insulin responsive elements in skeletal muscle (Draznin, 2006). Among HIV infected patients, markers of systemic inflammation decrease quickly with ART initiation but do not normalize (Brown et al., 2010; Friedstrom S and Fernandez H, 2015). It is postulated that the residual inflammation with effective ART contribute to the pathogenesis of comorbidities in HIV infected patients, including diabetes (Deeks, 2009). The chronic inflammation nature of the infection affects different body organs including the pancreas. Damage to the pancreas can result in insufficient insulin secretion and consequently insulin resistance/diabetes mellitus. HIV is also associated with various endocrine abnormalities including those of the growth hormone axis. These include deficiency of the growth hormone, as well as growth hormone resistance. The cardiovascular system is an important target organ for growth hormone (GH) and insulin like growth factors (IGF)-1 in humans, and GH/IGF-1 deficiency significantly increases the risk for cardiovascular diseases [CVD] (Strazhesko et al., 2017). Autoimmune diabetes has been reported to develop in some HIV infected patients after immune restoration during HAART. Patients presenting with diabetes after receiving HAART have been shown to develop antibodies to glutamic acid decarboxylase, at a time when CD4 counts shot up suddenly. It is postulated that the recovery of immune

function predisposes to autoimmune disease in form of type 1 diabetes. However, diabetes associated with HIV may be classified as type II diabetes rather than type 1 diabetes in the vast majority of patients (Kalra et al., 2011; Lane and Moin, 2020).

HIV and ARVs provide a direct link to hypertension and diabetes through the metabolic changes that take place in the body. Some ARVs cause side effects such as lipodystrophy, and metabolic syndrome which increases the risk of having hypertension and or diabetes mellitus. The indirect links of ARVs is the increased life expectancy they offer which predisposes one to age related co-morbidities and risk factors. ARVs intake also has an impact on lifestyle of the individual and nutritional status depending on a lot of social economical, physical and mental wellbeing which would increase the risk of hypertension and diabetes mellitus than in the general population. There is also a documented association between HIV, ARVs and immunological function and treatment related toxicity which have an effect on organ function, important in this case, renal and liver function (Montessori et al., 2004); (Corbeau and Reynes, 2011); (Margolis et al., 2014). In HIV persons on ARVs, this can precipitate hypertension and diabetes mellitus (Montessori et al., 2004).

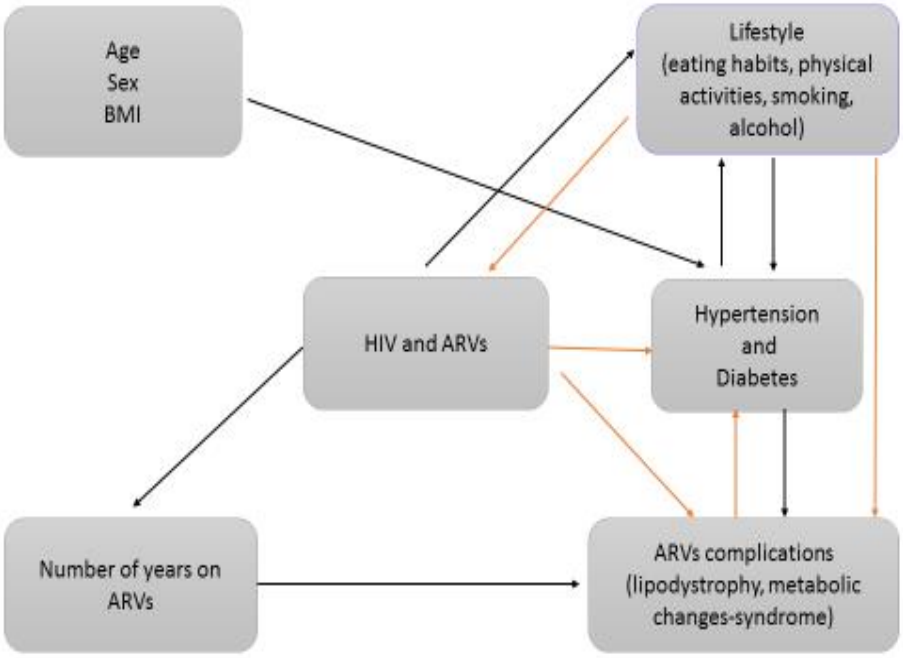


Figure 1: Possible linkages between HIV/ARVs with hypertension and diabetes mellitus

1.3 SIGNIFICANCE OF THE STUDY

The purpose of the study is to determine the prevalence and incidence of hypertension and diabetes among HIV positive patients and its association with ARVs use in Chongwe District.

Since HAART has been cited to play a role in increasing the incidence of hypertension and type II diabetes mellitus (Duguma et al., 2020); (Divala et al., 2016), It Is of public health importance to quantify by incidence and prevalence of these cases. It is also important to identify the HAART regimens associated with the risk of hypertension and diabetes mellitus for the benefit of both the health worker and clients in providing focused and holistic services for quality life respectively.

It is hoped that the findings of this study will provide baseline information for health authorities to raise awareness amongst health workers about the relationship between ARV use and NCDs. It will also raise awareness on the role of screening for early detection and eventually lead to recommendations that will enable health program planners to consider special and specific inclusions in policy documents and integrated treatment guidelines and protocols in the prevention and management of NCDs among PLHIV.

The findings would be used to form basis for hypertension and diabetes screening campaigns for PLHIV. Districts can also use the results to publicize and update hypertension and diabetes screening services/facilities in the fight against NCDs, particularly hypertension and diabetes. The study is also expected to provide information on the possible individual ARV classes used in Zambia that are probable lead contributors as risk factors to NCDs.

1.4 OBJECTIVES

1.4.1 General objective

To estimate the prevalence and incidence rates of hypertension and diabetes and determine the association between these co-morbidities and HAART/ART intake/use among people living with HIV in Chongwe District.

1.4.2 Specific objectives

1. To estimate the incidence and prevalence rates of hypertension among HIV positive patients in Chongwe District using.
2. To estimate the incidence and prevalence rates of diabetes among HIV positive patients in Chongwe District.

3. To determine HAART therapy combinations/classes that are associated with hypertension in Chongwe District.
4. To determine HAART therapy combinations/classes that are associated with Type II diabetes mellitus in Chongwe District.

1.5 HYPOTHESIS AND ASSUMPTIONS

There is no association between ARVs intake and hypertension.

There is no association between ARVs intake and type II diabetes mellitus.

1.5.1 Assumptions

1. Client vitals and biochemical parameters are recorded at every visit in client file.
2. HIV clients use a single file from ART clinic to general conditions (integrated management)
3. All hospital files on each individual are complete and correctly recorded

1.5.2 Limitations

1. Some patient files were unintegrated in some facilities (HAART files were separate from general patient files, hence patient case files were dropped.
2. The study findings are limited to the sampled study area – Chongwe district.
3. The design of the study being retrospective is not expected to show cause-effect relationship between NCDs and HAART.
4. There is potential channeling bias since some participants were switched from one line of HAART drug(s) to another since inception to end of study.

CHAPTER 2: LITERATURE REVIEW

This chapter discusses what has been done by other researchers concerning this topic on the incidence of hypertension and diabetes mellitus in HIV infected persons on HAART. The review of literature mainly highlights the results and conclusions from the works cited. Classical works (older than 10 years) are cited on works concerning incidence on the topic of interest so as to give a synopsis of the subject matter due to lack of substantial recent works. This chapter is organized into nine (9) sub-headings related to the objectives. The sub-headings are organized as follows: types of HAART, mechanism and side effects of HAART, hypertension and HAART, incidence and prevalence of HPTN in HAART, HIV/HAART and hypertension association, Type II diabetes mellitus and HAART, incidence and prevalence of DM in HAART, HIV/HART and Type II diabetes mellitus association, other risk factors to hypertension and diabetes.

2.1 TYPES OF HAART THERAPIES

Highly Active Antiretroviral Therapy (HAART) is a treatment regimen typically comprised of a combination of three or more antiretroviral drugs. HAART may also be called Antiretroviral Therapy (ART). A key aspect of HAART is the co-administration of different drugs that inhibit viral replication by several mechanism. There are more than 25 different medications in 6 different classes: Nucleoside Reverse Transcriptase Inhibitor (NRTI) (Abacavir, didanosine, lamivudine, Stavudine, Tenofovir, and zidovudine), Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI) (delavirdine, Efavirenz, Nevirapine, rilpivirine), Protease Inhibitor (PI) (Dolutegravir, elvitegravir, Raltegravir saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, Lopinavir, Atazanavir, tipranavir, and Darunavir), fusion inhibitor, chemokine

coreceptor antagonist (consisting of 2 subclasses: CCR5 antagonist and CXCR4 antagonist), and Integrase inhibitor (Günthard et al. 2016; Coffey and Peiperl 2019).

Recommended initial regimens include two nucleoside reverse transcriptase inhibitors (NRTIs; Abacavir/lamivudine or Tenofovir Disoproxil Fumarate/Emtricitabine) and a third single or boosted drug which should be an Integrase strand transfer inhibitor (INSTIs; Dolutegravir, elvitegravir, or Raltegravir), a nonnucleoside reverse transcriptase inhibitor (NNRTIs; Efavirenz or rilpivirine) or a boosted protease inhibitor (PIs; Darunavir or Atazanavir) (Günthard et al., 2014).

2.2 MECHANISM AND SIDE EFFECTS

The different classes of HAART agents target different stages in the viral lifecycle. Some agents maybe co-formulated to increase ease of patient compliance with the medication. In Zambia, currently there are only four classes of these agents in use and thus only these will be covered below. Refer to annex table 1 and 2: on the preferred first line and alternative regimen by specific populations in Zambia.

2.2.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs competitively bind to reverse transcriptase and cause premature DNA chain termination by inhibition of 3’ to 5’ phosphodiester bond formation. NRTIs firstly require intracellular phosphorylation through host enzymes before inhibiting viral replication. NRTIs block both the HIV reverse transcriptase and the mitochondrial polymerase gamma enzymes and it is documented that it is by the inhibition of the latter enzyme that is most likely the cause of the adverse effects associated with NRTIs. The inhibition of the mitochondrial enzymes gradually leads to mitochondrial dysfunction and cellular toxicity, the clinical manifestations resembling

the inherited mitochondrial disease presenting with hepatic steatosis, lactic acidosis, myopathy, nephrotoxicity, peripheral neuropathy and pancreatitis. Another side effect is fat redistribution syndrome or HIV-associated lipodystrophy documented pathophysiology which is suggested to be as a result of mitochondrial toxicity. The other side effects of NRTIs with less documented pathophysiology are diabetes, retinal lesions and ototoxicity (Eggleton and Nagalli 2020; PMC 2019; Saag et al. 2018; Kakuda 2000).

2.2.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs bind the enzyme HIV reverse transcriptase at an allosteric, hydrophobic site remote from the enzyme's active site to produce a conformational (sterochemical) change within the enzyme thereby inhibiting nucleoside binding and inhibition of DNA polymerase. NNRTIs are metabolized by hepatic CYP3A4 and CYP2B6 enzymes. NNRTIs are associated with several types of hepatic toxicity, which includes asymptomatic elevation in transaminases. Clinical hepatitis and hypersensitivity reactions with hepatitis. There is also a documented concern on increased risk of neural tube defects with EFV, more especially in pregnancy (Eggleton and Nagalli 2020; Waller and Sampson 2018; Siberry 2018).

Concern about increased risk of neural tube defects with EFV has NNRTIs associated with several types of hepatic toxicity, including asymptomatic elevation in transaminases, clinical hepatitis, and hypersensitivity reactions with hepatitis

2.2.3 Protease Inhibitors (PIs)

The HIV-protease inhibitors competitively prevent the proteolytic cleavage of the gag/pol polyproteins in HIV infected cells, arresting maturation and thereby resulting in immature non-infective nascent virions. PIs are generally used in patients failing initial HAART regimen and

are administered with boosting agents such as ritonavir or cobicistat. All approved PIs have gastrointestinal side effects and high serum aminotransferase concentrations. However, the most reported common side effects of the PIs are HIV- induced metabolic syndrome such as dyslipidemia, insulin resistance and lipodystrophy/lipoatrophy as well as cardiovascular and cerebrovascular diseases (Eggleton and Nagalli 2020; (Lv et al., 2015) Flexner 1998; Carr et al. 1998.

2.2.4 Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs are potent inhibitors of HIV replication by binding to the viral Integrase enzyme preventing the viral DNA from being incorporated into the host cell chromosome (Eggleton and Nagalli, 2020). INSTIs are a generally well tolerated class of HAART. The side effects profiles of INSTIs have included weight gain, gastrointestinal symptoms and neurological symptoms. They have also been associated with increase in creatinine levels with DTG blocking tubular uptake of creatinine from the blood (Kolakowska et al., 2019; Norwood et al., 2017; Elzi et al., 2017; Margolis et al., 2015).

2.3 HYPERTENSION AND HAART

Hypertension is blood pressure that is higher than normal. Blood pressure is taken as two readings which are tabulated and read as a fraction. The upper part of the high blood pressure reading is known as the systolic pressure and the lower reading is the diastolic pressure. People with persistently high blood pressure for less than a year defined by a blood pressure of 120/80 mm Hg in adults and 110/95 to 140/95 are at a greater risk of heart disease. An individual with high blood pressure has impaired quality of life and can suddenly die. High blood pressure stresses the heart since it has to pump extra hard to push the blood against resistant arteries

(Department of Nutrition, HIV and AIDS, 2009). Blood pressure is a function of cardiac output multiplied by peripheral resistance (the resistance in the blood vessels to the flow of blood). Thus, the diameter of the blood vessel markedly affects blood flow. When the diameter is decreased as in atherosclerosis, resistance and blood pressure increase. Conversely, when the diameter is increased as with vasodilator drug therapy, resistance decreases and blood pressure is lowered (Mahan and Raymond, 2017).

Figure 2: Definition of blood pressure by reading

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Figure 2*:* Definition of blood pressure by reading https://www.heart.org/-/media/images/health-topics/high-blood-pressure/rainbow-chart/blood-pressure-readings.

Hypertension is arbitrarily defined as sustained elevated blood pressure greater than or equal to 140/90 mmHg “arbitrarily defined” because problems associated with high blood pressure occur on a continuum with no obvious threshold of where risk begins, including the pre-hypertension

range of 120–139/80–89 mmHg (Dudek, 2013). Hypertension is known to be one of the most important modifiable risk factors for heart disease, stroke, kidney disease, and peripheral arterial disease (Department of Nutrition, HIV AND AIDS, 2009). High blood pressure (hypertension) is diagnosed if the blood pressure reading is equal to or greater than 130/80 mm Hg. A diagnosis of high blood pressure is usually based on the average of two or more readings taken on separate occasions (Principles of Epidemiology 2021).

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels which can manifest as coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. It is a primary cause of death worldwide with atherosclerosis being the most common pathological process that leads to it, involving a combination of vascular endothelial dysfunction, chronic inflammation, and dyslipidemia. According to the Global burden of disease study, current predictions estimate that by the year 2020, CVD, notably coronary heart disease (CHD), will become the leading global cause of total disease burden (Olaiya et al. 2018; Osegbe et al. 2016). Hypertension is associated with shorter overall life expectancy shorter life expectancy free of CVD, and more years lived with CVD. People in middle age who experience increases or decreases in blood pressure have higher and lower remaining lifetime risks for CVD, respectively. Prevention efforts should emphasize the importance of lowering blood pressure and avoiding or delaying hypertension to reduce the lifetime risk of CVD (Dudek, 2013).

Many systems maintain homeostatic control of blood pressure. The major regulators are the sympathetic nervous system (SNS) for short-term control and the kidney for long-term control. In response to a fall in blood pressure, the SNS secretes norepinephrine, a vasoconstrictor, which acts on small arteries and arterioles to increase peripheral resistance and raise blood pressure.

Conditions that result in overstimulation of the SNS (i.e., certain adrenal disorders or sleep apnea) result in increased blood pressure. The kidney regulates blood pressure by controlling the extracellular fluid volume and secreting renin, increases blood pressure. Angiotensin II, promotes the development of large dysfunctional adipocytes, which produce increased amounts of leptin and reduced quantities of adiponectin. Higher levels of leptin and lower amounts of circulating adiponectin activate the SNS, a key component of the hypertensive response (Mahan & Raymond, 2017). Prolonged viremia is associated with elevated systematic inflammatory markers, hyper-coagulation, damage to the endothelium, and premature atherosclerosis. Prolonged HAART intake is associated with linear increase in cardio vascular related mortality for up to five years of HAART exposure. The increase is related to the occurrence of lipodystrophy and metabolic aberrations such as elevated cholesterol and triglyceride levels, insulin resistance and impaired glucose tolerance (Triant et al., 2007).

The introduction and widespread use of highly active antiretroviral therapy (HAART) in the mid 1990's, has led to a reduction in morbidity and mortality among HIV-infected individuals. However, it has altered the course of HIV to chronic infection exposing them to the effects of aging and chronic conditions. In addition to including the influence of the same environmental risk factors known to act in the general population and contributing to the occurrence of obesity, hypertension, diabetes mellitus (DM), and cardiovascular diseases (Paula et al., 2013). Among HIV patients, CVD is the main cause of morbidity and mortality comprising 10% of non-HIV/AIDS related mortalities. Hypertension is increased in subjects with diabetes and dyslipidemia, which are more prevalent among HIV infected individuals than in the general population. Hypertension in HIV infected individuals is associated with a higher frequency of persistent proteinuria, coronary heart disease and myocardial infarction as compared to non-

hypertensive HIV infected individuals (Korem et al. 2018; Sanidas et al. 2018). Cardiovascular disease is a group of disorders of the heart and blood vessels which can manifest as coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. It is a primary cause of death worldwide with atherosclerosis being the most common pathological process that leads to the condition, involving a combination of vascular endothelial dysfunction, chronic inflammation, and dyslipidemia. According to the Global burden of disease study, predictions estimate that by the year 2020, CVD, notably coronary heart disease (CHD), will become the leading global cause of total disease burden (Osegbe et al. 2016).

2.3.1 Incidence and Prevalence of Hypertension in HAART

A study done in China by Fan and others (2020), found the incidence of hypertension at 7.6 per 100 PYs. The study was a retrospective study using secondary data of 2 prospective longitudinal multicenter studies of PLHIV initiating on ART in China. Data analysis methods used were the Cox proportional hazards model, which was used to evaluate the association between incident hypertension and traditional risk factors and HIV associated risk factors. The study concluded that the incidence was higher than in the general population and associated to the incidence were recent low CD4+/CD8+ ratio and detectable viremia while receipt of ART was associated with reduced risk of hypertension in part by excellent HIV care. The student t-test was used for parametric continuous variables, Mann-Whitney U test for non-parametric continuous variables and the chi-squared test for categorical variables were used to compare clinical characteristics between patients with and without hypertension

The reported prevalence of hypertension in HIV infected adults has been described ranging from 8 to 34%. An increased incidence of hypertension was observed in HIV infected individuals on

HAART for 48 weeks, as compared with HIV naïve adults at 26% and 7% respectively. A meta-analysis of seven hypertension studies reported the prevalence of diurnal blood pressure pattern that may contribute to high Cardio Vascular Disease (CVD) risk ranged from 29 to 82% among HIV infected individuals compared to 15 to 53% in HIV negative individuals (Fahme Sasha A., Bloomfield Gerald S., and Peck Robert 2018; Sanidas et al. 2018).

2.3.2 HIV/HAART and Hypertension Association

Hypertension is an important worldwide public health concern because of its high prevalence and is a concomitant risk factor for cardiovascular, brain, and kidney disease (Kearney et al., 2005). Advanced HIV disease may be associated with an increase in counter-regulatory hormones whereby excess free fatty acids in the circulation reduce insulin sensitivity, hypercortisolism with further stress response as HIV disease progresses, (Reeds et al., 2006)

Hypertension and Human Immunodeficiency Virus (HIV) infection are chronic conditions which are asymptomatic and manageable in early stage. The interaction between hypertension and HIV is complex. Renal insufficiency due to HIV infection contributes to secondary hypertension. The HIV infected on ART live longer and gain weight. Weight gain is a risk factor of hypertension. The weight gain can be explained in two ways. The HIV infected when on ART are less susceptible to opportunistic infections that cause malabsorption syndromes. Weight gain can also be a side effect of ART medicines'' ("Magande 2017).

ART medicines such as ritonavir-boosted Lopinavir (protease inhibitors), Efavirenz and Tenofovir are associated with hypertension. This is mediated through their side effects. Studies show that insulin resistance precedes lipodystrophy. The slowest step in glucose metabolism transport mediated by glucose transporter -4 (GLUT-4) in muscle and fat. This process is

worsened by protease inhibitors. This results in metabolic syndrome and eventually hypertension. Tenofovir causes renal tubular toxicity resulting in renal dysfunction and eventually hypertension when there is pre-existing renal disease (Magande, 2017).

Human immunodeficiency virus (HIV) infection has become associated with decreased morbidity and mortality since the advent of highly active antiretroviral therapy (HAART) in Western countries, non-Western Asian settings, and sub-Saharan regions. However, older age, HIV infection itself, antiretroviral therapy (ART), HIV related inflammation, current CD4 T cell count, nadir CD4 T cell count , 350 cells/mm3, and traditional risk factors for cardiovascular disease (smoking, obesity, physical inactivity, excess alcohol intake) substantially increase the risk of cardiovascular disease, including hypertension, stroke, coronary artery disease, peripheral artery disease, dyslipidemia, diabetes mellitus, metabolic syndrome, and lipodystrophy (Mandina Ndona et al., 2012).

2.4 DIABETES MELLITUS AND HAART

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration of fasting plasma glucose > 7.0 mmol/l, or random blood plasma glucose > 11.1 mmol/l or 2 hours after a meal. This caused by insulin deficiency, often combined with insulin resistance. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which, in turn, results in dehydration, thirst and increased drinking (polydipsia). Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins (Thaman and Arora, 2013); (Miranda et al., 2005).

Insulin is a hormone, which controls the movement of glucose from blood into the body cells. In the absence of insulin, glucose regulation falters and diabetes may set in. Diabetes mellitus is diagnosed by testing glucose levels in the urine, blood and other tests (Department of Nutrition, HIV AND AIDS, 2009).

Since the late nineties, studies on HIV-infected individuals have reported a wide spectrum of metabolic alterations associated with Highly Active Antiretroviral therapy (HAART) including changes in glucose homeostasis and fat redistribution. As the lifespan of HIV-infected individuals have been prolonged, due to a decline in HIV-associated morbidity and mortality on account of HAART, such metabolic imbalances could affect the long-term prognosis of NCDs due to progression of insulin resistance to diabetes mellitus (DM) and subsequent risk of end-organ disease (Rasmussen et al., 2012).

Metabolic syndrome (MetS) has been playing a major role as a marker for metabolic disorders. MetS encompasses a cluster of risk factors leading to CVD as primary clinical outcome and contribute to higher risk of Diabetes Mellitus. (Wannamethee, 2008).

Type II diabetes mellitus (T2DM) is characterized by a combination of insulin resistance and beta-cell failure. Endogenous insulin levels may be normal, depressed, or elevated, but they are inadequate to overcome concomitant insulin resistance (decreased tissue sensitivity or responsiveness to insulin.) As a result, hyperglycemia ensues. The inflammatory response to excess weight, insulin resistance, and beta-cell failure occurs approximately 5 to 10 years before the elevation of glucose above normal. Insulin resistance is demonstrated first in target tissues, mainly muscle, liver, and adipose cells. Initially there is a compensatory increase in insulin secretion (hyperinsulinemia), which maintains glucose concentrations in the normal or prediabetes range. In many persons the pancreas is unable to continue to produce adequate

insulin, hyperglycemia occurs, and the diagnosis of diabetes is made. Therefore, insulin levels are always deficient relative to elevated glucose levels before hyperglycemia develops (Mahan & Raymond, 2017).

2.4.1 Incidence and Prevalence of Diabetes Mellitus in HAART

Despite the unquestionable success of HAART, prevalence of DM, insulin resistance, blood pressure fat redistribution and mainly dyslipidemia have substantially increased after its global scaling up (Paula et al., 2013). A study done by Brown (2005) which looked at Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study found the rate of incidence of diabetes to be 4.7 cases per 100 person years among men on HAART as compared to 1.4 cases per 100 person years among HIV seronegative men. Thereby concluding that the incidence of T2DM in HIV infected men with HAART exposure was greater than 4 times than that of seronegative men. This study was a prospective cohort over a 4 years period.

In an on-going cohort study in Sweden, the incidence rate of T2DM was found to be 4.4 per 1000 PY, with strong associations to current treatment with NRTI, a combination of NRTI plus PIs and a combination of NRTIs plus PIs and NNRTIs but no association was found for treatment with NRTIs plus NNRTIs (Ledergerber et al., 2007).

A review of 44 synthesized studies of high methodological quality found a pooled incidence rate of overt diabetes and pre-diabetes to be 13.7 per 1000 PY and 125 per 1000 PY respectively. The study employed a random-effects model for the summary estimates of incidence across studies and Cochrane's Q statistic to assess for heterogeneity (Nansseu et al., 2018).

Though the actual numbers of MetS in HIV populations are still debatable, reported prevalence for MetS in the HIV population can be regarded as high, ranging from 11.2% up to 45.4%. The prevalence of Insulin Resistance (IR) in HAART has been reported in up to 35 to 63% of the patients. Insulin Resistance in HIV patients has been associated with increased risk of cardio vascular diseases, increased mortality and above all, the development of diabetes mellitus. The higher prevalence observed in the younger population has been attributed to HIV itself, vitamin D deficiency, co-infection with hepatitis C virus and the adverse effect of different antiretroviral drugs (Araújo et al. 2014; Szep et al. 2011; Samaras 2009). 0973011905

2.4.2 HIV/HAART and Diabetes Mellitus Association

The cause and origin of Diabetes mellitus is thought to differ in those with HIV from those of the general population. Apart from lipodystrophy which is associated with insulin resistance, Diabetes is thought to be as one of the complications of several ARV therapies (Worm et al., 2009) . The prevalence of DM as reported by Worm in their 2009 discourse puts it at 2% to 14% in the HIV infected populations with the difference being explained by demographic characteristics, lifestyle and antiretroviral exposure.

Many studies suggest that HIV itself is an inflammatory and insulin-resistant state which can precipitate overt diabetes mellitus,(Bhasin et al., 2001), although there has been a case report of a 52-year-old African man whose type 2 diabetes resolved when viral replication was suppressed with protease inhibitor-based ART (Limone, 2003).

The key risk factors for T2DM in the general population, body mass and waist circumference, disproportionately affect people from minority ethnic groups (Murea et al., 2012) and these risk factors were pronounced in this ethnically diverse group. Historically HIV was a disease

associated with wasting and premature death and therefore these conventional risk factors were of little relevance. However, PLHIV are now living longer and it has been demonstrated that the rates of overweight and abdominal obesity are increasing and are now comparable with the general population (Public Health England, 2015)

A rise in incidence was associated with age and obesity, and historic exposure to ARVs linked with metabolic toxicities. Conversely, a study of a Danish population showed no increased risk for T2D in HIV, however this study was confined to White participants, the cohort was relatively young, and had lower levels of obesity (Rasmussen et al., 2012).

The US Food and Drug Administration issued a warning in 1997 on the diabetogenic effects of protease inhibitors (PIs). Risk of glucose alterations in HIV-infected individuals have been largely attributed to this drug class. Additionally, nucleotide reverse transcriptase inhibitors (NRTIs) have been proposed to accelerate the pathogenic mechanisms of DM development, but the data is limited.

Insulin resistance and impaired glucose tolerance induced by HAART might act as a precursor of T2DM (Rasmussen et al., 2012). PIs have been shown to increase insulin resistance and reduce insulin secretion by interfering with GLUT-4 mediated glucose transport. The risk factors associated with the development of diabetes with PI therapy include positive family history of diabetes, weight gain, lipodystrophy, old age and hepatitis C infection (Kalra et al., 2011b). PIs interfere with cellular retinoic acid binding protein type 1 (CRABP 1) that interacts with peroximal proliferator-activated receptor (PPAR) g. Inhibition of PPAR-g promotes adipocyte inflammation, release of free fatty acids and insulin resistance (Lee et al., 2005).

All PIs do not have the same metabolic effects. Indinavir induces insulin resistance with no effect on lipid metabolism, whereas lopinavir and ritonavir increase fasting triglycerides and free fatty acids, but do not worsen insulin sensitivity. Indinavir and retonavir both block GLUT -4, but no such effect is noted with amprenavir, and Atazanavir. HIV-infected patients treated for 12 weeks with nelfinavir, indinavir, lopinavir or saquinavir, demonstrate alterations in first phase insulin release with a 25% reduction in b-cell dysfunction (Woerle et al., 2003); (Lee et al., 2005). The other class of drugs which is implicated is the nucleoside reverse transcriptase inhibitors (NRTIs). The collection on Adverse events of Anti-HIV Drugs (D:A:D) study has shown that this class of drugs increase the risk of diabetes (De Wit et al., 2008). The risk was highest with stavudine but also significant with zidovudine and didanosine after adjustment for risk factors for diabetes and lipids. The proposed mechanisms include insulin resistance, lipodystrophy and mitochondrial dysfunction (Fleischman et al., 2007). It is suggested that the two thymidine analogs directly contribute to insulin resistance potentially through mitochondrial toxicity (De Wit et al., 2008).

2.5 OTHER RISK FACTORS TO HYPERTENSION AND DIABETES

type II diabetes mellitus (T2DM) has a reported greater prevalence and poorer treatment outcomes in people living with HIV (PLHIV) than comparable HIV-uninfected cohorts. In Cambodia a cross-sectional study was conducted to set out the factors driving T2DM in PLHIV in an ethnically diverse cohort, and additionally observed how these have changed over time (Duncan et al., 2018).

Antiretroviral (ARV) therapy for people living with HIV (PLHIV) has led to a marked reduction in HIV-associated morbidity and mortality since its introduction in the mid-1990s (Duncan et al.,

2018). However much of the disease burden in PLHIV is now due to morbidities found in the general population. HIV itself, and some of the ARVs used to treat it, are associated with an increased risk and premature development of chronic comorbidities, including type II diabetes mellitus (T2DM), which is reported to be up to four times more prevalent in PLHIV than those without HIV (Duncan et al., 2018).

Risk factors for T2DM in the general population are well established (Duncan et al., 2018) but in HIV there are additional specific risk factors, including duration of HIV infection, degree of immunosuppression, and exposure to those ARVs known to be associated with dysglycaemia . Specific ARVs, with a variable contribution from HIV infection itself, are associated with an increased risk of metabolic diseases. These are not restricted to redistribution of fat and other manifestations of lipodystrophy, dyslipidemia, and higher rates of comorbidities associated with ageing, including myocardial infarction and T2DM. Despite improvements in ARVs, the prevalence of conventional T2DM risk factors appear to be increasing in HIV patients as the population ages (Phiri et al., 2016); (Maciel et al., 2018); (Duncan et al., 2018).

Duncan, Goff, and Peters (2018) concluded that, 'the alarmingly high prevalence of T2DM in our cohort of PLHIV has implications for the tens of millions of PLHIV worldwide. This is compounded by an increase in associated comorbidities in PLHIV, including cardiovascular disease. Additionally, there are distinct challenges associated with the management of T2DM in HIV. Some ARVs can impair glycosylated haemoglobin (HbA1c) assays resulting in underestimation and some ARVs significantly interact with hypoglycemic agents. Overall, it is known that HIV patients with T2DM have a poorer response to diabetes treatments compared to matched HIV negative individuals. Enhanced screening for diabetes risk in PLHIV should be considered and should account for the broad range of risk factors that affect PLHIV, both

conventional and HIV-specific. Interventions that tackle these risk factors are needed (Hadigan and Kattakuzhy, 2014); (Machingura, 2017).

In a study conducted in Kadoma city Japan, it was concluded that having no education, being above 40 years of age, smoking, drinking alcohol (sorghum beer, lagers and wines), and adding salt regularly to dishes were socio-demographic risk factors for uncontrolled hypertension among hypertensives on ART ("Magande, 2017)). Being female, doing manual work, walking and cycling were socio-demographic protective factors against uncontrolled hypertension. The significant medical risk factors for uncontrolled hypertension among clients on ART were; having BMI above 25 kg/m2, a history of elevated hypertension in the previous year, taking anti-hypertensive medicines in the preceding 2 weeks and a family history of hypertension. Having a waist circumference less than 75 cm and having Stavudine/Lamivudine/ Nevirapine as the first regimen were significant protective factors against uncontrolled hypertension (Magande, 2017).

CHAPTER 3: METHODOLOGY

This chapter describes the methods that were used in this study. It entails an account of the various subtopics under methodology which include study design, study setting, sample size, sampling procedure, research tools, data analysis and ethical considerations.

3.1 STUDY DESIGN

A retrospective cohort study was applied in this study. The study utilized existing data sets from the SMART CARE electronic database in Chongwe district to determine the incidence rate of hypertension and Type II diabetes mellitus in HIV infected persons on HAART.

3.2 STUDY SETTING

The study was conducted in Chongwe district. The ART program in Chongwe is on SMART CARE electronic database providing a reliable sampling frame.

3.3 STUDY POPULATION

Study participants were HIV positive individuals aged 18 years and above and on ART. Participants were drawn from six (6) high volume facilities in Chongwe district that have been on ART for a period of one year and longer. The study participants met a predefined eligibility criterion.

3.4 ELIGIBILITY CRITERIA

3.4.1 Inclusion Criteria

1. All study participants' case files are in the SMART CARE database.
2. All participants are 18 years and above.

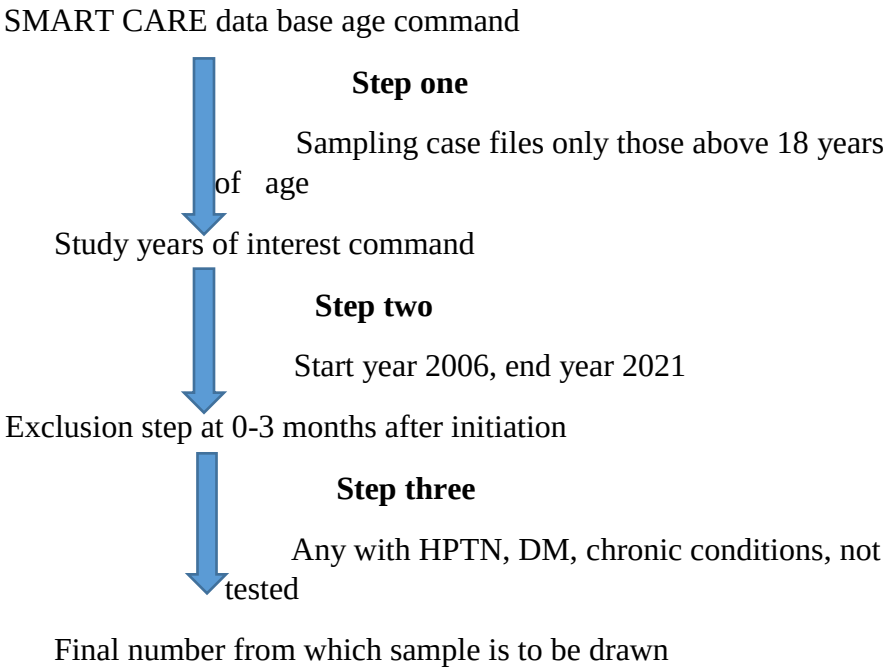
3. All study participants are on ART/HAART for equal to and above one year spanning from January 2006 to April 2021.

3.4.2 Exclusion Criteria

There were pre-determined exclusion criteria thus:

1. Those patients that were pre-hypertensive and diabetic, and were already hypertensive and diabetic before being put on ART.
2. Those patients with chronic conditions, illnesses (kidney disease(s), or liver conditions (including hepatitis C), heart conditions, thyroid problems and or polypharmacy before ART initiation. The exclusion of these chronic conditions reduces the risk of confounding factors as other causes not related to the independent variables of interest. These chronic conditions are linked to increasing the risk of developing either hypertension or diabetes or even both. For the exclusion of those with chronic conditions, the period was at initiation up to 3 months to allow for certainty if they were not tested at initial prescription.
3. Those terminally ill before initiation of HAART.
4. Those patients that were lost during follow up, transferred and those who died during the study period.

Figure 3: Summation of the exclusion criteria Stepwise

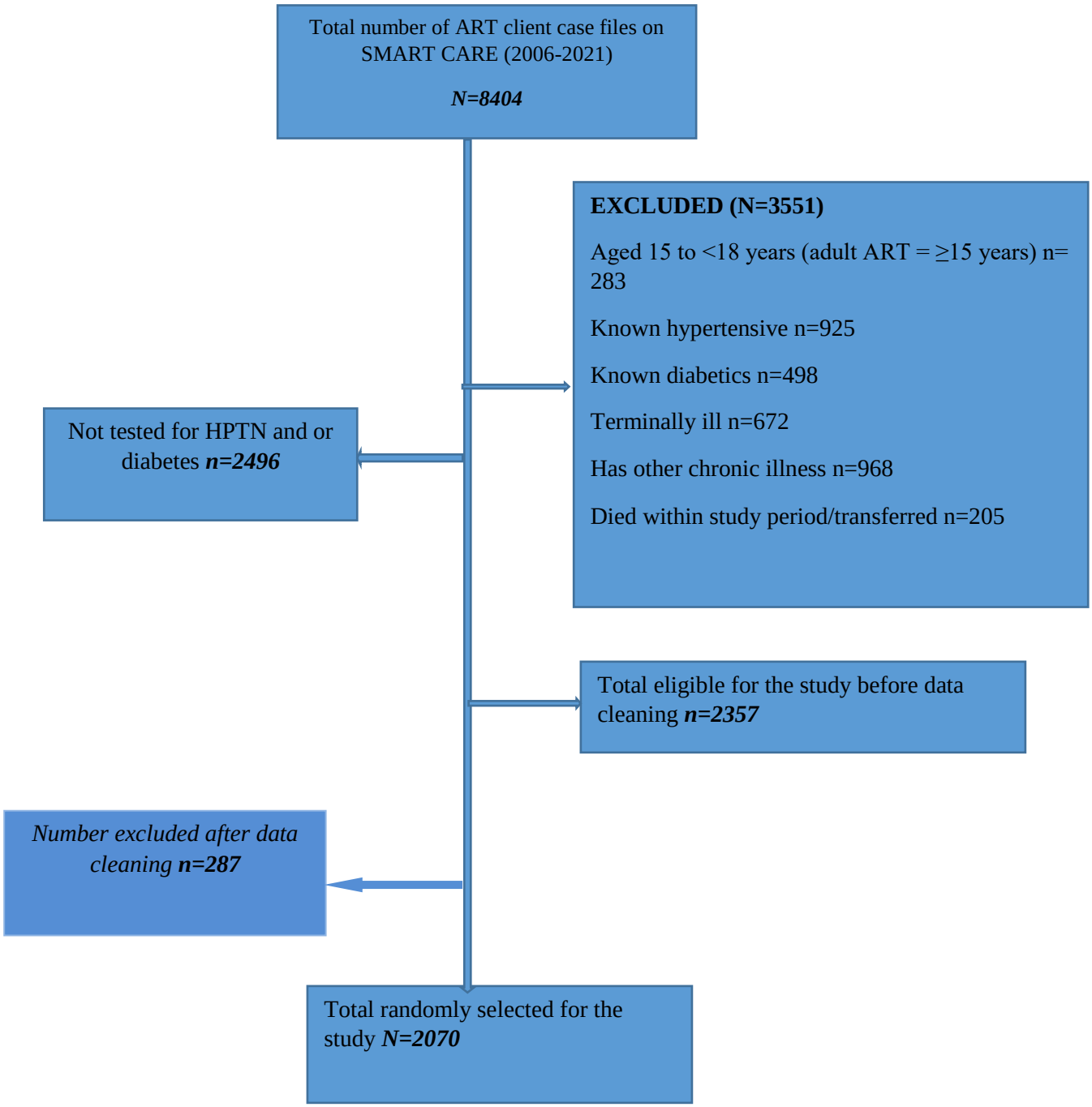


3.5 SAMPLING TECHNIQUE

The SMART CARE database was used as the sampling frame. The data base had a total of 50517 case files for the period of fifteen (15) years, spanning from 2006 to 2021. The inclusion and exclusion criteria were applied (figure 3) to remain with total population for the period 2006 to 2021, n=8404. Stratified random sampling was applied to arrive at the sample for the study. First, the case files (study population) were stratified into the different high-volume sites of six (6) strata namely ; Chongwe District Hospital (n=1,474), Chainda Rural Health Center (393), Chalimbana Rural Health Center (592), Chongwe Rural Health Center (3,899), Kasisi Rural Health Center (803) and Ngwerere Rural Health Center (1,243), before exclusions. From each

stratum, random sampling was applied. Stratified random sampling ensured that the sample was proportionally representative across the different high-volume sites (Figure 4).

Figure 4: Flow Chart of the Screening and selection Process for the case files



3.6 SAMPLE SIZE

The following Fishers' formula was used to arrive at the sample size:

$N = (Z)^2 P (1-P) / e^2$

Where,

N = Sample size

Z = z score value for 95% Confidence interval

P = Proportion of interest to the study (prevalence of sub-clinical cardiovascular disease in healthy HIV infected patients at the University Teaching Hospital in Lusaka, Zambia i.e., 36%, (Kabwe et al., 2016)

e = margin of error/design effect

$N = 1.96^2 \text{ X } 0.36 (1-0.0.36)/0.05^2 = 354.041856$

Therefore, calculated sample size = 355 per reporting domain (i.e., per health facility). Sample size for the six high volume health facility is 355*6 = 2130.However, after data extraction, the data was cleaned and a sample of 2070 case files remained that were eligible for the study. The six (6) high volume facilities are geographically representative. They include a representation of rural and peri-urban areas thus different socioeconomic strata.

3.7 DATA COLLECTION PROCEDURE AND TOOLS

Secondary data extracted from SMART CARE patient files was utilized. SMART CARE is an electronic Health Record (EHR) system used for management of client health records, generation of reports and auxiliary services such as pharmacy, labs, logistics and user provider management. SMART CARE provides continuity of care, no matter where the patient is or if they travel within the country.

The data extraction period spanned from January 2006 to April 2021, thus 15 years period which provides a period long enough for objective observations. The baseline readings from the database were collected at three (3) months of ART initiation. The data extraction was done by trained authorized information officers under MoH Zambia and the HIV case-based surveillance officers. The case files are stored electronically and data variables for exclusions were electronically applied so as to remain with files eligible as per inclusion criteria. However, data extraction was done manually as data cannot be imported electronically. The system does not allow for copying out. Each single individual information that was needed for the study was put on excel manually, then the data was cleaned. The extracted data was then entered in an excel data extraction form (appendices table 3) and then transferred into SPSS version 20 for analysis.

The collated data included demographic data, Socio-economic data, type of HAART/HAART combinations, history of NCDs/chronic illnesses, anthropometric records, and some lifestyle variables such as smoking and alcohol taking (appendices table 3).

3.8 STUDY VARIABLES

3.8.1 Data on the dependent (outcome) variables

Blood pressure readings (categorical) and random blood glucose (categorical) levels were collected at 12 months of ART initiation. This was collected from the SMART CARE files for all eligible cases that fit the inclusion criteria. Categorical hypertension was defined as normal for diastolic blood pressure <80 or systolic <120mmHg, Elevated/pre-hypertensive with diastolic blood pressure of 80-89 or systolic 120-129mmHg and Hypertensive/high blood pressure with diastolic blood pressure of ≥90 0r systolic ≥130mmHg. Random blood glucose levels were defined categorically for this study and cut-offs defined as normal <100mg/dl for fasting or <140mg/dl for random, prediabetic 100-125mg/dl for fasting or 140-199mg/dl for random and diabetic ≥126mg/dl for fasting or ≥200mg/dl for random. These defined by a diagnosis by the clinician or three elevated readings by cutoff definition.

3.8.2 Data on independent (explanatory) variables

Already pre-determined using the sampling frame was the HIV status and the fact that everyone on the sampling frame was on ARVs. Age (continuous, categorical) was collected twice. The first was age at inception of ART and the second at the time of data collection. To determine the duration each case had been on ART, age at data collection was subtracted from age at ART inception. This was also accessed from the SMART CARE files. Age was analyzed as both a categorical and continuous variable. It was divided into two as a categorical variable based on the Latent Dirichlet Allocation which uses a probabilistic “soft clustering”. A given age can belong to multiple ranges. The category 18 to 45 years which is a combination of two age groups (the young adults and the adults), is considered as the reproductive age group of biological

significance and of which alcohol intoxication and substance dependence are also associated with. Then the middle aged and old age cluster was also combined (El Hachem et al., 2023; Geifman et al., 2013).

Body mass index was also tracked using the case files in the database from the baseline ART initiation time and quarterly thereafter to current date of data collection. BMI in kg/m^2 was classified as <18.5; underweight, 18.5 to 24.9; normal, 25 to 29.9; overweight and ≥30; overweight.

Sex/gender was collected from the SmartCare database from individual case files. Socio-economic data recorded included area of residence, and educational level.

Type of ARVs/Combination therapy (nominal variable) was also collected from the individual case files using SMART CARE and any switch in the drug regimen was noted. Any drugs related to hypertension and diabetes were noted from case patient files too.

3.9 DATA ANALYSIS

The data collected was analyzed using SPSS version 20. Descriptive statistics were used to determine the incidence of hypertension and diabetes mellitus in HIV infected persons on HAART. The incidence rate was calculated using the formula (Ford, 2020):

$$Incidence_{Rate} = \frac{Times\ of\ new\ cases\ of\ disease\ or\ injury\ during\ a\ specified\ period}{Time\ each\ person\ contributed}$$

The incidence was calculated using number of personal years of follow up (PYFU). The incidence formula used calculates the at-risk for every person for a specific period of time that

each individual contributes to the study in terms of person years. It allows for the consideration of time each person was observed for of the period from time of enrollment on HAART up to tagging of the condition.

Descriptive statistics were also used to estimate the proportion of people on different types of HAART combinations in the study population in Chongwe against the incidence of hypertension and diabetes mellitus.

Demographic (sex and age) and other data on patients' blood pressure, glucose level, BMI were summarized using means, frequencies and percentages.

Chi-square test was used to establish if any differences exist between selected categorical variables. The chi-square test was also used to test the null hypotheses at ***p-value = 0.05*** on the non-relationship between ARVs intake and the two NCDs of interest (hypertension and type II diabetes mellitus). Lavene's Test was conducted to assess the homogeneity of variances of indicators of the NCDs among different ART combinations and to inform on the post hoc analysis to be used for each factor. Analysis of Variance (ANOVA) was used to establish mean differences in the distribution of continuous indicators of diabetes and hypertension among patients on the different types of HAART therapies. Since the factors were not normally distributed, analysis of variances were conducted using Kruskal Wallis test. Logistic regression model was used to establish the determinants of hypertension and type II diabetes mellitus. Since the sample was large (>2000), Kolmogorov-Smirnova (K-S) test was used to test for normality of the distribution of the continuous variables/factors. Kolmogorov-Smirnova (K-S) test was done to determine normality of the variables of interest before deciding on which regression model to use. Independent variables included in the final model are age, sex of patient,

antiretroviral therapy, alcohol drinking, and cigarette smoking. A statistical level of significance of 5% ($p < 0.05$) was used for the model fit.

3.10 CONTROL FOR CONFOUNDERS AND EXTRANEOUS VARIABLES

At design level, inclusion of the extraneous variables in the study (traditional risk factors; age, sex, BMI and time) were employed to control for confounders. At analysis level, these factors were included in the regression model to account for their confounding effects.

3.11 ETHICAL CONSIDERATIONS

The proposal and research protocol were subjected to an ethical review by the University of Zambia Biomedical Research Ethics Committee (UNZABREC) to comply with the university's ethical principles and the Ministry of Health-Zambia governing regulations. A researcher's certificate was also obtained from National Health Research Authority (NHRA).

This study used secondary data and therefore there was no contact with study participants. This implies that the study had minimal to no risk at all to study participants. The study had no direct benefits for individual study participants but the study outcome will benefit the nation as a whole through implementation of problem-specific interventions towards NCDs in adult HAART clients.

CHAPTER 4: RESULTS

4.1 SAMPLE POOL DESCRIPTION

A total of 2070 participants' records were extracted from the SMART CARE electronic database for HIV positive persons on HAART in Chongwe district in relation to hypertension and Type II diabetes mellitus incidences. The records were from 2006 to April 2021 covering 6 high volume health facilities in Chongwe district. Table 1 shows the sample pooled from each facility.

Table 1: Research facility Sample Pool

Facility	n	%
Chongwe District Hospital	354	17.1
Chainda RHC	304	14.7
Chalimbana RHC	265	12.8
Chongwe RHC	364	17.6
Kasisi RHC	425	20.5
Ngwerere RHC	358	17.3
Total	**2070**	**100**

4.2 SOCIO-DEMOGRAPHIC CHARACTERISTICS

The mean age of the participants was 40.4 years, ranging from 18 to 68 years old. The mean age was 39.8 among male participants and 41.0 among female participants. Of the 2070 case files, 1014 (49.0%) of the clients were males while 1056 (51.0%) were females. Over 60% of the clients/participants were married, 17.7% were single/never married, 9.1% were divorced, and 5.2% were widowed, yet 7.9% did not record their marital status. Majority of the participants completed primary education (46.3%); 21.8% had secondary education, 6.5% had tertiary education, and more than 20% of participants did not attend formal schooling. Most of the participants reside in the urban setting (44.6%); 33.4% reside in the rural setting and 22.0% reside in the peri-urban settings (Table 2).

Table 2: Socio-demographic Characteristics of the study Sample

Variable	Frequency/Mean	Percent; ±SD
Mean Age in Years (N=2070):		
Male	39.8	±9.7
Female	41.0	±10.7
Total	**40.4**	**±10.3**
Sex:		
Male	1014	49.0
Female	1056	51.0
Marital Status:		
Married	1245	60.1
Single/never married	366	17.7
Widowed	107	5.2
Divorced	188	9.1
Not known/recorded	164	7.9
Education Level:		
Never went to school	423	20.4
Primary	959	46.3
Secondary	452	21.8
Tertiary	135	6.5
Not known/recorded	101	4.9
Residential Status:		
Rural	691	33.4
Peri-urban	456	22.0
Urban	923	44.6

4.2 Clinical Characteristics of Study Population

The nutritional status as determined by BMI of the participants at initiation of HAART was 13.9 % (n=288) underweight, 60.3% (n=1248) normal, 14.8% (n=307) overweight and 11% (n=227) obese. About 81% (n=1682) and 85.8% (n=1777) of the study population had on record no family history of hypertension and diabetes respectively, whilst 18.7% (n=388) and 14.2 (n=293) on record, had family history of hypertension and diabetes respectively. The mean number of

years on ART treatment was 5.7 years with minimum 1 year and maximum 15 years. There was a total of five (5) different ART combinations with the highest 35.5% (n=734) of study population being on EFV + FTC +TDF and least 6.8% (n=140) being on 3TC + ABC + LPV/r combinations. The rest were on 3TC+DTG+TDF 23.2% (n=481), DTG + FTC + TAF 17.5% (n=363), and 3TC + EFV + TDF 17% (n=352), [Table 3].

Table 3: Clinical Characteristics of study Population

Variable	Frequency (n)	Percent (%)
BMI Category at initiation (N=2070):		
Underweight (BMI<18.5 kg/m2)	288	13.9
Normal (BMI 18.5-24.9 kg/m2)	1248	60.3
Overweight (BMI 25.0-29.9 kg/m2)	307	14.8
Obese (BMI>=30 kg/m2)	227	11.0
Family History Hypertension:		
No	1682	81.3
Yes	388	18.7
Family History of Diabetes Mellitus:		
No	1777	85.8
Yes	293	14.2
ART combination on initiation:		
3TC + ABC + LPV/r	140	6.8
3TC+DTG+TDF	481	23.2
3TC + EFV + TDF	352	17.0
DTG + FTC + TAF	363	17.5
EFV + FTC +TDF	734	35.5
Mean number of years on ART	5.7	±3.3

4.3 Prevalence of hypertension and type II diabetes mellitus in the study population

The prevalence of hypertension among study participants, recorded and diagnosed as hypertensive by clinicians in the case files was 33.8% (n=700) and type II diabetes mellitus was 14.9% (n=308). This prevalence excludes the clinically undiagnosed but with elevated readings

by cut-off definition; 56% (n=1159) for hypertension and 24.4% (n=505) for type II diabetes mellitus and the pre-hypertensive (n=791; 38.2%) and those with elevated blood glucose levels/pre-diabetics (n=303; 14.6%) [Table 4].

Table 4: Prevalence of hypertension and type II diabetes mellitus by record of diagnosis and reading.

Variable	Frequency (n)	Percent (%)
Diagnosis on file record for hypertension:		
No	1370	66.2
Yes	700	33.8
Diagnosis on file record for Diabetes Mellitus type 2:		
No	1762	85.1
Yes	308	14.9
Hypertension category confirmed by reading:		
Normal (Diastolic<80 or Systolic<120 mm Hg)	120	5.8
Elevated /pre-hypertension (Diastolic 80-89 or Systolic 120-129 mm Hg)	791	38.2
Hypertension/ High Blood Pressure (Diastolic>=90 or Systolic >=130 mm Hg)	1159	56.0
type II diabetes mellitus category confirmed by reading:		
Normal (<100mg/dL for fasting or <140mg/dL for random)	1262	61.0
Pre-diabetic (100-125mg/dL for fasting or 140-199mg/dL for random)	303	14.6
Diabetic (>=126mg/dL for fasting or >=200mg/dL for random)	505	24.4

The highest prevalence of hypertension on different types of HAART combinations was observed in those on 3TC (Lamivudine NRTI) + ABC (Abacavir NRTI)+ LPV/r (Lopinavir PI) at 100% (n=86), 3TC (Lamivudine NRTI) + EFV (Efavirenz NNRTI) + TDF (Tenofovir NRTI) at 100% (n=19), DTG (Dolutegravir, INSTI) + FTC (Emtricitabine NRTI) + TAF (NRTI) at 100% (n=23)), and with the least prevalence on 3TC (Lamivudine NRTI) +DTG (Dolutegravir, INSTI) +TDF (Tenofovir NRTI) at 51.7% (n=823), [Table 5].

The highest prevalence for diabetes was on HAART regimen EFV (Efavirenz NNRTI) + FTC (Emtricitabine NRTI) +TDF (Tenofovir NRTI) at 31% (n=45), and those on 3TC (Lamivudine NRTI) + EFV (Efavirenz NNRTI) + TDF (Tenofovir NRTI) having the lowest prevalence at 5.3% (n=1), (Table 5).

Table 5: Prevalence of Hypertension and type II diabetes mellitus by different ART combinations

Variable	Clients on the ART Combination		Diagnosed with Diabetes		Diagnosed with hypertension	
	n	%	n	%	n	%
ART Combination:						
3TC + ABC + LPV/r	86	4.2	11	12.8	86	100.0
3TC+DTG+TDF	1591	76.9	385	24.2	823	51.7
3TC + EFV + TDF	19	0.9	1	5.3	19	100.0
DTG + FTC + TAF	23	1.1	4	17.4	23	100.0
EFV + FTC +TDF	145	7.0	45	31.0	96	66.2
3TC + ABC + DTG	206	10.0	59	28.6	112	54.4
Total	2070	100.0	505	24.4	1159	56.0

4.4 Incidence rate of hypertension and type II diabetes mellitus in the study population

The incidence rate of hypertension of 2070 case files observed over a period fifteen (15) years contributing 13,519 person years of follow up based on SMART CARE records from 2006 to 2021 was 85.7 cases per 1000 enrolled ART clients per year among the HIV infected persons on HAART. While the incidence rate for Type II diabetes mellitus (T2DM) among the HIV infected persons on HAART was 37.4 cases per 1000 registered ART clients per year.

Table 6*: HIV infected persons on HAART tested for hypertension and diabetes*

Year	Total Registered on ART	New Clients	Total eligible and tested for NCDs of interest	Total with raised HPTN	Total with raised BGS
2006	1378	0	14	8	0
2007	1536	158	43	32	6
2008	1706	170	20	15	2
2009	1907	201	32	27	7
2010	2078	171	77	43	27
2011	2257	179	69	51	34
2012	2448	191	209	100	56
2013	2952	504	176	90	44
2014	3243	291	162	108	23
2015	3473	230	171	133	33
2016	3728	255	163	90	68
2017	3983	255	228	129	62
2018	4134	151	270	125	55
2019	4302	168	273	121	32
2020	5446	1144	148	80	55
2021	5946	500	15	7	1
TOTAL	**50517**	**4568**	**2070**	**1159**	**505**

4.5 Distribution of different risk factors to NCDs

The results show that there was significant difference ($F[4, 2065] = 31.528$; $p<0.001$) of systolic blood pressure distribution among the four different ART combination groups and a significant difference ($F[4, 2065] = 13.884$; $p<0.001$) of diastolic blood pressure distribution among the four different ART combination groups as shown in Table 7. Analysis of variances results however showed no significant difference in the blood sugar levels among the different ART combination groups ($p=0.592$).

Table 7: Analysis of Variances of median NCD risk factors among different ART Regimes

Variable	Sum of Squares	df	Mean Square	F	Sig.
Systolic Blood Pressure					
Between groups	14717.525	4	3679.381	31.528	0.000
Within groups	240986.784	2065	116.701		
Total	255704.310	2069			
Diastolic Blood Pressure					
Between groups	4392.206	4	1098.051	0.701	0.000
Within groups	163319.721	2065	79.089		
Total	167711.927	2069			
Blood Sugar Levels					
Between groups	6482.589	4	1620.647	0.701	0.592
Within groups	4776964.476	2065	2313.300		
Total	4783447.065	2069			

Median test showed significant differences in median Systolic Blood Pressure (mgHg) levels ($\chi2$=170.126, df=4; p<0.001), median Diastolic Blood Pressure (mgHg) levels ($\chi2$=14.628, df=4; p=0.006) and in median blood sugar levels ($\chi2$=27.979, df=4; p<0.001) among the different ART combinations (Table 9).

Table 8: Median Test Result for median differences of NCD Risk factors among ART Regimens.

		ART combination on diagnosis					Median Test			
Variable		3TC + ABC + LPV/r	3TC+DTG+TDF	3TC + EFV + TDF	DTG + FTC + TAF	EFV + FTC +TDF+ FDC	Median	χ^2	df	Sig.
Systolic BP (mmHg)	> Median	86	691	19	23	96	128	170.126	4	0.000
	<= Median	0	900	0	0	49				
Diastolic BP (mmHg)	> Median	48	766	17	11	73	82	14.628	4	0.006
	<= Median	38	825	2	12	72				
Blood Sugar (mg/dL)	> Median	54	744	12	9	95	100	27.979	4	0.000
	<= Median	32	847	7	14	50				

Pearson Chi square tests (Table 10) shows that there was a significant difference in hypertension incidences among clients on different ART combinations (χ2=118.7, df=5; p<0.001). Majority of clients on all the different ART combinations developed hypertension (56%). All the clients on these three combinations - 3TC + ABC + LPV/r, 3TC + EFV + TDF and DTG + FTC + TAF combinations developed hypertension.

There was a significant difference in type 2 diabetes incidences among clients on different ART combinations (χ^2=16.173, df=5; p=0.006). Nearly one in four (24.4%) of clients on all the different ART combinations were diagnosed with type 2 diabetes. Clients on 3TC + EFV + TDF combination least developed Type II diabetes mellitus (5.3%) followed by those on 3TC + ABC + LPV/r combination (12.8%), whilst clients on EFV + FTC +TDF combination developed Type II diabetes mellitus most (31.0%). Even after excluding ART combinations with few cell values (n<5; - 3TC + EFV + TDF and DTG + FTC + TAF), there was still a significant difference in diabetes incidence among the different ART combinations (χ^2=17.449, df=4; p=0.002).

Table 9: Pearson Chi-square tests for hypertension and type II diabetes mellitus

		Confirmed hypertension					Diabetes II				
		Cases		Pearson Chi-Square Test			Cases		Pearson Chi-Square Test		
Variable	N	No	Yes	χ^2	df	Sig	No	Yes	χ^2	df	Sig.
ART combination											
3TC + ABC + LPV/r	86	0	86				75	11			
3TC+DTG+TDF	1591	768	823				1206	385			
3TC + EFV + TDF	19	0	19				18	1			
DTG + FTC + TAF	23	0	23				19	4			
EFV + FTC +TDF FDC	145	49	96				100	45			
3TC + ABC + DTG	206	94	112				147	59			
Total	2070	911	1159	118.700	5	0.000	1565	505	16.173	5	0.006

4.6 Predictors of Hypertension and Diabetes Mellitus II Outcomes

Logistical regression analysis was run to predict the determinants of diabetes II and hypertension.

4.6.1 Predictors of Diabetes

Results in Table 12, show that ART combination (p=0.001), age category (p=0.011) and cigarette smoking (p=0.0460) significantly added to the prediction model for T2DM outcome. The model correctly classified 75.6% of the cases collectively explained only 2.8% of the variability in the model ($\chi 2$ (df = 11) = 39.389, p<.001; Nagelkerke R^2 = 0.028) indicating that there are other factors that majorly contribute to diabetes outcome that were not part of this study, including dietary patterns, lipid profile, and individual variances and pathophysiological changes due to disease prognosis.

Table 10: Regression Coefficients for Predictors of Diabetes Mellitus II in Chongwe District

Variable	B	Wald	df	*p*	Exp(B)	95% CI
ART_Combi_Diag		20.236	5	0.001		
ART_Combi(1) - 3TC+DTG+TDF	0.991	8.460	1	0.004	2.693	1.381, 5.251
ART_Combi(2) - 3TC + EFV + TDF	-0.817	0.569	1	0.451	0.442	0.053, 3.689
ART_Combi(3) - DTG + FTC + TAF	0.527	0.664	1	0.415	1.694	0.477, 6.019
ART_Combi(4) -EFV + FTC +TDF +FDC	1.423	13.287	1	0.000	4.148	1.930, 8.912
ART_Combi(5) -3TC + ABC + DTG	1.336	12.460	1	0.000	3.803	1.811, 7.985
Age Category (AgeCAT)		9.041	2	0.011		
AgeCAT(1) - 46-55 yrs	-0.368	8.399	1	0.004	0.692	0.539, .888
AgeCAT(2) - >=56 yrs	0.060	0.095	1	0.757	1.062	0.724, 1.559
Sex(1)	-0.130	1.344	1	0.246	0.878	0.705, 1.094
History of Diabetes Mellitus II (1)	0.189	1.302	1	0.254	1.208	0.873, 1.670
Alcohol drinking (1)	0.129	1.371	1	0.242	1.138	0.917, 1.411
Cigarette smoking (1)	0.237	3.965	1	0.046	1.267	1.004, 1.600
Constant	-2.206	36.862	1	0.000	0.110	

The odds of having diabetes mellitus II was four times [Exp (B)= 4.148; 95% CI: 1.930, 8.912] greater for clients on ART_Combi_Diag(4) - EFV + FTC +TDF+FDC than for clients on ART_Combi_Diag of 3TC+ABC+LPV/r, the odds were however lower for clients on ART_Combi_Diag(2) - 3TC + EFV + TDF [Exp(B)=0.442; 95% CI: 0.053, 3.689] than for the ART_Combi_Diag of 3TC+ABC+LPV/r. The odds of having diabetes mellitus II was lower among the 46-55 years category [Exp (B)= 0.692; 95% CI: 0.539, 0.888] than for the 18-45 years age category. The odds of having diabetes mellitus II was 26.7% greater [Exp (B)=1.267; 95% CI: 1.004, 1.600] for cigarette smoking clients than for non-cigarette smoking clients.

4.6.2 Predictors of Hypertension

Results of logistical regression analysis for the determinants of hypertension show that ART combination (p=0.004), sex (p=0.001), family history of hypertension (p=0.007) and cigarette smoking (p=0.001) had significant associations with hypertension, and significantly added to the prediction model for hypertension outcome (Table 12). Jointly the model explained only 13.4% of variability in the prediction, correctly classifying 59.0% of the cases ($\chi 2(df = 11) = 218.539$, $p<.001$; Nagelkerke $R^2 = 0.134$).

The odds of having hypertension was 1.374 times [Exp (B) = 1.374; 95% CI: 1.137, 1.659] greater for male clients than for female clients.

Table 11: Regression Coefficients for Predictors of Hypertension in Chongwe District

Variable	B	Wald	df	*p*	Exp(B)	95% CI
ART_Combi_Diag		17.023	5	0.004		
ART_Combi(1) - 3TC+DTG+TDF	20.166	0.000	1	0.996	572603599	
ART_Combi(2) - 3TC + EFV + TDF	-0.266	2.968	1	0.085	0.767	0.566, 1.037
ART_Combi(3) - DTG + FTC + TAF	20.153	0.000	1	0.998	565263358	
ART_Combi(4) -EFV + FTC +TDF +FDC	20.157	0.000	1	0.998	567398182	
ART_Combi(5) -3TC + ABC + DTG	0.469	4.241	1	0.039	1.598	1.023, 2.496
Age Category (AgeCAT)		5.882	2	0.053		
AgeCAT(1) - 46-55 yrs	0.062	0.337	1	0.562	1.064	0.862, 1.314
AgeCAT(2) - >=56 yrs	-0.395	4.930	1	0.026	0.674	0.475, .955
Sex (1)	0.317	10.872	1	0.001	1.374	1.137, 1.659
History of Diabetes Mellitus II (1)	0.401	7.265	1	0.007	1.494	1.116, 2.000
Alcohol Drinking (1)	-0.008	0.006	1	0.937	0.992	0.820, 1.201
Cigarette Smoking (1)	0.338	10.803	1	0.001	1.402	1.146, 1.714
Constant	-0.018	0.014	1	0.906	0.982	

The odds of having hypertension was 1.494 times greater among clients with family history of hypertension [Exp (B)=1.494; 95% CI: 1.116, 2.000] than those without family history of the same. The odds of having hypertension was 1.402 times [Exp (B)=1.402; 95% CI: 1.146, 1.714] greater for cigarette smoking clients than for non-cigarette smokers.

CHAPTER 5: DISCUSSION

5.0 INTRODUCTION

This retrospective cohort study was conducted to determine the prevalence and incidence of hypertension and diabetes type 2 in HIV infected persons on HAART in Chongwe district from 6 high volume health facilities. The research specifically targeted adults of 18 years and above on HAART for a period of one year and longer registered in the SMARTCARE electronic data base from 2006 to 2021.

5.1 Prevalence of hypertension and type II diabetes mellitus

5.1.1 Prevalence of Hypertension

This study found a prevalence of 33.8% of hypertension by diagnosis and 56% (n=1159 of 2070 case files) by cutoffs readings. The prevalence of hypertension was significantly higher ($\chi^2=49.238$, $df=1$; $p<0.001$) among men (64%) than among women (49%). The difference in the prevalence between genders is alluded to the pathophysiology of the female sex hormones that support renal hemodynamics and prevent sodium re-absorption by kidneys (Hejazi et al., 2013). The prevalence of hypertension also differed significantly ($\chi^2=11.194$, df=2; p=0.004) among different age categories and was highest (57.2%) among the 18-45 years age bracket. This study also found a significant correlation between hypertension and age of client in years (p=0.009). These results are within range with a study that was conducted in Cameroon that found the prevalence of hypertension at 38%, which is consistent with the diagnosed prevalence and the same study also found that hypertension was associated with male gender and older age (Dimala et al., 2016). A similar study done in Ethiopia on 400 adults aged ≥18 years HIV clients using data retrieved from medical records found the prevalence of hypertension to be as high as 53%, within range with this study's 56% prevalence by cutoffs readings (Korem et al., 2018b). This

study as well found that the prevalence of hypertension was significantly higher in males than in females (Korem et al., 2018b), which is also consistent with another retrospective study done in Uganda which similarly found that there were more males than females with hypertension (Lubega et al., 2021). ART combination, family history of hypertension and smoking of the client were also statistically significant predictors of hypertension, among PLHIV/A in Chongwe district.

5.1.2 Prevalence of Type II diabetes mellitus

This study found the prevalence of Type II diabetes mellitus by diagnosis to be at 14.9% (n=308) and 24.4% (n=505) by cutoffs reading. The prevalence of Type II diabetes mellitus in this study is higher than the findings reported in other studies. Divala et al (2016) reported the prevalence of type II diabetes mellitus to be at 4.1% in a study conducted in Malawi. Duguma et al (2020) reported a prevalence of 11.4% in a study conducted in Ethiopia. The prevalence of Type II diabetes mellitus is lower in both studies than the prevalence in the current study. However, Duncan et al., (2018) found the prevalence of Type II diabetes mellitus at 15.1%, which is similar to this study. The difference in the lower prevalence's could be alluded to methodological differences of the studies, duration of the study and lower sample sizes in the cited studies. The HAART regimen could also be the reason for the differences in the prevalence rates from these different studies. The study period for this study catered for a longer observational period than the cross-sectional nature of the other cited studies. The longer duration on HAART, the higher the risk one could develop diabetes than those on shorter duration of taking HAART (Duncan et al., 2018).

This study also established no significant difference in the prevalence of type II diabetes mellitus between women (26%) and men (23%). However, the prevalence of diabetes differed

significantly ((χ^2=10.043, df=2; p=0.007) among different age categories and was highest (27.5%) among the 56 years and older age bracket. This study's findings are consistent with the study done by Duncan and others (2018) in a London population that associated their high prevalence findings to increasing age of their study cohort.

5.2 Incidence Rates

5.2.1 Incidence Rate of Hypertension

The observed incidence rate in this study was 85.7 cases per 1000 PYFU for hypertension among the HIV infected persons on HAART. The observed incidence rates in this study are lower than that of a five year retrospective study done in Cameroon that had a higher incidence rate of 18.5% reporting the number of cases at 109.1 cases per 1000 PYFU (Yoah, 2021). The Cameroon study results are in conformity to several other studies, such as one in rural Uganda restricted to patients on ART, 111.5 cases per 1000 PYFU, Tanzania, 9.6% reportedly 120 cases per1000 PYFU and a recent study on Incidence of hypertension in people with HIV who are treated with integrase inhibitors versus other antiretroviral regimens conducted in Europe and Australia, 23.0% reportedly 126.2 cases per 1000 PYFU (Okello et al., 2015; Rodríguez-Arbolí et al., 2017; Byonanebye et al., 2022). All these studies reported higher incidence of hypertension in HAART than this particular study. While several studies as cited, have linked an increase in risk of hypertension to HAART exposure, a large population based South African survey has associated ART exposure to decreased odds of hypertension (Malaza et al., 2012).

5.2.2 Incidence Rate of Type II diabetes mellitus

The incidence rate for diabetes mellitus type II (D2M) among the HIV infected persons on HAART for this study was 37.4cases per 1000 PYFU. This is higher than other studies of similar nature; the D.A.D prospective study that found the incidence of diabetes in persons on HAART

to be at 5.72 per 1000 PYFU (De Wit et al., 2008), the pooled incidence of a systematic review and meta-analysis study that found the incidence of overt diabetes in persons on HAART at 13.7 per 1000 PYFU (Nansseu et al., 2018). The incidence of type II diabetes mellitus for this study is way higher than the range of other studies cited, 5.72/1000 PYFU to 13.7/1000 PYFU. The disparity in the incidence rates of these three studies could be due to the duration of the study follow up and the sample size. The duration of this study was longer than the cited studies and the sample size was high at 2070 case files. The variation in drug classes, drug combination and cultural specific practices could also contribute to the differences in the incidence rate.

5.3 Association of ARV use to different NCDs

5.3.1 HAART Combinations Associated with Hypertension

In this study, the study cases were on triple therapy regimens containing either two NRTI and a PI or two NRTI plus a NNRTI and or two NRTI and an INSTI. This study showed that 3TC/ABC+LPV/r (two NRTIs plus a PI), FTC/TAF+DTG (two NRTIs plus an INSTI) treatment regimens were associated to hypertension. The effects of each drug on hypertension could not be examined since each regimen is made up of three drugs and at least two classes of drugs. However, this study noted that there was a higher proportion of people diagnosed with hypertension on an NRTI plus PI regimen and NRTI plus an INSTI combination regimen. The combinations were composed of the HAART drugs 3TC-Lamivudine/ABC-Abacavir+LPV/r-Lopinavir and FTC-Emtricitabine/TAF-Tenofovir Alafenamide+DTG-Dolutegravir, respectively. Trends in published studies of a similar subject have shown conflicting findings, some showing an association and others showing no association between HAART drugs/classes of drugs and hypertension (Yoah, 2021). The results of this study are in line with a study done by (Pangmekeh et al., 2019b), the study reported combinations of Tenofovir-TDF/Lamivudine-

3TC/Efavirenz-EFV, Zidovudine-AZT/Lamivudine-3TC/Nevirapine-NVP, Zidovudine-AZT/Lamivudine-3TC/ Efavirenz-EFV and Tenofovir-TDF/Lamivudine-3TC+Nevirapine-NVP as being associated with hypertension. The association was assumed to be due to the presence of Tenofovir and Lamivudine in the combinations, both being NRTIs (Pangmekeh et al., 2019b). A meta-analysis study also explained on the mechanism through which Protease Inhibitors (PIs) are associated to hypertension. This has been demonstrated through triggering of the inflammatory pathways leading to overproduction of ROS which in turn is associated with vascular collagen deposition, arterial stiffening and kidney injury (Fahme Sasha A. et al., 2018). Ritonavir-boosted Lopinavir (LPV/r) a PI has also been attributed to the activation of the adipocyte renin-angiotensin system (Fan et al., 2020b). Efavirenz an NNRTI, has also been associated with hypertension through its side effects that eventually cause renal dysfuction and eventually hypertension (Magande 2017). These results are similar to another study that found a higher prevalence of hypertension in HAART clients on INSTIs (Byonanebye et al., 2022). However, the Byonanebye study conflicts with this study's findings in which it finds no association between PIs and hypertension (Byonanebye et al., 2022). The mechanism association of INSTIs to hypertension is thought to be through weight gain and adipogenesis, oxidative stress and insulin resistance, all of which have been associated with hypertension and termed under metabolic abberations (Byonanebye et al., 2022).

This study however, is not in tandem with several other studies that found no association between HAART drugs/classes of drugs to hypertension. A five years cohort study conducted in Cameroon found no association between HAART regimens based on single tablet triple combinations of TDF/(3TC or FTC)/EFV. The study however, precluded a comprehensive analysis of whether exposure to specific drugs was associated with risk of hypertension (Yoah,

2021). Noteworthy is a D.A.D study that found Abacavir, Nevirapine, Ritonavir and Indinavir to be associated with hypertension after adjusting for confounders, but concluded that there was no independent association between intake of HAART drugs and hypertension (Hatleberg, et al., 2015).

5.3.2 HAART Combinations Associated with type II diabetes mellitus

Information on HAART drugs/combinations associated with type II diabetes mellitus is very conflicting and studies are of varied methodologies. Some studies have found no association between Type II diabetes mellitus prevalence and HIV infection or antiretroviral therapy (A Prioreschi et al., 2017). This study found highest prevalence and incidence of type II diabetes mellitus on HAART drugs/combinations FTC-Emtricitabine (NRTI)/TDF-Tenofovir (NRTI)+EFV-Efavirenz (NNRTI), HAART regimen 3TC-Lamivudine (NRTI)/ABC-Abacavir NRTI) + DTG-Dolutegravir (INSTI) and regimen 3TC-Lamivudine (NRTI)/TDF-Tenofovir (NRTI)+ DTG-Dolutegravir (INSTI). These are either combinations of two NRTIs and a NNRTI or two NRTIs plus an INSTI. This is in line with a Swiss HIV cohort study which found treatment combination regimens containing a PI/NRTI to be associated with the risk of developing Type II diabetes mellitus (Ledergerber et al., 2007). In this study, all treatment regimens found with a higher prevalence and incidence of type II diabetes mellitus contained an NRTI combination. A multi-center study also found similar results in which NRTI were associated with increased odds of hyperinsulinemia with each additional year of exposure (Brown et al., 2005). The probable mechanism is hypothesized to be through the NRTIs blockage of the mitochondrial polymerase gamma enzymes. The inhibition of the mitochondrial enzymes gradually leading to nephrotoxicity among other clinical presentations. Other side effects of NRTIs is fat redistribution syndrome or HIV-associated lipodystrophy which is

suggested to be as a result of mitochondrial toxicity, with less documented pathophysiology of diabetes (Eggleton and Nagalli 2020; PMC 2019; Saag et al. 2018; Kakuda 2000). The study by (Blümer et al., 2008) also conformed to this study's findings as they found that the PI boosted NRTI on regimen LPV/r-Lopinavir (PI)+ZDV-Zidovudine (NRTI)/3TC- Lamivudine (NRTI) resulted in disturbed glucose metabolism. Their results showed that the NRTI combination treatment led to a 25% decrease in insulin mediated peripheral glucose disposal and a 22% increase in lipolysis after three months therapy (Blümer et al., 2008).

In contrast to the above studies, a systematic review and meta-analysis of twenty articles of African population concluded that the meta-analysis showed no association between Type II diabetes mellitus prevalence and HIV infection or antiretroviral therapy. However, the results were limited by the high heterogeneity of the included studies and moderate-to-high risk of bias, as well as, the small number of studies included (A. Prioreschi et al., 2017).

6.0 CONCLUSION, STRENGTHS AND RECOMMENDATIONS

6.1 CONCLUSION

In this study, HIV positive clients on HAART had high prevalence and incidence of hypertension and type II diabetes mellitus. Male gender was more predisposed to developing hypertension than women. Aging was correlated to a higher risk to the development of both hypertension and type II diabetes mellitus. HAART combination regimen of two NRTI classes plus either a PI or INSTI were associated with higher incidence of hypertension whilst combination regimens of two NRTIs plus an NNRTI or INSTI and combination therapy of NRTI+NNRTI+INSTI were associated with higher incidence of type II diabetes mellitus in HAART treated clients.

6.2 STRENGTHS

This study utilized routinely collected clinical data from heterogenous cohorts using an existing national data base that included more than one reading per case, thus all reported prevalences and incidences are true diagnosis.

The study utilized a large number of case files and hence increasing the statistical strength of this study.

The study period spanned 15 years, contributing 13,519 person years of follow up which increased the statistical strength too.

6.3 RECOMMENDATIONS

The incidence of hypertension was generally higher in people on HAART. Therefore, there is need for such individuals to be considered for lifestyle modification/nutrition counselling and closer blood pressure monitoring.

There is need for focused screening and preventive programs such as NCDs and cardiovascular risk assessment screening as part of consideration for HAART initiation in the HIV positive clients as the high incidence is not only limited to hypertension in this study but to type II diabetes mellitus too.

Further research into individual drug comparisons including NRTIs, PIs and especially INSTIs given that they are increasingly the preferred treatment option, should be considered in larger cohorts, in a Zambian setting.

There is need to explore/research on other factors too such as the study findings indicate that there are other factors that majorly contribute to diabetes outcome that were not part of this study, including dietary patterns, lipid profile, and individual variances and pathophysiological changes due to disease prognosis.

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APPENDICES

Table 1: Preferred 1st line ART and alternative regimen by specific populations in Zambia

Specific Populations	Description	Preferred 1st line ART	Alternative regimen
Pregnant & Breastfeeding Women[b]	All	TDF + XTC + DTG	TDF + XTC + EFV_{400} or ABC + 3TC + DTG*
Children (0-2 weeks)	All	AZT + 3TC + NVP	AZT + 3TC + RAL
Children (2 weeks to < 5 years old)	< 20 Kg	ABC + 3TC + LPV-r	AZT + 3TC + LPV-r AZT + 3TC + RAL
	20 – 24.9 Kg	ABC + 3TC + DTG	AZT + 3TC + LPV-r ABC + 3TC + LPV-r
	≥ 25 Kg	TAF + 3TC + DTG	ABC + 3TC + DTG
	≥ 30Kg	TAF + 3TC + DTG	TDF + 3TC + DTG
Children co-infected with TB	<20 kg	ABC + 3TC + RAL (Double dose of RAL) or ABC + 3TC + AZT	AZT + 3TC + EFV (> 3 months)
	20 – 29.9 kg	ABC + 3TC + DTG Increase the frequency of DTG to 50mg twice daily	ABC+3TC+LPV-r (LPV-r should be superboosted, otherwise consult expert opinion) ABC + 3TC + EFV ABC + 3TC + RAL
	≥ 30Kg	TDF + 3TC+DTG Increase the frequency of DTG to 50mg twice daily	
Adolescents (10 to <19 years old) weighing **≥ 30Kg**	All	TDF (or TAF[c]) + XTC[d] + DTG[e]	TDF (or TAF[c]) + XTC[d] + EFV_{400}[a] or ABC + 3TC + DTG*
Adults			

Table 2: Preferred 1st line ART and alternative regimen for HIV-2 in Zambia

Specific Populations	Description	Preferred 1st line ART	Alternative regimen
HIV-1 / HIV-2 co-infected	Adolescents and adults	TDF (or TAF[a]) + XTC + DTG[b]	TDF or TAF + XTC + LPV-r[d] (or DRV – r) or ABC + 3TC + LPV-r or (DRV-r) ABC + 3TC +DTG[f]
HIV-1 / HIV-2 co-infected	Children	ABC + 3TC + LPV-r	

Adapted from the Zambia 2020 Consolidated Guidelines for Treatment and Prevention of HIV infection.

APPENDICES

DATA EXTRACTION TABLES AND VARIABLES

Appendix 12: Data Extraction Form

Table

3: Data Extraction Form

Sno	Sex of Client 1=Male 2=Female	Date of Birth (YYYY)	Date of ART initiation	BMI at initiation	Marial Status	Education Level	Residential Area	Family history of HPTN? 1=Yes 2=No	Known HPTN at initiation? 1=Yes 2=No	Family history of DM 2? 1=Yes 2=No	Known DM at initiation? 1=Yes 2=No	Has other chronic condition at initiation? 1=Yes 2=No	ART drug (combination) on initiation	Development of DM (diagnosed /flagged) 1= Yes 2= No	Development of type 2 DM (diagnosed /flagged) 1= Yes 2= No	Date on NCD (either HPTN or DM or both)	ART drug (combination) on NCD diagnosis (either HPTN or DM or both)	BMI at NCD diagnosis	HPTN: systolic (upper)	HPTN: diastolic (lower)	DM: fasting or random values	Smoking YES=1 NO=2	Drinking YES=1 NO=2			

DATA AGGREGATION TABLES

Appendix 13: Demographic Characteristics of Sampled Population

VARIABLE	CHARACTERISTIC	NUMBER	PERCENTAGE
Sex	Male		
	Female		
Age	18-45		
	46-55		
	≥56		
Marital status	Single		
	Married		
	Divorced		
	Widowed		
Educational level	No education		
	Primary		
	Secondary		
	Tertiary		
Residential area	Urban		
	Per-urban		
	Rural		

Appendix 14: Family and/or Medical History at ART initiation

VARIABLE	CHARACTERISTIC	SEX	NUMBER	PERCENTAGE
Family history of hypertension	Yes	Male		
		Female		
	No	Male		
		Female		
Known hypertensive at initiation	Yes	Male		
		Female		
	No	Male		
		Female		
Family history of type 2 diabetes	Yes	Male		
		Female		
	No	Male		
		Female		
Known diabetic	Yes	Male		
		Female		
	No	Male		
		Female		
Existing condition/disease at inception	Yes	Male		
		Female		
	No	Male		
		Female		
BMI at ART initiation	≤ 18.5	Male		
		Female		
	18.6-24.9	Male		
		Female		
	25-29.9	Male		
		Female		

	≥ 30	Male		
		Female		

Appendix 15: Duration, Drugs Information and NCDs Development

VARIABLE	CHARACTERISTIC	sex	NUMBER	%AGE
Duration on ART	1-<5 years			
	5-10 years			
	≥10 years			
ART drug (combinations) on initiation	1.			
	2.			
	3.			
	4.			
	5.			
	6.			
	7.			
	8.			
	9.			
	10.			
Development of hypertension (diagnosis/flagged)	Yes	Male		
		Female		
	No	Male		
		Female		
Development of type 2 diabetes (diagnosis/flagged)	Yes	Male		
		Female		
	No	Male		
		Female		
Duration on ART at NCD diagnosis (either hypertension or diabetes type 2 and or both)	1-<5 years	Male		
		Female		
	5-10 years	Male		
		Female		
	≥10 years	Male		

		Female		
ART drug (combination)on diagnosis of NCD (either hypertension or diabetes type 2 and or both)	1.			
	2.			
	3.			
	4.			
	5.			
	6.			
	7.			
	8.			
	9.			
	10.			
BMI at NCD diagnosis	≤ 18.5	Male		
		Female		
	18.6-24.9	Male		
		Female		
	25-29.9	Male		
		Female		
	≥ 30	Male		
		Female		

Appendix 9: Categorization of Hypertension and type II diabetes mellitus

VARIABLE	CHARACTERISTIC	SEX	NUMBER	%AGE
Hypertension	**SYSTOLIC**			
	<120	Male		
		Female		
	120-129	Male		
		Female		
	130-139	Male		
		Female		
	140-<180	Male		
		Female		
	≥180	Male		
		Female		
	DIASTOLIC			
	<80	Male		
		Female		
	80-89	Male		
		Female		
	90-<120	Male		
		Female		
	≥120	Male		
Diabetes	**Fasting blood glucose (FBS)**			
	<6.1 mmol/l or <	Male		
		Female		
	6.1-6.9 mmol/l	Male		
		Female		
	≥7.0 mmol/l	Male		
		Female		

	Random blood glucose			
	<7.8 mmol/l or <140mg/d	Male		
		Female		
	7.8-11mmol/l or 140-199mg/dl	Male		
		Female		
	≥11.1mmol/l or ≥200mg/dl	Male		
		Female		

ETHICAL APPROVAL LETTERS

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

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16th November 2021

Your REF. No. 1924-2021.

Ms. Bona Mwiinga Hamoonga,
University of Zambia,
Department of Human Nutrition,
Lusaka.

Dear Ms. Hamoonga,

RE: "INCIDENCE OF HYPERTENSION AND DIABETES MELLITUS IN HIV INFECTED PERSONS ON HAART: A RETROSPECTIVE STUDY OF CHONGWE DISTRICT IN LUSAKA PROVINCE, ZAMBIA" (REF. NO. 1924-2021)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 15th November, 2021. The proposal is **approved**. The approval is based on the following documents that were submitted for review:

a) Study proposal
b) Questionnaires
c) Participant Consent Form

APPROVAL NUMBER : REF. 1924-2021

This number should be used on all correspondence, consent forms and documents as appropriate.

APPROVAL DATE : 16th November 2021
TYPE OF APPROVAL : Standard
EXPIRATION DATE OF APPROVAL : 15th November 2022

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the UNZABREC Offices should be submitted one month before the expiration date for continuing review.

SERIOUS ADVERSE EVENT REPORTING: All SAEs and any other serious challenges/problems having to do with participant welfare, participant safety and study integrity must be reported to UNZABREC within 3 working days using standard forms obtainable from UNZABREC.

MODIFICATIONS: Prior UNZABREC approval using standard forms obtainable from the UNZABREC Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
TERMINATION OF STUDY: On termination of a study, a report has to be submitted to the UNZABREC using standard forms obtainable from the UNZABREC Offices.

NHRA: You are advised to obtain final study clearance and approval to conduct research in Zambia from the National Health Research Authority (NHRA) before commencing the research project.
QUESTIONS: Please contact the UNZABREC on Telephone No. +260977925304 or by e-mail on
unzarec@unza.zm.
OTHER: Please be reminded to send in copies of your research findings/results for our records. You're also required to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study. Use the online portal: unza.rhinno.net for further submissions.

Yours sincerely,

Dr. Victor Chisha Zulu., PhD
VICE-CHAIRPERSON

NATIONAL HEALTH RESEARCH AUTHORITY CERTIFICATE