SCHOOL OF PUBLIC HEALTH

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EFFECT OF DOLUTEGRAVIR-BASED REGIMEN ON METABOLIC SYNDROME AMONG PEOPLE LIVING WITH HIV IN THE GREATER ACCRA REGION

BY

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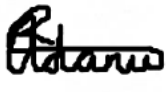
DECLARATION

I, Marian Offei hereby declare that apart from references to other people's works which have been duly acknowledged, this thesis is as a result of my own independent work under the supervision of my supervisors. It has not been submitted for the award of any degree in any institution.



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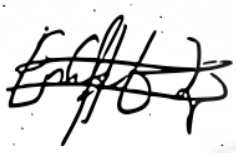

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ABSTRACT

Introduction: Globally, the expansion of antiretroviral therapy (ART) coverage has improved survival among people living with HIV (PLHIV) and has also reduced AIDS-related mortality in low-resource settings, including Ghana. However, as PLHIV live longer, they are exposed to environmental and behavioural risk factors in addition to HIV and ART which may increase their risk of metabolic disorders and cardiovascular diseases. A cluster of three or more of these metabolic disorders (elevated blood pressure, abnormal cholesterol level, elevated blood sugar, insulin resistance and abdominal obesity) is known as Metabolic Syndrome (MetS). Dolutegravir-based regimen which is the current ART being used for HIV treatment has been shown to cause a significant weight gain (major risk factor for cardiometabolic conditions). Thus, the need to assess the effect of this drug combination on MetS. This study assessed the effect of dolutegravir-based regimen on the incidence of MetS and estimated the risk of Cardiovascular disease (CVD). It also assessed the challenges and level of adherence to the baseline requirements before ART initiation and routine checks.

Method: A prospective cohort study was conducted among HIV-positive patients from Tema General Hospital HIV clinic. A sample size of 300 was estimated using command stpower cox in STATA version 14 (150 per cohort – those switching and those starting on the dolutegravir-based regimen) for the cohort study. These 300 participants were sampled from 588 participants who consented and were screened for eligibility to participate in the study using systematic sampling. The cohort was followed for 12 months and data was collected at baseline, 6 months and 12 months. MetS which was the primary outcome of measure was defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria (i.e. having ≥3 of the following characteristics: elevated fasting blood glucose, elevated waist circumference, low

high density lipoprotein cholesterol (HDL-C), elevated triglycerides and elevated blood pressure). Evaluation included laboratory data that were obtained after 8 hours overnight fast and a survey using a questionnaire to assess traditional risk factors associated with metabolic syndrome, HIV/ART-related factors and comorbidities. Prevalence was calculated as the number of cases divided by the total screened population. Incidence rate was calculated as the number of incident cases divided by the total person-months at risk. Cox proportional hazard model was used to estimate the hazard of MetS. The cardiovascular risk score assessment tools (5-year D:A:D CVD risk score, 10-year Framingham risk score and 10-year WHO/ISH risk prediction chart) were used to estimate the risk level of CVD among the study participants. In-depth interviews were conducted among newly diagnosed HIV-positive patients and heads in 10 of the 41 comprehensive HIV care clinics in the Greater Accra Region to ascertain some of the challenges they are encountering in adhering to the new ART guidelines. A sample of 50 patient's folders were reviewed to abstract data on the tests, physical examination and information on medical and social history collected at baseline before ART initiation and routinely during the course of treatment to assess the facilities adherence to the ART guidelines.

Results: Among the 588 participants that were screened, the mean age was 40.61 $\pm$ 10.73years with 411 (69.9%) being females. The prevalence of MetS was 46.8% using the NCEP-ATPIII definition for MetS. Of the 300 sampled participants (150 per each cohort) followed up for 12 months, those who switched to dolutegravir-based regimen cohort were older in mean age (43.50$\pm$9.48) than those who had been newly diagnosed with HIV and were initiated on dolutegravir-based regimen [37.80$\pm$10.89]. Using the NCEP-ATPIII diagnostic criteria, the incidence rate of MetS per 100 person-months on dolutegravir-based regimen was 3.47 (CI:2.89-4.17) with incidence of 115 (38.3%). Among the metabolic subcomponents, 100 people had

increased waist circumference, representing the component with the highest incidence at an incidence rate of 3.31 (CI: 2.72 – 4.02) per 100 person-months. Seventy-three (73) participants had elevated blood pressure, representing the component with the lowest incidence at an incidence rate of 3.54 (CI: 2.82 – 4.46) per 100 person-months. Dolutegravir-based regimen was found to be a significant risk factor in the development of MetS among the two cohorts even though those who had being on other drug regimen before the dolutegravir had 2.0 hazard of developing MetS compared to those who started with it. Use of dolutegravir-based regimen [HR=2.0; 95% CI (1.12, 3.55)], age groups [HR=58.4; 95% CI (4.27, 80.0)], sex [HR=0.38; 95% CI (0.16, 0.87)], employment status [HR=0.01; 95% CI (0.00, 0.13)], marital status [HR=8.31; 95% CI (2.22, 31.0)], number of adults in household [HR=3.45; 95% CI (1.20, 9.95)], WHO Stage [HR=17.9; 95% CI (1.45, 71.0)], family history of hypertension [HR=19.9; 95% CI (5.22, 75.9)], platelets counts [HR=1.01; 95% CI (1.01, 1.02)], creatinine levels [HR=9.32; 95% CI (1.65, 52.6)], HDL-C [HR=2.11; 95% CI (1.29, 3.45)], triglyceride levels [HR=3.23; 95% CI (1.78, 5.88)], fasting blood glucose [HR=10.98; 95% CI (2.73, 44.16)], waist circumference [HR=5.13; 95% CI (1.76, 14.9)], body mass index [HR=11.2; 95% CI (4.13, 30.6)] and blood pressure [HR=2.05; 95% CI (1.08, 3.92)] were found to be significant risk factors for MetS. Majority of the participants were at low risk of developing CVD in the next 10 years using the 10-year FRS (65.7%) and the 10-year WHO/ISH prediction risk scores (76.3%). Using the D:A:D 5-year score, 56.2% of the participants were at moderate to high risk of developing CVD in 5 years. In terms of adherence to the ART guidelines, majority of the facilities surveyed (90%) were not adhering to it with inadequate staff and logistics being a major challenge they are encountering thus the non-adherence.

Conclusion: The incidence of metabolic syndrome was high among HIV-infected persons on dolutegravir-based regimen irrespective of whether they started with it or switched from one medication to it. The traditional risk factors also played a more significant role in its development. Therefore, there is a need for routine screening for MetS subcomponents throughout the course of ART (dolutegravir-based regimen) in Ghana and Sub-Saharan Africa as a whole.

DEDICATION

I dedicate this dissertation to my husband, daughters and family – I am blessed and highly favoured to have you in my life.

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LIST OF ABBREVIATIONS

ABBREVIATIONS	MEANING
3TC	Lamivudine
ABC	Abacavir
AACE	American Association of Clinical Endocrinologists
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
apoB	Apolipoprotein B
ART	Antiretroviral Therapy
ARVs	Antiretrovirals
AST	Aspartate Transaminase
ATV/r	Atazanavir/ritonavir
AZT/ZDV	Zidovudine
CATS	Community Adolescent Treatment Supporters
$CD4^+$	Cluster Differential 4^+
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CRP	C-reactive protein
CVD	Cardiovascular Disease
D:A:D	Data Collection on Adverse Events of Anti-HIV drugs
DALYS	Disability-adjusted Life Years
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
DRV/r	Darunavir/ritonavir

ABBREVIATIONS	MEANING
DSD	Differentiated Service Delivery
DTG	Dolutegravir
EFV	Efavirenz
EGIR	European Group Insulin Resistance
FFAs	Free Fatty Acids
FIs	Fusion Inhibitors
FRS	Framingham Risk Score
FPG	Fasting Plasma Glucose
FTC	Emtricitabine
GAC	Ghana AIDS Commission
GGT	Gamma-glutamyl Transferase
GDHS	Ghana Demographic Health Survey
GLUT4	Glucose Transporter Type 4
HbA1c	Glycated Haemoglobin
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HIV-1	HIV-Type 1
HIV-2	HIV-Type 2
HSS	HIV Sentinel Surveillance
HTLV-III	Human T lymphotropic virus type III
IDF	International Diabetes Federation
INSTIs	Integrase Strand Transfer Inhibitors
IQR	Interquartile range

ABBREVIATIONS	MEANING
JHS	Junior High School
LAV	Lymphadenopathy-Associated Virus
LDL	Low Density Lipoprotein
LPV/r	Lopinavir/ritonavir
MetS	Metabolic Syndrome
MTCT	Mother-to-child transmission
NACP	National AIDS/STI Control Programme
NCDs	Non-communicable Diseases
NCEP	National Cholesterol Education Program
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
NFM3	New Funding Model 3
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Insurance Scheme
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NtRTIs	Nucleotide Reverse Transcriptase Inhibitors
PCP	Pneumocystis Carinii Pneumonia
PEP	Post-Exposure Prophylaxis
PGL	Persistent Generalized Lymphadenopathy
PI3K	Phosphoinositide 3-kinase
PIs	Protease Inhibitors
PLHIV	People Living with HIV
PMTCT	Prevention of Mother-To-Child Transmission
PrEP	Pre-Exposure Prophylaxis

ABBREVIATIONS	MEANING
RAL	Raltegravir
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
SBP	Systolic Blood Pressure
SDGs	Sustainable Development Goals
SHS	Senior High School
SSA	Sub-Saharan Africa
STI	Sexually Transmitted Disease
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TG	Triglyceride
TGH	Tema General Hospital
UNAIDS	Joint United Nations Programme on HIV/AIDS
VLDL	Very Low-Density Lipoprotein
WC	Waist Circumference
WHO	World Health Organisation
WHO/ISH	World Health Organisation/International Society of Hypertension

DEFINITION OF TERMS

Terms	Meaning
Atherosclerosis	Build-up of fats, cholesterol and other substances in and on the artery walls
Dyslipidaemia	Abnormal levels of lipids (cholesterol or fats) in the blood
Euglycaemia	Over secretion of insulin by the pancreatic beta cells to maintain normal blood glucose concentration
Gluconeogenesis	Metabolic pathway that synthesize glucose from non-sugar precursors, such as lactate, pyruvate, and the carbon skeleton of glucogenic amino acids.
Glycogenolysis	Biochemical pathway in which glycogen breaks down into glucose-1-phosphate and glycogen
hypercholesterolemia	Presence of high levels of cholesterol in the blood
Hyperglycemia	Presence of high levels of sugar or glucose in the blood
Hyperinsulinemia	Over secretion of insulin by the pancreatic beta cells
Hypertriglyceridemia	Abnormal concentration of triglyceride in the blood. i.e. blood level >150 mg/dL (1.7 mmol/L)
Hypoxia	Low oxygen in the tissues
Lipolysis	Biochemical pathway by which fats (triacylglycerol) are hydrolyzed into fatty acids (FAs) and glycerol
Lipotoxicity	Deleterious effects of lipid accumulation in non-adipose tissues
Metabolic Syndrome	Cluster of three or more metabolic disorders (high blood pressure, abnormal cholesterol level, high blood sugar, central obesity and insulin resistance)
Opportunistic Infections	Infections and infection-related cancers that occur more frequently or are more severe in people with weakened immune systems than in people with healthy immune systems

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Human immunodeficiency virus (HIV) is a retrovirus which uses ribonucleic acid (RNA) to replicate itself within living cells. The virus upon entering a living cell, attacks the cluster of differentiating Cluster Differential 4^+ ($CD4^+$) T-helper cells (responsible for immune system functioning) thereby compromising the immune system function through the reduction of the $CD4^+$ T-helper cells. The effect of HIV on the immune system and organs, if not controlled after several years leads to acquired immune deficiency syndrome (AIDS) disease. In the 1990s, there was a global response to HIV through the introduction of antiretroviral therapy (ART) to help reduce HIV morbidity and related mortality among people living with HIV (PLHIV) using 3 to 4 anti-retroviral (ARV) drug combinations. This has caused the HIV epidemic to decline over time. By the end of 2022, a total of 39.0 million people were living with HIV globally with about 66% residing in sub-Saharan Africa (Joint United Nations & Programme on HIV/AIDS, 2023). Also, the global annual deaths from AIDS-related illness among PLHIV (all ages) has fallen from a peak of 2.0 million in 2004 to 630 000 in 2022 (Joint United Nations & Programme on HIV/AIDS, 2023).

In Ghana, the number of people living with HIV and AIDS was estimated at 354,927 with HIV prevalence of 1.66% in 2022 of which Greater Accra region recorded the 3rd highest prevalence [2.05%] (National AIDS/STI Control Programme et al., 2023). The ART was started in 2003 in Ghana with five (5) of the seven classes of ARVs currently available for HIV treatment.

In order to keep up with the current global trends to advance HIV prevention, treatment, care and support, Ghana in August 2019, revised its guidelines for Antiretroviral Therapy to update the ART drug regimen which replaces Efavirenz with Dolutegravir as the preferred 1st line drug regimen for adults and adolescents. This guideline also provide information on the assessment to be performed before initiation of ARTs which may influence the choice of therapy. The NRTIs/NtRTIs in the form of Zidovudine (AZT/ZDV), Tenofovir (TDF), Lamivudine (3TC), Abacavir (ABC), Emtricitabine (FTC) and one INSTI (Dolutegravir [DTG]) are the preferred first-line ARVs being used since 2019 in Ghana. This is administered using the three fixed dose combinations to improve adherence to the treatment (Ghana Health Service & National AIDS/STI Control Programme, 2019).

The introduction of the ART has resulted in PLHIV living longer and those who do not access the ART treatment surviving only at an estimated time of 11 years after infection (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2007). However, the chronic nature of the HIV infection requires lifelong ART to continuously suppress HIV replication (Dahabieh et al., 2015) hence it's usage has been associated with various chronic metabolic disorders such as high blood pressure, abnormal cholesterol level, high blood sugar, obesity and insulin resistance (De Wit et al., 2008; Gabriel, Prieto-Carrasquero, & Kobori, 2006; Jeric´o et al., 2005; Leow et al., 2003; Maseko & Masuku, 2017; Samaras et al., 2007). A cluster of three or more of these metabolic disorders is referred to as metabolic syndrome.

The combination of these metabolic disorders to diagnose MetS has several perspectives emerging over the years. The first diagnostic criteria for MetS were described by the World Health Organization (WHO) in 1998, followed by the European Group for the study of Insulin Resistance (EGIR) in 1999. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-

ATP III) defined it in 2001 and subsequently the American Association of Clinical Endocrinologists (AACE) in 2003. In 2005, the International Diabetes Federation (IDF) proposed a new definition for MetS (Kaur, 2014). The most widely used criteria especially in sub-Saharan Africa (SSA) are the ones provided by the IDF, NCEP-ATP III and sometimes the one by WHO (Ofori-Asenso et al., 2017; Todowede et al., 2019). This different criteria used to diagnose MetS have been a source of perplexity for clinicians and researchers thereby making the estimating of its true prevalence in any setting a challenge (O'Neill & O'Driscoll, 2015; Ofori-Asenso et al., 2017).

Despite these challenges, the IDF estimates nearly a quarter of the world's population have MetS (International Diabetes Federation, 2015) with the global pooled prevalence of MetS among PLHIV estimated to range from 16.7% to 31.3% (Nguyen et al., 2017b). This prevalence varies greatly across countries depending on factors such as region, area of residence, ethnicity, gender, age, race of the population been studied and the diagnostic criteria used (Aguilar et al., 2015; Gundogan et al., 2013; Kaur, 2014; Ofori-Asenso et al., 2017; Xiao et al., 2016). This estimated global prevalence used data from developed nations with few from sub-Saharan Africa (SSA) due to limited studies. This is evident in a recent systematic review and meta-analysis conducted by Todowede, Mianda & Sartorius (2019) in SSA which found only 18 articles with one from Ghana presenting on the prevalence results for MetS among PLHIV. This study found the overall prevalence of MetS among PLHIV to be 21.5% irrespective of the diagnostic criteria used. It also found 6.0%, 12.4% and 21.2% based on the WHO, NCEP-ATP III and IDF diagnosis respectively.

In Ghana, only one study has looked at the prevalence of MetS which found a higher prevalence of 24.5% according to WHO criteria, 48.3% by NCEP‑ATP III criteria, and 42.3% by IDF criteria as compared to prevalence obtained from the review from SSA and the global pooled prevalence

(Nguyen et al., 2016; Obirikorang et al., 2016; Todowede et al., 2019). This high MetS prevalence among PLHIV in Ghana calls for the need for more research in this area to ascertain the actual burden and risk factors associated with MetS especially the effects of the ART which found an extremely high prevalence of 61.6% using the NCEP-ATP III diagnosis (Obirikorang et al., 2016).

Metabolic syndrome has also been attributed to ageing, higher socio-economic status, increasing sedentary lifestyle, nutritional changes, genetics, high body mass index, pro-inflammatory state and hormonal changes (International Diabetes Federation (IDF), 2006). These factors have also been associated with most non-communicable diseases (NCDs). Decades ago, NCDs were attributed to economic development thus it was referred to as a disease of the rich. Currently, NCDs appear to be sweeping the entire World, with an alarmingly increased trend in developing countries. This trend is predicted to account for 80% of the global burden of disease by 2020 and also causing 7 out of 10 deaths in developing nations (World Health Organisation, 2002). Thus, preventative strategies must consider the growing trend of risk factors correlated to these diseases which are consequents of MetS.

In addition, the current epidemiological transition occurring in SSA compounded by the growing burden of metabolic disorders globally has caused the continent to be affected by the dual burden of infectious and NCDs putting more pressure on our weak health systems (National Research Council, 2012). Even though the coexistence of infectious diseases and NCDs is well acknowledged in developed countries, the intensity of this comorbidity is not well documented in SSA (Bygbjerg, 2012) including the increased risk of MetS and its risk components especially among PLHIV (Alvarez et al., 2010; Bosho et al., 2018). Therefore, it is important to explore the burden of MetS especially among PLHIV who have been shown to be at a higher risk (Ofori-Asenso et al., 2017; Todowede et al., 2019).

1.2 Statement of Problem

The introduction of the ART has improved the quality of life and prolonged life expectancy of people living with HIV globally. Dolutegravir (DTG) which is now the preferred first line regimen in place of Efavirenz (EFV) has been shown to cause more weight gain among PLHIV which is a risk factor for MetS (Calza et al., 2019; Clayden & HIV i-Base, 2019; Norwood et al., 2017; Osterholzer & Goldman, 2014; Quercia et al., 2015). This is shown in a study by Venter et al. (2019) where PLHIV who received TDF+FTC+DTG regimen gained twice the mean weight (3.2kg) of those on TDF+FTC+EFV (1.7kg). PLHIV and are on the ARTs have higher risk of MetS compared to HIV negatives (Calza et al., 2019; Hansen et al., 2009; Idiculla et al., 2018; Krishnan et al., 2012; Maseko & Masuku, 2017; Nolan et al., 2017).

In Ghana, a study conducted by Obirikorang et al. (2016) found an extremely high prevalence of MetS among PLHIV on ART (29.6%-61.6%) compared with 15.1% to 26.9% in SSA (Todowede et al., 2019) and the global pooled prevalence range of 16.7% to 31.3% (Nguyen et al., 2016). This prevalence was also higher compared to healthy adults that were found in a systematic review and meta-analysis of studies carried out in Ghana [6.0%-21.2%] (Ofori-Asenso et al., 2017).

Lifestyle factors (alcohol intake, smoking habit, exercise, etc), socio-demographic factors (age, sex, ethnicity, occupation, etc), the HIV itself and ART history including ART duration have been shown to increase the risk of MetS among PLHIV.

Persons with MetS have been found to be about two times and three times more likely to die or experience cardiovascular disease or stroke respectively compared to persons without the condition. They are also about five times more likely to develop type 2 diabetes mellitus (International Diabetes Federation, 2015) which is currently the major cause-specific mortality among PLHIV in addition to liver related diseases. Metabolic syndrome has also been associated

with various cancers including breast, pancreatic, colon and liver cancer (O'Neill & O'Driscoll, 2015).

Additionally, although the toxicities of the ARTs (include MetS) have also been acknowledged in the Consolidated Guidelines for HIV care in Ghana, PLHIV are not routinely screened for them to ascertain its burden in Ghana. This is evident in a preliminary assessment in five ART centres in Accra which showed that the centres are not adhering to the baseline assessments or tests to be carried out before the ART initiation and the routine checks after initiation. This implies that PLHIV who may have MetS before or after the initiation of ART may be missed. These patients may be inappropriately managed thus increasing their risk of major complications associated with MetS.

Thus, this study generated knowledge about the burden and characteristics of MetS in HIV-infected patients on DTG and possible related risk factors. It also determined and classified cardiovascular disease risk score and determined the challenges in adhering to the baseline assessment before ART initiation and routine assessment after initiation.

1.3 Conceptual framework

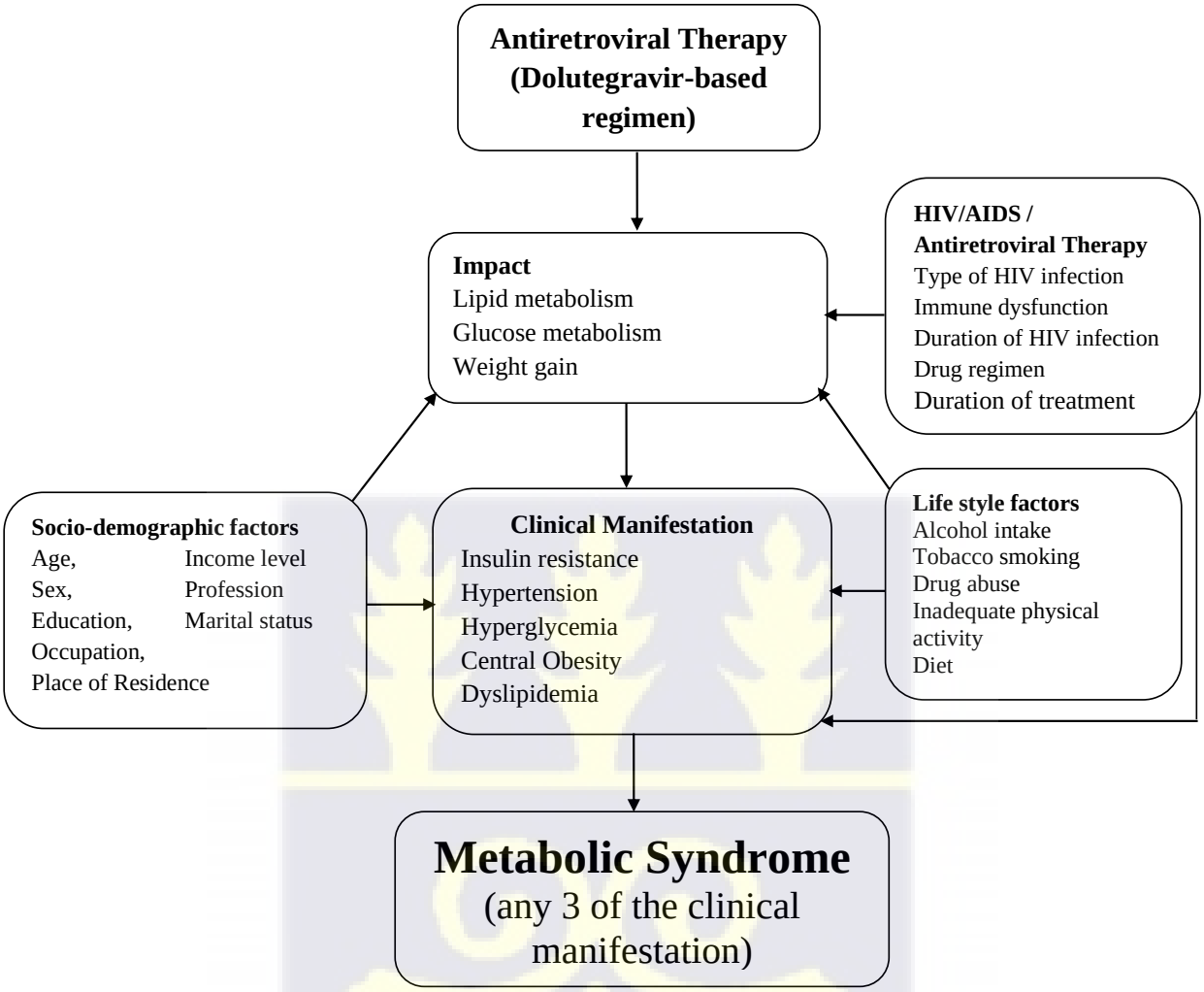


Figure 1. 1: Conceptual framework showing the relationship between various factors and the development of metabolic syndrome among HIV-infected patients

From figure 1.1, the intake of dolutegravir-based regimen influences several biological and physiological processes that can contribute to the development of metabolic syndrome. The use of DTG has been associated with significant weight gain particularly when visceral fat is involved. This may lead to central obesity which is a known risk factor for metabolic syndrome. Evidence suggests that DTG may affect lipid profiles which may alter triglyceride levels, LDL cholesterol levels and HDL levels (Kaur, 2014). This may contribute to dyslipidemia, a key component of

metabolic syndrome. DTG may also influence insulin secretion. This can increase the risk of insulin resistance or type 2 diabetes leading to hyperglycemia, a component of metabolic syndrome (Maseko & Masuku, 2017). Weight gain and insulin resistance associated with DTG use can also indirectly increase blood pressure which is another component for metabolic syndrome (Calza et al., 2019). The association between DTG use and metabolic syndrome can vary depending on some factors. Socio-demographic factors (age, gender, ethnicity, etc) may mediate the effect of DTG on metabolic outcomes. Lifestyle Factors (diet, physical activity, etc) can amplify or mitigate the metabolic effects of DTG. Longer duration of DTG use is also associated with a higher risk of metabolic changes (van Wyk et al., 2021). HIV itself can also cause lipid abnormalities including high triglycerides and decreased total cholesterol and high-density lipoprotein cholesterol. This is as a result of damage to the cells of the blood vessels which promotes atherosclerosis and causes immune dysfunction as a result of the reduction in the level of $CD4^+$ T-cells and other immune function cells (Maseko & Masuku, 2017).

1.4 Justification

Non-communicable diseases are major public health concern in many developing countries, and it has also been known that serious co-morbidities are likely to occur among PLHIV than in the general population. As Ghana strives to achieve health for all through the Sustainable Development Goals (SDGs), there is the need to ascertain the prevalence and incidence of MetS among PLHIV in the country to help throw more light on the burden. This will highlight the importance of strengthening the implementation of MetS screening with a defined diagnosis, integrating HIV/AIDs and NCDs interventions and enforcing the need for routine checks for co-morbidities among PLHIV. Preventing this will reduce the double burden of infectious and NCDs

in Ghana so not to add more constraints to the poor environmental conditions and our weak health systems.

An evaluation of the factors associated with MetS among PLHIV and an estimation of CVD risk score in the Ghanaian population is also very important. This will help define the scope of the problem, characterise the burden of CVDs among PLHIV and understand the impact of modifiable risk factors. Outcomes of this study will help identify individuals with early signs of MetS who could benefits from interventions to prevent or delay the onset of further complications.

With the introduction of DTG-based regimen in this era of Test & Treat and also in the context of an unfolding epidemiological transition with increasing burden of non-communicable diseases including the incidence rate of MetS with its related risk factors (especially obesity), outcomes of this study will identify the risk of metabolic complications due to DTG-based regimen to help plan health systems and formulation of policies. It will also help in policy implementation and practice.

Results will help understand the risk and impact of MetS and its components among HIV patients to identify optimal models of care to address this MetS challenge as PLHIV are growing older with medications which will eventually improve their wellbeing and prevent them from dying from NCD-related causes. Assessing adherence to the guidelines will also help identify the bottle necks and establish measures to improve them.

1.5 Hypothesis

- **H_0:** The risk of MetS and its subcomponents among PLHIV switching to TDF+3TC/FTC+DTG is the same among those starting on TDF+3TC/FTC+DTG regimen.

- **H_1:** The risk of MetS and its subcomponents among PLHIV switching to TDF+3TC/FTC+DTG is higher than those starting on TDF+3TC/FTC+DTG regimen.

1.6 Objectives

1.6.1 General Objective

To determine the incidence of MetS and its subcomponents and to evaluate the relationship between dolutegravir use and other risk factors with MetS development among PLHIV in the Greater Accra Region.

1.6.2 Specific Objectives

1. To determine the incidence of metabolic syndrome and its components among HIV-infected patients at the Tema General Hospital.
2. To determine whether treatment on dolutegravir-based regimen increases the risk of developing metabolic syndrome among those starting and those switching from efavirenz-based regimen.
3. To determine the risk factors associated with metabolic syndrome among HIV-infected patients.
4. To determine and classify cardiovascular disease risk score for HIV-infected patients.
5. To assess the level of adherence and challenges to the baseline assessments before the ART initiation among health facilities providing comprehensive HIV care to HIV-positive patients in Greater Accra Region.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome

Acquired Immunodeficiency Syndrome is caused by the Human Immunodeficiency Virus. This occurs in the advanced stage of HIV infection. Depending on the individual, it takes about 2 to 15 years to develop. The HIV infection gradually destroys the immune system by destroying the $CD4^+$ receptor white blood cells which protects the body against infection. Individuals infected with the HIV progressively become immunodeficient as the virus destroys and impairs the function of the immune cells which results in increased susceptibility to a wide range of opportunistic infections, cancers and other diseases that healthy immune systems can fight off.

2.1.1 Background to HIV/AIDS

Even though HIV is believed to have originated in Kinshasa in the Democratic Republic of Congo in the 1920s, the number of people infected with HIV or developed AIDS was unknown till the 1980s (AVERT, 1999). AIDS was recognised as a new disease in 1981 by the Centres for Disease Control and Prevention (CDC) when a rare form of lung infection called *Pneumocystis carinii pneumonia (PCP)* (currently known as *pneumocystis jiroveci*) and other opportunistic infections were reported in homosexual men (Centres for Disease Control (CDC), 1981). Several similar immune deficiency syndromes were reported afterwards in 1982 and that was when the CDC first used the term AIDS describing it as "a disease at least moderately predictive of a defect in cell mediated immunity, occurring in a person with no known case for diminished resistance to that disease" (Centres for Disease Control and Prevention (CDC), 1982). In 1983, a group of doctors

led by Luc Montagnier who worked at the Pasteur Institute in France identified a new retrovirus as the causative organism of AIDS called Lymphadenopathy-Associated Virus (LAV) (Popovic et al., 1983). Another group working with the National Cancer Institute also confirmed AIDS as being caused by retrovirus Human T lymphotropic virus type III (HTLV-III) which is similar to the LAV in 1984 (Marx, 1984). This was followed by series of consultations and discussions among various scientists and doctors until the virus was renamed as the Human Immunodeficiency Virus in 1986 instead of HTLV-III or LAV by the International Committee on the Taxonomy of Viruses as the main causative virus for AIDS (Case, 1986).

2.1.2 HIV Life Cycle and Pathogenesis

HIV is a retrovirus that contains ribonucleic acid as its genetic material. HIV upon entering the cells uses a special enzyme called reverse transcriptase to transcribe its RNA into deoxynucleic acid (DNA). The pathogenesis of HIV infection is mainly attributable to the decrease in a specific lymphocyte (T cells) number which bear the $CD4^+$. HIV uses $CD4^+$ immune cells to replicate itself which lasts between 1 to 2 days (World Health Organization (WHO), 2018). There are seven stages of the HIV lifecycle namely the binding, fusion, reverse transcription, integration, replication, assembly and budding as shown in figure 2.1 (AIDSinfo, 2019).

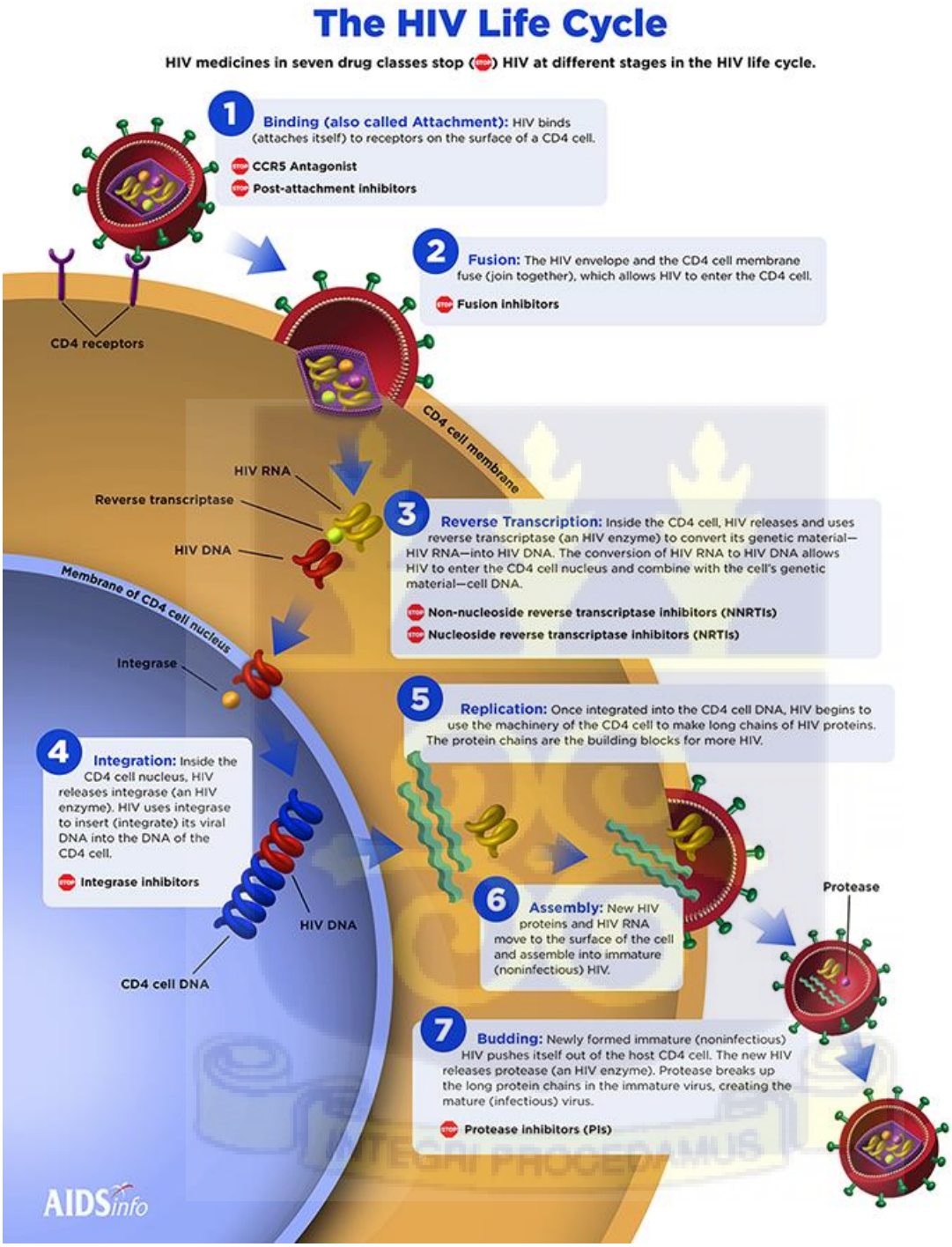
The single-stranded positive-sense enveloped HIV RNA infiltrates into the target cells of the human body ($CD4^+$ T-lymphocytes). The viron envelope glycoprotein (gp41 and gp120) on the outer surface of the HIV then binds with the chemokine co-receptors beta-chemokine receptor or the alpha-chemokine receptor. The HIV then loses its outer shell and is absorbed into the main body of the cell leaving the viral capsid with HIV and three key enzymes (reverse transcriptase (RT), integrase and protease) in the cell which the HIV uses to replicate. The enzyme RT reverse-

transcribes the single strand viral RNA into a double-stranded DNA to suit that of the human DNA. The new double-stranded viral DNA enters the central nucleus of the hosts $CD4^+$ cells and integrates into the host's cellular DNA by the viral enzyme integrase. After integration into the host's DNA, the virus takes over the human cells cellular functioning and dictates its replication activity. The virus at this stage either becomes latent and avoid detection together with its host cell from the host's immune system or becomes active and starts transcription (HIV i-Base, 2019).

During transcription, the virus is transcribed through messenger RNA (mRNA) encoding for viral proteins and the assembling of the Gag and Gag-Pol multi-protein complexes. This is then translated into infectious viral RNA which buds off from the cell membrane surface into the extracellular fluid or the blood stream to infect other healthy $CD4^+$ cells. The protease enzyme is involved in this cutting and assembling process (Reyskens & Essop, 2014). The HIV moves from one $CD4^+$ cell to another using the hybrid spreading mechanism (Zhang & Yew, 2015). Also, during HIV replication, it is prone to making small genetic mistakes or mutations as a result of transcription error by the RT resulting in viruses that vary slightly from each other. This ability to create minor variations allows HIV to evade the body's immunologic defences leading to lifelong infection, and also made it difficult to make an effective vaccine (World Health Organization (WHO), 2018).

The viral replication continues rapidly after infection when the virus has gained ground through infection of the lymphoid tissues (Moir et al., 2011). There is also intense production of inflammatory cytokines and chemokines during this early stage of infection which is in contrast with the activities of other viral infections (Maartens et al., 2014). HIV is thus characterised by the combined effect of reduced $CD4^+$ T-cells production and continuous destruction of their

subtypes (T-helper-17 cells and mucosal associated T-cells) needed for bacterial defence (Cosgrove et al., 2013).



Source: (AIDSinfo, 2019)

Figure 2. 1: HIV life cycle and target antiretroviral drugs at the various stages

2.1.3 Stages of HIV Infection

HIV infection advances in three different stages without treatment and getting worse over time. These are the Acute HIV infection, Chronic HIV infection and AIDS. The acute HIV infection is the immediate stage of HIV infection which mostly develops within 2 to 4 weeks after infection with HIV. During this stage, HIV multiplies rapidly and spreads throughout the body attacking and destroying the infection fighting $CD4^+$ cells of the immune system. This increases the level of HIV in the blood thus increasing the risk of HIV transmission as well. Infected individuals experience flu-like symptoms such as fever, headache, sore throat, nausea and rash (AIDSinfo, 2019).

The second stage of HIV infection is the chronic HIV infection also known as asymptomatic HIV infection or clinical latency stage. HIV continues to multiply at very low levels in the body at this stage. Even though it is still possible to transmit HIV to others during this stage, people who adhere to ART intake maintain an undetectable viral load and at no risk of transmitting HIV to an HIV-negative partner through sex. Most people at this stage may not experience any symptoms. In the absence of ART, the chronic HIV infection usually advances to AIDS in 10 years or longer, whiles in some people it advances faster (AIDSinfo, 2019).

The final and most severe stage of HIV infection is AIDS which is diagnosed by a $CD4^+$ count of <200 cells/mm^3 or if they have certain opportunistic infections. They also experience the symptoms that occur at the early stage of infection. Persons with AIDS have very high viral load and can easily transmit HIV to others. People with AIDS typically survive about 3 years without treatment (AIDSinfo, 2019).

2.1.4 HIV Infection Classification

In 2005, the WHO developed an interim clinical staging of HIV/AIDS to facilitate the scale-up of access to antiretroviral therapy in the African Region which was later finalised after several consultations with Member States in all WHO regions (World Health Organization (WHO), 2005). This is designed to assist in clinical management of HIV especially in resource-limited settings where there is limited laboratory capacity. The clinical staging is used after HIV infection has been confirmed by serological and/or virological evidence. Individuals at this stage (primary HIV infection) are asymptomatic and may have acute retroviral syndrome (World Health Organization (WHO), 2007).

The WHO system categorises patients into one of four hierarchical clinical stages (stage 1 to stage 4) when they demonstrate at least one clinical condition in that stage's criteria. These categories apply to adults and adolescents aged 15 years and older. A modified version of the WHO Clinical Staging System is also available for infants and children under 15 (WHO, 2005).

- Stage I: Infected individuals who are asymptomatic or have persistent generalized lymphadenopathy (PGL) of at least two sites excluding inguinal for longer than 6 months (Weinberg & Kovarik, 2010).
- Stage II: This is a mildly symptomatic stage where infected individuals may demonstrate several clinical manifestations. This includes unexplained weight loss of <10% of total body weight and recurrent respiratory infections (such as sinusitis, bronchitis, otitis media, and pharyngitis). They may also have a range of dermatological conditions including herpes zoster flares, angular cheilitis, recurrent oral ulcerations, papular pruritic eruptions, seborrheic dermatitis and fungal nail infections (WHO, 2005).

- Stage III: A moderately symptomatic stage where additional clinical manifestations may appear as the disease progresses. Those classified as belonging to this stage may have a weight loss of >10% of total body weight with a prolonged (more than 1 month) unexplained diarrhoea, pulmonary tuberculosis and severe systemic bacterial infections (pneumonia, pyelonephritis, empyema, pyomyositis, meningitis, bone and joint infections, and bacteraemia). They may also have mucocutaneous conditions such as recurrent oral candidiasis, oral hairy leukoplakia and acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis (WHO, 2005)
- Stage IV: The WHO clinical stage 4 is the severely symptomatic stage and an infected individual at this stage is said to have AIDS. Clinical manifestations for this stage that allow presumptive diagnosis of AIDS to be made includes HIV wasting syndrome, Pneumocystis pneumonia (PCP), recurrent severe or radiological bacterial pneumonia, extrapulmonary tuberculosis, HIV encephalopathy, central nervous system (CNS) toxoplasmosis, chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration), esophageal candidiasis and Kaposi's sarcoma (WHO, 2005).

2.1.5 Immunological Staging of HIV Infection

Even though the clinical staging alone can be used to determine the severity of the HIV infection, the $CD4^+$ count can also be used in conjunction with it to determine the degree of immunosuppression as shown in Table 2.1. This will support and reinforce the clinical decision-making.

Table 2. 1 CD4+ levels in relation to the severity of immunosuppression among adults (>15years)

HIV-associated immunodeficiency	**$CD4^+$ count**
None or not significant	>500/mm^3
Mild	350−499/mm^3
Advanced	200 −349/mm^3
Severe	<200/mm^3

Source: WHO, 2005

2.1.6 HIV Types

There are two main types of HIV namely HIV-Type 1 (HIV-1) and HIV-Type 2 (HIV-2). HIV-1 which is believed to have been discovered first is the most widespread accounting for around 95% of all infections worldwide whiles the HIV-2 is estimated to be more than 55% genetically distinct from HIV-1. HIV-2 is most common in West Africa and is slowly starting to appear in other regions, including the United States, Europe and India. It is also less infectious and progresses more slowly than HIV-1 which results in fewer deaths (Esbjörnsson et al., 2018). As a result of mutation, there are several genetically distinct HIV subtypes within the two main types.

Four groups of HIV-1 strains have been isolated that is M, N, O and P. Groups N, O and P are quite uncommon with group O representing 5% of all HIV infections in most West and Central African countries. Group M is the major group which is the cause of the major global HIV epidemic and is also characterised by nine genetically distinct subtypes of HIV-1. These are subtypes A, B, C, D, F, G, H, J and K. Subtype B is the most dominant among the Americas, Western Europe and Australasia and also represent 12% of global HIV infections whiles the

subtype C is the most commonest type found in Southern Africa, as well as in the horn of Africa and India and also accounting for 50% of HIV-1 infections worldwide (AVERT, 2018).

HIV-2 is made up of seven subtypes namely A, B, C, D, E, F, G with subtypes A and B being the most dominant among individuals infected with HIV-2 (NAM AIDSMAP, 2019). HIV-2 is less transmissible than HIV-1. Mother-to-child HIV transmission of HIV-2 is about 20 to 30 times lower than HIV-1 (Ingole et al., 2013). Individuals infected with HIV-2 tend to have a lower viral load than people with HIV-1 (Campbell-Yesufu & Gandhi, 2011).

2.1.7 HIV Transmission

HIV is transmitted through certain body fluids such as blood, semen, pre-seminal fluids, rectal fluids, vaginal fluids and breast milk from one person to another. This transmission is through three main routes namely, unprotected sex (including anal sex), contaminated blood transfusions and hypodermic needles and mother-to-child transmission during pregnancy, childbirth or breastfeeding (AIDSinfo, 2019).

2.1.7.1 Sexual intercourse

Having unprotected sex either anal or vaginal is the most frequent mode of HIV transmission especially among heterosexuals who are responsible for nearly 70% of HIV-1 infections worldwide (Shaw & Hunter, 2012). The risk of HIV infection through anal sex is estimated at 1 in 3 exposures which is higher than 1 in 10 exposures for vaginal sex (Powers et al., 2008). Although there is little to no risk of getting HIV from oral sex, it is theoretically and biological plausible (Centers for Disease Control and Prevention (CDC), 2019a; Patel et al., 2014). Risk factors that increase sexual transmission of HIV includes genital ulcer disease, HIV disease stage, anal

intercourse, high viral load, multiple sexual partners and presence of other sexually transmitted infections (Hughes et al., 2012; Maartens et al., 2014; Patel et al., 2014) whereas factors that decrease risk are use of antiretrovirals for treatment, pre-exposure prophylaxis, male condom use and male circumcision (Baeten et al., 2012; Davis & Weller, 2006; Fernando, 2018; Sharma et al., 2018; Weller & Davis-Beaty, 2002). It has also been estimated via systematic review that the use of antiretroviral treatment together with condom use could reduce HIV transmission by up to 99.2% (Patel et al., 2014).

2.1.7.2 Contaminated blood/ blood products

Even though is quite rare for one to be infected with HIV through contaminated blood or blood products (such as organs or tissues) due to effective screening, HIV can still be transmitted from one person to another. This can occur when a person receives HIV-contaminated blood in a blood transfusion, exposed to needles that are contaminated with HIV-infected blood during intravenous drug usage, injured with blood-contaminated needles, syringes, razor blades or other sharp instruments or use of unsterile razors, knives, needles or other instruments for cultural practices [circumcision, scarification, or bloodletting] (Health24, 2016). After HIV infection through skin exposure to HIV-infected blood, the average risk of infection is about 0.3% with the needle stick injury been approximately 0.37% (Health24, 2016).

2.1.7.3 Mother-to-child transmission

Mother-to-child transmission (MTCT) also known as vertical transmission can occur before, during or after birth and it accounts for 90% of childhood HIV infection (Coutsoudis et al., 2010). The child may be at risk of infection from the mother through various mechanisms including

maternal disease state, immunologic status and viral load, foetal exposure to infected maternal body fluids during gestation and delivery, and breastfeeding (Newell, 1998). The risk of perinatal HIV transmission without ART varies between 15% and 45% depending on maternal risk factors and whether breastfeeding is practiced (John & Kreiss, 1996). Several studies have shown that maternal plasma and breast milk viral load are the most important risk factors for MTCT of HIV (Connor et al., 1994; Jackson et al., 2003; Jamieson et al., 2003; John et al., 2001; Shaffer et al., 1999). The implementation and application of strategic interventions (early screening of pregnant women for HIV and HIV medicines) for prevention of mother-to-child transmission of HIV during pregnancy, delivery and breastfeeding over the years has reduced the rate of transmission to 1% or less in some countries like United States and Europe (AIDSinfo, 2019).

2.1.8 HIV/AIDS Epidemiology Worldwide

The epidemic of HIV infection in the early 1980s has gradually increased the disease burden in most countries especially in the developing countries where there is limited resource. Thus, HIV/AIDS is now considered a major global public health issue and the "single greatest reversal in human development" in modern history (Maartens et al., 2014). Globally, HIV was the leading cause of disability-adjusted life years (DALYs) among people aged 30-44 in 2010 and the fifth (5^{th}) leading cause for all ages. It also accounted for 2.8% of global deaths. This distribution of HIV/AIDS burden is not equal across demographics and regions (Ortblad et al., 2013).

In 2022, about 39 million people were living with HIV of which 1.5 million were children under 15 years globally. Of the 37.5 million who were adults (15+ years), majority were women (53%). This global HIV epidemic is disproportionately concentrated in sub-Saharan Africa (SSA) where 66% of the estimated 39 million people living with HIV reside which is an increase from 61% in

2018 (Joint United Nations & Programme on HIV/AIDS, 2023; UNAIDS, 2019). Also, young women aged 15–24 years are two times more likely to be living with HIV than men in SSA. HIV/AIDS being the leading cause of morbidity and mortality in sub-Saharan Africa, its socio-economic impact is enormous especially in countries with high prevalence (UNAIDS, 2019).

Over the years, the incidence of HIV infections and AIDS-related mortality has been declining. Between 1995 and 2022, the incidence of HIV infections had reduced by 59%. Similarly, the number of new HIV infections for all ages has decreased globally by 38% from 2.1 million in 2010 to 1.3 million in 2022 (Joint United Nations & Programme on HIV/AIDS, 2023). Most of these new HIV infections in 2022 were among key populations (sex workers, people who use drugs, gay men and other men who have sex with men, transgender people and prisoners) and their sexual partners (Joint United Nations & Programme on HIV/AIDS, 2023). An estimated 660 000 new infections were also accountable to SSA in 2022. Four in five of these new infections were among adolescent girls and young women aged 15–24 years (Joint United Nations & Programme on HIV/AIDS, 2023).

As in the case with incidence of HIV infection, there was a 51% reduction in AIDS-related death between 2010 and 2022 and 69% between 2004 and 2022 globally (Joint United Nations & Programme on HIV/AIDS, 2023). The global decline in AIDS-related mortality between 2010 and 2022 has largely been driven by progress in sub-Saharan Africa, especially eastern and southern Africa which is home to 53% of the world's people living with HIV. AIDS-related deaths declined by 58% from 2010 to 2022 in the eastern and southern Africa (Joint United Nations & Programme on HIV/AIDS, 2018; UNAIDS, 2019). By comparison, AIDS-related deaths in western and central Africa also declined by 53% from 2010 to 2022 (Joint United Nations & Programme on HIV/AIDS, 2023). There has also been a great decline in incidence-prevalence ratio over the years

from 11.2% in 2000 to 6.6% in 2010 and to 4.7% in 2022 globally (Joint United Nations & Programme on HIV/AIDS, 2023). This shows that huge progress has been made against the HIV/AIDS epidemic.

These reductions have been as a result of concerted efforts by all countries (global community) to end the HIV epidemic through the Millennium Development Goal 6 (Combat HIV/AIDS, malaria, and other diseases) and the recent Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages) which explicitly calls for the end of the HIV epidemic by 2030. The goal set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) fast-track strategy to diagnose and treat infected individuals by 2020 and 2030 has also markedly helped reduce both new HIV infections and AIDS-related deaths (Dwyer-Lindgren et al., 2019).

The large-scale expansion of antiretroviral therapy coverage has also improved survival among PLHIV causing a decline in number of new HIV infections and resulting in an overall increase in HIV prevalence since 2000 (Fettig et al., 2014). By the end of 2022, the number of people living with HIV accessing ART had increased from 7.7 million in 2010 to 29.8 million. This means that about 76% of all PLHIV were accessing treatment. Majority of pregnant women living with HIV (82%) had access to ART to prevent mother-to-child HIV transmission in 2022 which is similar (82%) to female adults (≥15 years), 72% of male adults (≥15 years) and 57% of children aged 0-14 years also accessed ART. Within SSA, 21 million PLHIV were receiving ART in 2022. In 2022, 86% of all PLHIV knew their HIV status of which 76% of them accessed treatment and 71% of those who accessed treatment were virally suppressed globally (Joint United Nations & Programme on HIV/AIDS, 2023).

Currently, PLHIV are dying from NCDs and tuberculosis (TB) co-infection. TB is the leading cause of death among PLHIV accounting for about one-third of all AIDS-related deaths. This is

because most PLHIV are unaware of their coinfection with TB or with other co-morbidities thus, are not receiving care and those without TB are also not taking the TB preventative therapy which has been shown to reduce the risk of developing TB and TB/HIV death rate by 40%. In 2018, it was estimated that 49% of PLHIV were unaware of their TB status (UNAIDS, 2019).

2.1.9 HIV/AIDS Epidemiology in Ghana

HIV/AIDS has been spreading in epidemic proportion since its identification in 1986 and recognising the potential impact that HIV/AIDS could have on the socio-economic development of the country, the National AIDS/STI Control Programme (NACP) was established in 1987. The NACP implement and coordinate the health sector's response to HIV/AIDS. In 2000, the Ghana AIDS Commission (GAC) was also established to effectively mobilize, manage and coordinate HIV/AIDS resources and activities being conducted by various organisations. Ghana AIDS Commission together with the NACP formulates policies on HIV care to reduce the burden of HIV/AIDS in the country.

HIV/AIDS epidemic in Ghana has had consistent prevalence of more than 1% in the general population over the years. In 2022, the prevalence of HIV was 1.66% which is lower than that of 2021 of 1.69% (National AIDS/STI Control Programme et al., 2023). Over the past decade, the national HIV prevalence has seen drastic fluctuations with some marginal decrease in the last three years. Even though HIV prevalence has been reducing from 2.9% in 2009 to 1.6% in 2014, there was a sharp increase to 2.4% in 2016 and 2018 and declined to 1.66% in 2022. Despite these increases, HIV prevalence in seven out of the ten regions shows a declining linear trend from 2009 to 2022. Eastern region recorded the highest prevalence (2.29%) with North East region recording the lowest (0.45%). (National AIDS/STI Control Programme et al., 2023).

In Ghana, the HIV prevalence estimates are derived from the HIV sentinel surveillance (HSS) which focuses on HIV testing among pregnant women seeking antenatal for the first time and patients newly diagnosed with sexually transmitted infections (STI) attending STI clinics in the sentinel sites. Although data from HSS is useful in monitoring trends in HIV levels, there are limitations. These limitations include the exclusion of information on HIV prevalence among males, non-pregnant women, women who seek antenatal outside the surveillance sites, etc. This does not give a good estimate to the HIV prevalence in the adult population. In line with this, the Ghana Demographic Health Survey (GDHS) in 2013 introduced an instrument to measure the ser-prevalence of HIV in the country. This population-based GDHS data is intended to improve the quality of annual HSS data so that trends in HIV infection can be measured accurately in the intervals between population survey (World Health Organization (WHO) & Joint United Nations Programme on HIV/AIDS (UNAIDS), 2000).

In 2022, there were 357,915 people living with HIV in Ghana of which 23,266 were children 14 years and below (National AIDS/STI Control Programme et al., 2023). The HIV prevalence reported by the UNAIDS in 2022 among adults (15-49 years) was twice as high in women (2.4) than in men (1.0). The HIV incidence per 1000 population (all ages) was 0.53 with incidence per prevalence ratio of 4.67 (UNAIDS, 2023). The percentage of new HIV infections has also declined by 27% from 2010 to 2022 whiles AIDS related death has also declined by 53% within the same period. Antiretroviral coverage in 2022 was 63%. In terms of achieving the 95-95-95 targets by 2030, 72% of all PLHIV knew their HIV status of which 63% of them accessed treatment in 2022 but data on those who accessed treatment and were virally suppressed was unknown (Joint United Nations & Programme on HIV/AIDS, 2023). This means that in the absence of adequate resource

to monitor the viral load of PLHIV and on the ART, the targets cannot be fully measured or achieved in Ghana.

NACP is also currently working with Global Fund and partners to implement the new funding model 3 (NFM3) activities towards attaining the 95-95-95 targets by 2030. The NFM3 is prevention-oriented to strengthen HIV & TB response. Various interventions have been put in place by NACP to accelerate the progress towards epidemic control. This include: enhancing onsite supportive supervision and mentorship; Scaling-up Differentiated Service Delivery (DSD) implementation and decentralization of ART to Prevention of Mother-To-Child Transmission (PMTCT) sites; engaging Regional Health Directorates and facility heads to improve ownership and oversight for HIV interventions at the sub-national level; Improve differentiated HIV care at the community level by sharing some tasks with the Community Health Workers such as Models of Hope, Community Adolescent Treatment Supporters (CATS) and Mentor Mothers; and also improve elimination of mother to child transmission interventions through lessons learnt from the conduct of the HIV positive babies' audits (National AIDS/STI Control Programme et al., 2023).

2.1.10 Therapeutic Management of HIV Infection

HIV infection has been managed over the years with the ARVs. These ARVs are grouped into seven main classes based on the stage of HIV cycle they interfere with. These are:

- Fusion inhibitors (FIs)/ Entry inhibitors: They interfere with the entry and fusion of the HIV into the target host cells. Thus, it prevents the formation of the "hairpin" structure needed for the fusion of the viron to the membrane of the host by attaching itself to the HIV envelop glycoprotein gp41. The monoclonal antibodies (mAbs) also block the HIV from entering the T-cell (AIDSinfo, 2019).

- Chemokine co-receptor antagonists (CCR5 antagonists): They are entry inhibitors which blocks proteins on the $CD4^+$ cells that are required for the virus to enter the target cell (AIDSinfo, 2019).
- Nucleoside and Nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs): The ARVs in this class act as DNA-chain terminators during the viron's reverse transcription process by targeting the enzyme used by the virus during the reverse transcription of viral RNA genome into genomic RNA (AIDSinfo, 2019).
- Non-nucleotide reverse transcriptase inhibitors (NNRTIs): These ARVs bind to a spot close to the enzyme's active site (allosteric site) and cause a conformational change in the active site (non-competitive inhibition) thus inhibiting the viron's reverse transcriptase enzyme (AIDSinfo, 2019).
- Integrase strand transfer inhibitors (INSTIs): They inhibits the viral enzyme integrase thereby interfering with the integration of the viral double-stranded DNA into the host's DNA (AIDSinfo, 2019).
- Protease inhibitors (PIs): Protease inhibitors interfere with the HIV replication activity by inhibiting the viral protease required for the assembling of the inner core (Gag and Gag-Pol multiprotein complexes) of viral proteins before they bud off from the cell surface as matured virus (AIDSinfo, 2019).
- $CD4^+$ post-attachment inhibitor: These ARVs prevent the HIV from entering certain immune cells thus also stops viral replication (AIDSinfo, 2019).

The management of HIV involves the continuous monitoring of immunological, virological and clinical parameters in PLHIV. The use of ARVs in ART since its introduction in 1990 has changed the natural history of HIV infection by preventing clinical progression to AIDS. Although

significant progress has been made towards ending AIDS as a public health threat, only 63% of PLHIV were receiving ART in 2022 (Joint United Nations & Programme on HIV/AIDS, 2023). In addition, the average life expectancy of PLHIV after diagnosis with HIV and adhering to appropriate treatment has increased over time. This increased from 10.5 years in 1996 to 22.5 years in 2005 and now approaching that of the general population (Harrison et al., 2010).

As a result of scientific evidence on the safety, efficacy and programmatic experience on the use of DTG, EFV 400 mg and Raltegravir (RAL), the WHO reviewed its 2016 guidelines in 2018 and updated it in 2019 to provide the new preferred option for ART regimen. They approved DTG, EFV 400mg and RAL in both first- and second-line ART for adults and adolescents including during pregnancy and tuberculosis co-treatment, and for children (World Health Organization (WHO), 2019). It also updated the use of ARVs for HIV post-exposure prophylaxis. These guidelines provide adequate information on DTG as the preferred ARV drug in first- and second-line regimens due to the declining estimate of neural tube defect risk among pregnant women (Phillips et al., 2020). WHO also recommends use of the integrase inhibitor dolutegravir in people who are currently on the old first-line ART regimen if they have a recent viral load measurement less than 1000 copies/mL (World Health Organization, 2018).

Dolutegravir supports once-daily dosing without the need for pharmacokinetic boosting due to its' unboosted and long plasma half-life (approximately 14 hours) properties (Walmsley et al., 2013). The dolutegravir-based regimens are associated with lower risk of development of major drug resistance mutations, leads to higher viral suppression, lower potential for drug–drug interactions and lower risk of discontinuing treatment compared with efavirenz-based regimens (Cottrell et al., 2013; Llibre et al., 2015). Dolutegravir therapy also has superior outcomes compared with a boosted protease inhibitor-based regimen in people starting second-line therapy with at least one

active nucleoside reverse transcriptase inhibitor (Brenner & Wainberg, 2017; Wainberg & Han, 2015). This reassurance comes at a time when pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTI) is increasing in low- and middle-income countries, creating demand for access to alternative non-NNRTI ARV drugs (World Health Organization (WHO), 2019).

Recommendations from WHO for first-line treatment include:

- Dolutegravir in combination with two NRTIs backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART.
- Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART.
- A raltegravir-based regimen may be recommeromnded as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available.
- RAL-based regimen may be recommended as the preferred first-line regimen for neonates.

Recommendations from WHO for second-line treatment include:

- DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.
- Boosted protease inhibitors in combination with an optimized NRTI backbone is recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing (World Health Organization (WHO), 2019)

Post-exposure prophylaxis (PEP) is a 28-day antiretroviral treatment that is administered after possible exposure to HIV through needle sticks, forced sex or rape and condom breakage which

reduces one's risk of infection significantly. This treatment should be started within two to 72 hours after the incident preferably within two hours as the sooner treatment with ART is started, the higher the chance of destroying the virus before it attaches itself to the cells (UNAIDS, 2018).

2.1.11 Antiretroviral Therapy in Ghana

Antiretroviral therapy was started in Ghana in 2003 which has reduced the burden of HIV-related morbidity and mortality over the years. The ART coverage in Ghana has been increasing over the years which has resulted in the reduction of new HIV infections especially among children (Ghana Health Service & National AIDS/STI Control Programme, 2019).

In order to keep up with the current global trends to advance HIV prevention, treatment, care and support, Ghana in August 2019, revised the 6th edition of the Guidelines for Antiretroviral Therapy to update the ART drug regimen which replaces Efavirenz with Dolutegravir as the preferred 1st line drug regimen for adults and adolescents. This new Consolidated guidelines for HIV care in Ghana include a multidisciplinary team approach to provide all-inclusive HIV care to improve quality of life and reduce HIV related morbidity and mortality.

The National HIV Strategic Plan and Health Sector Strategic Framework 2016-2020 in Ghana is also focused on preventing and managing HIV infection as per the UNAIDS' Fast-Track targets for 2020. This target aimed to ensure that 90% of PLHIV know their status of whom 90% will be on treatment with 90% having their viral loads suppressed. This they hoped will help in the reduction of both new HIV infections and deaths from AIDS-related illness to fewer than 500 000 globally (UNAIDS, 2018). Currently, they are working on achieving the 95-95-95 target by 2030 which is also focused on prevention and management of PLHIV to suppress their viral loads

through treatment. These targets do not emphasize the need to screen and treat the drug toxicities which includes metabolic syndrome components which is currently ravaging PLHIV.

2.1.11.1 Antiretroviral Initiation

HIV infection care requires lifelong therapy hence is essential to ensure the client is willing, ready and able to sustain therapy before the ART initiation. Treatment interruption can lead to development of drug resistance and increase the likelihood of transmission of a resistant virus. Hence, the new ART consolidated guidelines provides guide on evaluations to be performed before initiation of ARTs. These include complete physical examination, laboratory evaluation, comprehensive medical and social history to help identify past HIV related illnesses, current HIV related illness requiring treatment, and co-existing medical conditions which may influence the choice of therapy (Ghana Health Service & National AIDS/STI Control Programme, 2019).

The laboratory evaluation must be conducted within good clinical practice where it does not become a barrier to the ART initiation, urgent laboratory confirmations are carried out and opportunistic infections are treated first before the initiation. All these evaluations will also help confirm HIV infection and type; presence of pregnancy (for females) and opportunistic infections and co-morbid diseases (National AIDS/STI Control Programme et al., 2023).

The Medical History must include:

- Date of initial HIV diagnosis, type of HIV infection and HIV stage.
- Current symptoms and concerns including a symptom screen for tuberculosis and Hepatitis B and C.
- Past medical history including diagnosis of tuberculosis.
- Drug history including treatment for TB and Hepatitis B.

- Previous ARV exposure.
- Sexual history and past symptoms of STI.
- Obstetrics and Gynaecological history including family planning.
- Social history including family support systems and income.
- History of drug use.

The physical examination must comprise of:

- Client's weight and height
- Skin: Herpes Zoster (old scars and new lesions), Herpes simplex, Molluscum contagiosum, Kaposi's sarcoma, Pruritic Papular Dermatitis or Eruptions or Prurigo and Plane warts.
- Mouth: Oropharyngeal mucosa, Candidiasis, Oral hairy Leukoplakia, Gingivitis, Mouth ulcers and Kaposi sarcoma.
- Lymphadenitis/lymphadenopathy
- Respiratory (sinusitis, Otitis, pneumonia, TB) and Cardiovascular system (Cardiomyopathy)
- Genito-urinary system
- Gastrointestinal system (Oesophagitis, Diarrhoea).
- Anorectal area for discharge, ulcers, enlarged glands and growths.
- Nervous and musculo-skeletal systems including mental status, motor and sensory deficits.
- Fundoscopy whenever possible for retinitis or papilloedema and Cytomegalovirus (CMV) retinitis.
- Detailed examination of Genital Tract for discharge, ulcers, enlarged glands and growths.

The laboratory evaluation must include some baseline investigations as shown in Table 2.2.

Table 2. 2: Baseline Laboratory Investigations

Test	Type
Haematological test	Full blood count
Biochemical test	Blood Urea, Electrolytes and Creatinine, Liver Function tests, Fasting Blood Sugar, Cholesterol and lipid profile
Routine examinations	Urinalysis (Urine R/E) and Stool R/E
Respiratory examinations	TB screening, Gene Xpert, Chest X-ray
Serological Test	Hepatitis B Surface antigen
Immunological Test	$CD4^+$
These tests are performed depending on signs and symptoms	Histology on skin and lymph node, Biopsy, Kidney biopsy, Screening for STIs, Pap smear, HPV DNA, Abdominal Ultrasound

Source: National AIDS/STI Control Programme et al., 2019

The ARVs for HIV treatment are provided by the NACP but the laboratory tests are paid out of pocket with a subsidy from the National Health Insurance Scheme (NHIS). Even though NHIS covers a percentage of the cost of the test, some patients are not able to afford the top-up thus they start on the medication whiles they organise some funds to do the test later. The laboratory tests are not necessarily a prerequisite to start on the ARTs which can cause serious medical problems especially as most of the drugs affect the liver.

2.1.11.2 Recommended Antiretrovirals

The current consolidated guidelines for HIV care in Ghana is using the Test, Treat & Track strategy in accordance with UNAIDS 90/90/90 targets (National AIDS/STI Control Programme et al., 2019). Currently, the recommended ARVs in Ghana include the Nucleoside Reverse Transcriptase Inhibitors (Zidovudine (AZT/ZDV), Lamivudine (3TC), Abacavir (ABC), Emtricitabine (FTC)), Nucleotide Reverse Transcriptase Inhibitor (Tenofovir Disoproxil Fumarate (TDF)), Non-

Nucleoside Reverse Transcriptase Inhibitors (Nevirapine (NVP), Efavirenz (EFV)), Protease Inhibitors (Ritonavir boosted Lopinavir (LPV/r), Ritonavir boosted Atazanavir (ATV/r), Darunavir/r (DRV/r)) and Integrase strand transfer inhibitors (Raltegravir (RAL), Dolutegravir (DTG)) (Ghana Health Service & National AIDS/STI Control Programme, 2019).

The preferred formulation in Ghana is the triple fixed dose drug combinations which has been found to improve adherence to treatment. The drug combinations for adults including pregnant women (>20years); Adolescents including pregnant adolescents (10-19 years); HIV-1, Dual HIV-1 and HIV-2 infection; and HIV-2 infection is shown in Table 2.3. The first-line regimen is given to all HIV-positive patients who fit the treatment criteria. The second-line regimen is used when there is evidence of treatment failure with the first-line regimen after viral load monitoring. A third-line or salvage therapy is recommended for those who have failed second-line treatment. In consultation with a specialist, a baseline investigation including viral load and drug resistance testing will be done for the patient before the third-line treatment (Ghana Health Service & National AIDS/STI Control Programme, 2019).

Table 2. 3: ART Regimen for Adults (>20years) and Adolescents (10-19 years) - Including Pregnant Women)

	DRUG	COMMENT/CAUTION
First-line ART Regimen		
Preferred Regimen	TDF+3TC or FTC +DTG	• Caution with TDF in renal dysfunction. • DTG cannot be used with some anticonvulsants (such as carbamazepine) and should not be simultaneously administered with antacids, laxatives and multivitamin supplements because of the risk of chelation
Alternate Regimen	TDF+3TC or FTC +EFV	• Caution with TDF in renal dysfunction • Caution with EFV in liver disease • Discontinue EFV if severe agitation or psychosis occurs.
	ABC+3TC or FTC +EFV	• ABC is contraindicated in and hypersensitivity
Second-line ART Regimen		
First Alternative	AZT/ZDV + 3TC or FTC + LPV/r or ATV/r	• Use ABC if client: - not eligible for ZDV due to Hb <8g/dL or had a TDF-based first line - Hb is <8g/dL or drops >25% from the baseline value for a client started on ZDV as second line. • Use ZDV for clients who had ABC as first line • Use PI for clients who were on DTG as first line
Second Alternative	TDF + 3TC or FTC + DTG	• Use DTG for clients who were on EFV as first line • ZDV can be used in place of TDF for clients who had ABC as first line or have renal impairment so cannot use TDF
	TDF + 3TC or FTC + LPV/r or ATV/r	• Consider ABC if client has used TDF in first line and • ZDV is contraindicated due to Hb is <8g/ dL or Hb drops >25% from the baseline value for a client started on ZDV as second line
Third-line ART Regimen		
First Alternative	DRV/r + RAL + 1 or 2 NRTI	• If possible, consider optimization using genotyping before selecting 3rd line regimen. • DRV/r must be taken with food. • RAL can be taken with or without food for PI-experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily. • DTG can be used as 3rd line in place of RAL but should be taken twice daily
Second Alternative	DRV/r +2NRTIs ± NNRTI	• DRV/r must be taken with food in PI- experienced patients • DRV/r should be given 600mg/100mg twice daily • DTG can be used as 3rd line in place of RAL but should be taken twice daily

Source: Ghana Health Service & National AIDS/STI Control Programme, 2019

2.1.12 HIV Infection Prevention

HIV can be prevented through abstinence, condom use or through pre-exposure prophylaxis (PrEP) medication. PrEP is an HIV preventive method where people who do not have HIV but are at very high risk of getting HIV take HIV medicine daily to reduce their risk of getting HIV when exposed to the virus. Currently, the only U.S. FDA-approved medication for PrEP is a single pill under the brand name Truvada (a combination of two anti-HIV drugs, emtricitabine and tenofovir). PrEP is mostly prescribed to HIV-negative adults and adolescents who are at high risk for getting HIV through sex or injection drug use. This stops the HIV from establishing a permanent infection thus it is highly effective for preventing HIV when taken daily. Studies have shown that when PrEP is taken daily, it reduces the risk of getting HIV from sex by about 99% and at least 74% among people who inject drugs (Centers for Disease Control and Prevention (CDC), 2019b).

2.2 Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of three or more of the most debilitating heart attack risk factors (high blood glucose, abdominal obesity, high blood pressure, insulin resistance, low high-density lipoprotein cholesterol and high triglycerides). MetS is gradually becoming a major public and clinical health challenge in this new era of rapid urbanisation, globalisation, increased obesity and sedentary life styles (Kaur, 2014). People with MetS have a 5-fold and a 2-fold increase in developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) respectively as compared with those without (Alberti et al., 2009). It also directly increases the risk of all-cause mortality (Kaur, 2014).

2.2.1 Background of Metabolic Syndrome

Metabolic syndrome originated in 1920 when a Swedish physician named Kylin demonstrated the association between high blood pressure (hypertension), high blood glucose (hyperglycaemia) and gout (Kaur, 2014). This was followed by a description by Vague in 1947 who associated the metabolic abnormalities in cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) to visceral obesity (Vague, 1947). Later in 1965, Avogaro and Crepaldi described a syndrome comprising of hypertension, hyperglycaemia and obesity (Kaur, 2014). Reaven in 1988 also described "a cluster of risk factors for diabetes and cardiovascular diseases" and named it "Syndrome X" which contributed to the introduction of the insulin resistance concept (Reaven, 1988). He however excluded obesity and visceral obesity from the definition which was later added as a crucial abnormality (Kaur, 2014). This syndrome was renamed by Kaplan in 1989 as "The Deadly Quartet" to include upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension (Kaplan, 1989). It was again renamed "The Insulin Resistance Syndrome" in 1992 (Haffner et al., 1992) after which several groups have tried to develop diagnostic criteria for MetS diagnosis.

In 1998, the World Health Organization (WHO) provided a definition for MetS (Alberti & Zimmet, 1998) which was countered by the European Group for the study of Insulin Resistance (EGIR) in 1999. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) in 2001 also released its definition, followed by the American Association of Clinical Endocrinologists (AACE) in 2003. In order to ensure uniformity in the definitions, the International Diabetes Federation (IDF) proposed a new definition of the MetS in April 2005 (Kaur, 2014). The 2001 NCEP-ATP III definition was revised again in 2004 by lowering the

thresholds for central obesity and fasting glucose as well as including patients being treated for dyslipidemia, hyperglycemia, or systemic hypertension (Grundy et al., 2004).

This was subsequently modified again in 2005 by the American Heart Association in collaboration with the National Heart, Lung, and Blood Institute (Grundy et al., 2005). A harmonized consensus definition was later approved by the International Diabetes Federation, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity in 2009 (Alberti et al., 2009).

2.2.2 Definition of Metabolic Syndrome

Metabolic syndrome (MetS) is defined by a collection of interconnected biochemical, clinical, physiological and metabolic factors (Kaur, 2014). The most used criteria for defining MetS are from the WHO, EGIR, NCEP-ATP III, AACE and IDF. Even though all these definitions have similar features, they differ in several parameters which makes it difficult in terms of applicability, uniformity and positive predictive values of the definitions (Kaur, 2014). The AACE, WHO and EGIR definitions are dependent on insulin resistance. The measure of insulin resistance which is determined by an oral glucose tolerance test and hyperinsulinemic-euglycemic clamp is labour intensive (Ritchie & Connell, 2007) thus most studies in sub-Saharan Africa use the NCEP-ATP III and IDF definitions (Todowede et al., 2019). The definitions for the NCEP-ATP III and IDF use measurements and laboratory results that are readily available to physicians which facilitate their clinical and epidemiological application.

2.2.2.1 National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III

The NCEP-ATP III defines MetS as the presence of any three or more of the following: high blood pressure, high blood sugar, abdominal obesity, low HDL cholesterol and high triglycerides.

2.2.2.2 International Diabetes Federation (IDF)

The IDF definition for MetS was based on the NCEP-ATP III definition. It defines MetS as the presence of abdominal obesity and any two or more of the following: high blood pressure, high blood sugar, low High-Density Lipoprotein (HDL) cholesterol and high triglycerides (TG).

2.2.2.3 World Health Organisation (WHO)

The WHO defines MetS as a pathologic condition characterized by the presence of insulin resistance and any two or more of the following: high blood pressure, high blood sugar, abdominal obesity, low HDL cholesterol and high triglycerides.

2.2.2.4 European Group for the study of Insulin Resistance (EGIR)

The EGIR defines MetS as the presence of insulin resistance and any two or more of the following: high blood pressure, high blood sugar, abdominal obesity, low HDL cholesterol and high triglycerides.

2.2.2.5 American Association of Clinical Endocrinologists (AACE)

The AACE defines MetS as the presence of insulin resistance and any of the following: high blood pressure, high blood sugar, abdominal obesity, low HDL cholesterol and high triglycerides.

2.2.3 Diagnosis of Metabolic Syndrome

The diagnosis of MetS is the presence of three or more metabolic abnormalities based on the definition criteria used as shown in Table 2.4. Even though all the groups acknowledge the core components of the metabolic syndrome to be obesity, insulin resistance, dyslipidaemia and hypertension, it is difficult to decide which metabolic syndrome criteria to adopt in clinical practice. This is because each of the clinical measures used gives conflicting results based on the various definitions used. For instance, in the study by Turpin et al., (2008), none (0%) of the participants was found to have MetS when the WHO definition was used, although 10% were diagnosed to have MetS per the NCEP-ATPIII classification. Similarly, Gyakobo et al. (2012) found over 2-fold increase in MetS prevalence when the IDF definition was applied in contrast to the NCEP-ATP III classification. The existence of these multiple classifications makes precise estimation of MetS burden a difficult task. Thus, there is the need for countries to adopt specific diagnostic criteria to estimate the burden of MetS in their respective countries.

Table 2. 4: Diagnostic criteria proposed for the clinical diagnosis of the MetS

Clinical measures	**WHO (1999)**	**EGIR (1999)**	**AACE (2003)**	**NCEP-ATP III (2005)**	**IDF (2006)**
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity **Plus any 2**	Plasma insulin >75th Percentile **Plus any 2**	IGT or IFG **Plus any 2**	None **But any 3**	None
Body weight	Men: waist-to-hip ratio >0.90; Women: waist-to-hip ratio >0.85 or BMI > 30 kg/m2	Men: WC ≥94 cm Women: ≥80cm	BMI ≥ 25 kg/m2	Men: WC ≥ 102cm Women: ≥88 cm	Increased WC (population specific) **Plus any 2**
Lipids	TGs≥1.7mmol/L (150mg/dL) and/or HDL-C Men:<0.9 mmol/L (35 mg/dl) Women: <39 mg/ dL in women	TGs≥1.7mmol/L (150mg/dl) and/or HDL-C <39 mg/dL in men or women	TGs≥1.7mmol/L (150mg/dl) and/or HDL-C Men:<40mg/dL Women: <50mg/dL	TGs≥1.7mmol/L (150mg/dl) HDL-C Men<40mg/dL Women:<50mg /dL	TGs≥1.7mmol/L (150mg/dl) or on TGs Rx. HDL-C Men:<40mg/dL Women:<50mg/dL or on HDL -C Rx
Blood pressure	≥140/90mmHg	≥140/90mmHg or on hypertension Rx	≥130/85mmHg	≥130/85mmHg	≥130mmHg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	> 6.1 mmol/L (110 mg/dl), 2 h glucose > 7.8 mmol (140 mg/dl)	IGT or IFG (but not diabetes)	IGT or IFG (but not diabetes)	>110mg/dL (includes diabetes)	≥100mg/dL (includes diabetes)
Other	Microalbuminuria: Urinary excretion rate of >20mg/min or albumin: creatinine ratio of >30mg/g		Other features of insulin resistance		

Source: Kaur, 2014

The IDF recognising the challenges with the application of the WHO and NCEP-ATP III definitions to different ethnic groups in terms of obesity cut-off points, again proposed a new set of criteria with ethnic/racial specific cut-offs (Alberti et al., 2009) [Table 2.5]. This is evident that the different populations, ethnicities and nationalities have different distributions for body weight and waist circumference measures. It also identifies that the association between these

measurements and the risk of type 2 diabetes mellitus (T2DM) or CVD differs in different populations (Kaur, 2014).

Table 2. 5: Gender waist circumference cut-offs for different countries/ ethnic groups

Country/ Ethnic Group	**Waist circumference cut-off (cm)**	
	Male	**Female**
Europids NCEP-ATP III values (102 cm males; 88 cm females) are likely to continue to be used for clinical purposes in USA	≥94	≥80
South Asians (based on a Chinese, Malay, and Asian-Indian population)	≥90	≥80
Chinese	≥90	≥80
Japanese	≥90	≥80
Ethnic South and Central Americans	South Asians recommendation is used until more specific data are available	
Sub-Saharan Africans	European data is used until more specific data are available	
Eastern Mediterranean and Middle East (Arabs) population	European data is used until more specific data are available	

Source: Alberti et al, 2009

2.2.4 Epidemiology of Metabolic Syndrome worldwide

Metabolic syndrome as with all non-communicable diseases was mostly a problem in developed countries but with the rapid globalisation and the spread of western lifestyles, it is now a global disease of concern. The global prevalence of MetS ranges from <10% to as high as 84%, depending on factors such as the population studied, ethnicity, geographical region, urban or rural environment, gender, and the definition of MetS used (Kaur, 2014). Overall, it is estimated that 20-25% of the world's adult population have MetS and are also two times as likely to die from

heart attack and thrice as likely to have a stroke compared with people without the syndrome (International Diabetes Federation (IDF), 2006). The highest increase in prevalence occurs among young men (25–29 years) in less developed countries and also among urban dwellers (Saklayen, 2018). Also, the prevalence of MetS has been shown to increase with age and more prevalent in women than men. This means that countries experiencing an ageing population are likely to have higher prevalence. (Cameron, Shaw & Zimmet, 2004; Ford, Giles & Dietz, 2002). In Africa, the prevalence of MetS is also deemed to be increasing and more frequent in women and urban dwellers (Ofori-Asenso et al., 2017).

Although higher socioeconomic status, education, genetic background, smoking, family history of diabetes and obesity all influence the onset of MetS and its components (Cameron et al., 2004), the consumption of high calorie-low fibre fast food and physical inactivity due to increased use of automobiles, spending more time indoors watching TV or playing video games and sedentary life styles are the two basic driving forces increasing the prevalence of MetS (Centres for Disease Control, 2017). The total cost of MetS including the cost of health care and loss of economic activity is in trillions which needs concerted global, governmental and societal efforts to change the lifestyle that is promoting it (Saklayen, 2018).

2.2.5 Epidemiology of Metabolic Syndrome in Ghana

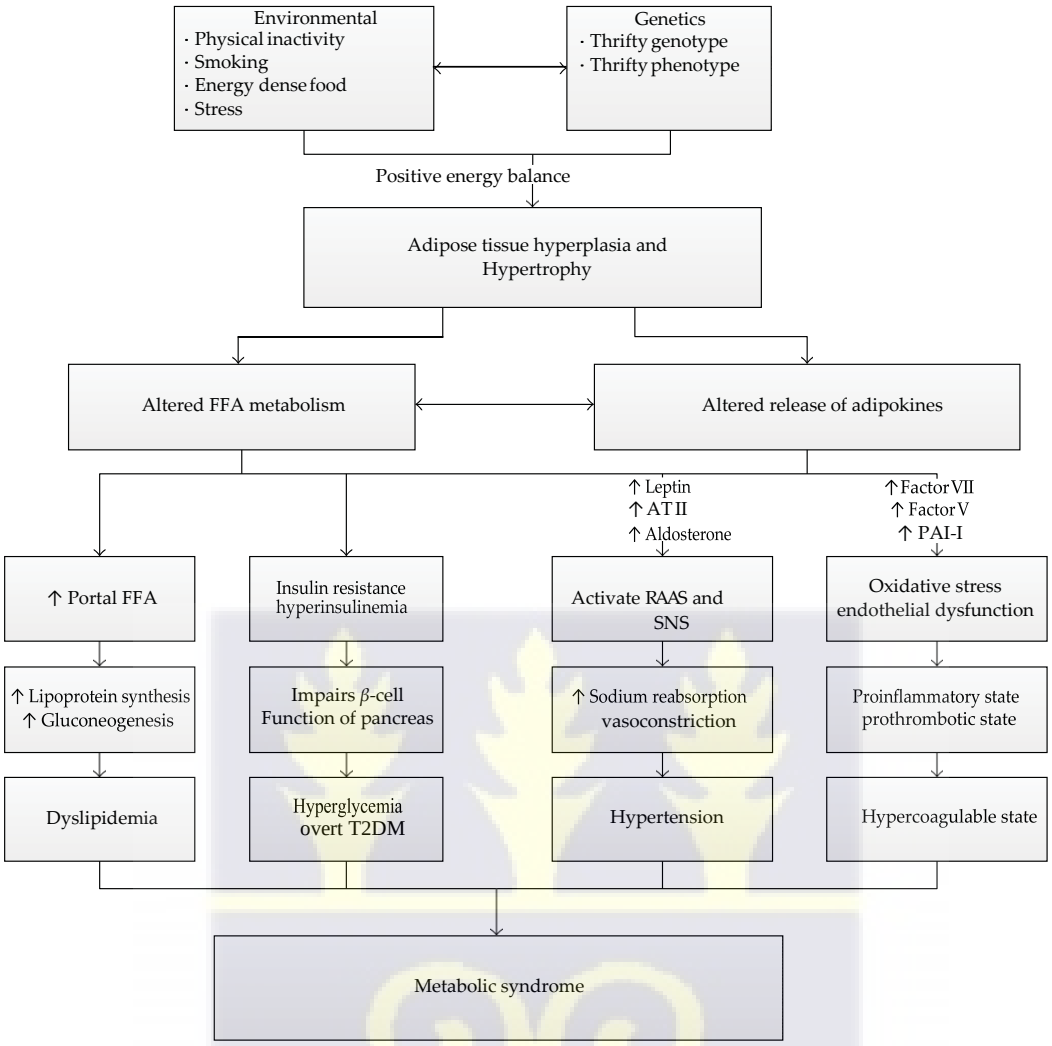
Even though the individual metabolic syndrome components have been extensively studied in Ghana, yet the burden of MetS is unknown (Ofori-Asenso et al., 2017). Currently, Ghana is also experiencing rapid epidemiological transition which could result in an escalation of metabolic disorders if this ongoing changes in lifestyle among the Ghanaian population is not addressed in time (Ofori-Asenso et al., 2017; Ofori-Asenso & Garcia, 2016). A systematic review conducted in

Ghana showed that, the prevalence of MetS among "healthy" Ghanaian adults is higher among women than men and ranged from 6.0%-21.2% using the NCEP-ATP III, WHO and IDF classifications. From the meta-analysis, the prevalence of MetS using the IDF classification was higher (21.2%) as compared to the NCEP-ATP III (12.4%) and WHO (6.0%) classifications. This shows a high prevalence of MetS in the population as compared to studies conducted in other countries thus the need for preventive measures to address the risk components of MetS such as obesity and hypertension which are rapidly rising in Ghana (Ofori-Asenso et al., 2017). The prevalence of metabolic syndrome among diabetics in Ghana in 2007 was reported at 55.9% by the NCEP-ATP III criteria and 10% by the WHO criteria which is higher than the healthy population (Titty et al., 2008).

Non-communicable diseases (NCDs) which are currently equally prevalent in the developing countries as in the developed ones, has a more devastating impact in developing countries. A 2018 WHO report identified CVDs and diabetes as accounting for 19% and 3% respectively of total deaths in Ghana in 2016 (World Health Organisation, 2018). Also, in Ghana and other countries in Africa, the prevalence of hypertension, diabetes mellitus, hyperlipidaemia and obesity which are all individual components of MetS is on the increase (Ofori-Asenso et al., 2017). In addition to this, it is estimated that by the year 2020, the number of deaths in Africa due to NCDs in general will exceed that due to communicable diseases (World Health Organisation, 2002). This impending epidemic is enough reason for the early institution of appropriate interventions to reduce the risk factors for MetS. Also, most studies conducted in Ghana did not address the association between identified risk factors for the development of MetS from other countries.

2.2.6 Pathophysiology of Metabolic Syndrome

The pathophysiology and pathogenesis of MetS occurs as a result of interaction between genetic and environmental/life style factors which is characterised by various complex underlying mechanisms including insulin resistance with fatty acid flux, chronic low grade inflammation and oxidative stress (Roberts et al., 2013). Visceral adiposity has been proven to be a primary trigger for most of the pathways involved in MetS, thus underscoring the importance of a high caloric intake as a major causative factor (Alberti, Zimmet, & Shaw, 2005). Insulin resistance, visceral adiposity, dyslipidaemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state and chronic stress appear to be the main players in the initiation, progression and transition of MetS that leads to CVD and T2DM (Kaur, 2014; Rochlani et al., 2017) as shown in Figure 2.2.



Source: Rochlani et al., 2017

Figure 2. 2: Pathophysiological mechanisms in metabolic syndrome. (FFA: free fatty acid, ATII: angiotensin II, PAI-1: plasminogen activator inhibitor-1, RAAS: renin angiotensin aldosterone system, SNS: sympathetic nervous system.).

2.2.6.1 Insulin Resistance

Insulin is a polypeptide hormone which is secreted by the beta cells of the pancreatic islet of Langerhans, and acts through glycoprotein receptors located in the main peripheral target tissues of the liver, skeletal muscle and adipocytes (McCracken et al., 2018). Insulin promotes glucose storage and inhibits gluconeogenesis and glycogenolysis. It stimulates genetic transcription of

enzymes involved in glycolytic and fatty acid synthetic pathways and directly inhibits transcription and the activity of the hepatic gluconeogenic enzymes (Kim et al., 2011).

The over secretion of insulin by the pancreatic beta cells (hyperinsulinemia) to maintain normal blood glucose concentration (euglycemia) as a result of excess circulating fatty acids released from an expanded adipose tissue mass produces a condition known as insulin resistance. This means that a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target and is driven by inappropriate lipolysis of excess fatty acids in the body (Aganović & Dušek, 2007). Even though hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, it may cause an overexpression of insulin activity in some normally sensitive tissues. The stress from insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of MetS (Gill et al., 2005).

Insulin resistance in adipose tissue impairs insulin-mediated inhibition of lipolysis which leads to an increase in circulating free fatty acids (FFAs). Thus, inhibiting the antilipolytic effect of the insulin. Free fatty acids inhibit protein kinase activation in the skeletal muscle resulting in a reduction in glycogen synthesis and glucose transport. It also increases protein kinase activation in the liver causing an increase in the production of glucose, triglycerides and secretion of very low-density lipoproteins (VLDL). This reduces the insulin signalling pathway's effectiveness which promotes the reduction in glucose transformation to glycogen and increased lipid accumulation in triglyceride (Aganović & Dušek, 2007; Boden & Shulman, 2002; Choi et al., 2010; Roberts et al., 2013).

The net effect is the creation of a hyper insulinemic state to maintain euglycemia which eventually fails and insulin secretion reduces. The FFAs are lipotoxic to beta cells of the pancreas thus also causing a decrease in insulin secretion (Tooke & Hannemann, 2000). The inability of the

pancreatic beta cells over time to produce adequate insulin to correct the worsening tissue insulin resistance leads to hyperglycaemia and overt T2DM (Petersen & Shulman, 2006).

Insulin resistance gives rise to the development of hypertension due to loss of the vasodilator effect of insulin and vasoconstriction caused by FFAs, the increased sympathetic activation and sodium reabsorption in the kidneys (Tripathy et al., 2003). Insulin resistance also causes an increase in serum viscosity, induction of a prothrombotic state and release of pro-inflammatory cytokines from the adipose tissue which contributes to increased risk of CVD (Juhan-Vague et al., 2003).

The binding of insulin to the insulin receptor (a ligand-activated tyrosine kinase) allows for physiological insulin signalling to occur resulting in a tyrosine phosphorylation of downstream substrates and activation of two parallel pathways: the Phosphoinositide 3-kinase (PI3K) pathway which also activates the protein kinase B (Akt) and the Mitogen activated protein (MAP) kinase pathway. Insulin resistance inhibits the PI3K-Akt pathway leading to a reduction in endothelial nitric oxide production. This results in an endothelial dysfunction and a reduction in Glucose transporter type 4 (GLUT4) translocation which leads to a decreased skeletal muscle and fat glucose uptake. Even though the PI3K-Akt pathway is affected by the insulin, the MAP kinase pathway is unaffected thus there is a continued endothelin-1 (ET-1) production (Kaur, 2014). Hence, an insulin resistance also leads to the vascular abnormalities that influence the development of atherosclerosis (Kaur, 2014). Even though clinically insulin-resistant individuals need not be obese, they however mostly have an abnormal fat distribution characterized by a major upper body fat (abdominal obesity). This pattern of abdominal obesity strongly correlates with insulin resistance and MetS than does lower body obesity (Kaur, 2014).

2.2.6.2 Abdominal Obesity

Obesity is not dependent on the amount of body weight but on the distribution of adipose tissue (body fat). Adipose tissue is a heterogeneous mix of adipocytes (specialized cells that play a crucial role in converting excess energy to storage compounds (triacylglycerol) to be used during food deprivation), stromal pre-adipocytes, immune cells, and endothelium which can respond rapidly to alterations in excess nutrient by increasing the cell size (adipocytes hypertrophy) or cell number [adipocytes hyperplasia] (Halberg et al., 2008).

The progressive increase of adipocytes reduces its blood supply which eventually also reduces the oxygen supply to the tissues known as hypoxia (Cinti et al., 2005). Hypoxia has been suggested to be the cause of dead cells or tissues and macrophage infiltration into adipose tissue which leads to an overproduction of biologically active metabolites called adipocytokines or adipokines. This includes glycerol, free fatty acids, pro-inflammatory mediators (tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6)), plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein [CRP] (Lau et al., 2005). The dysfunction of these adipocytokines results in a localized inflammation in adipose tissue that promote an overall systemic inflammation associated with the development of obesity. This is causally linked to a wide range of metabolic diseases (Cao, 2014; Trayhurn & Wood, 2004).

Visceral fat deposits also contribute to insulin resistance due to increased supply of FFAs to the liver through the splanchnic circulation by visceral lipolysis. Even though most obese individuals are insulin resistant, patients of normal weight with increased amount of visceral adipose tissue can also be insulin resistant known as metabolically obese normal-weight individuals (Aganović & Dušek, 2007; Rochlani et al., 2017).

2.2.6.3 Dyslipidaemia

Insulin inhibits the secretion of very low-density lipoproteins into the systemic circulation thus an insulin resistance causes an increased VLDL secretion by the liver which is associated with dyslipidemia (Ginsberg et al., 2005). This occurs via several means. Insulin suppresses lipolysis in adipocytes thus an impaired insulin signaling increases lipolysis which results in increased FFA levels. Free fatty acids serve as a substrate for the synthesis of triglycerides (TGs) in the liver and stabilize the production of apolipoprotein B (apoB) causing an excess production of VLDL. Also, insulin mostly degrades apoB via PI3K-dependent pathways thus insulin resistance directly increases VLDL production. Finally, insulin regulates the activity of lipoprotein lipase (rate-limiting and major mediator of VLDL clearance) hence, hypertriglyceridemia in insulin resistance is due to both an increase in VLDL production and a decrease in VLDL clearance (Kaur, 2014).

The TGs in VLDL are transported to high density lipoprotein (HDL) by the cholesterol ester transport protein in exchange for cholesteryl esters. This results in TG-enriched HDL and cholesteryl ester enriched VLDL particles. The TG-enriched HDL is cleared rapidly from the circulation since is a better substrate for hepatic lipase. This leaves fewer HDL particles to participate in a reverse cholesterol transport from the vasculature (Kaur, 2014). Insulin resistance causes an influx of free fatty acids to the liver which increases hepatic triglyceride synthesis and storage leading to high production of triglyceride which is secreted as VLDL associated with dyslipidemia (Aganović & Dušek, 2007). Consequently, the high level of triglycerides in the blood indicates insulin resistant condition which is one of the most important criteria used for metabolic syndrome diagnosis by the WHO, EGIR and the AACE groups.

2.2.6.4 Hypertension

The association between insulin resistance and hypertension has been well established by several studies. They suggest that both hyperglycemia and hyperinsulinemia activate the Renin angiotensin system by increasing the expression of angiotensinogen, Angiotensin II and the Angiotensin I receptor resulting in the development of hypertension especially among individuals with insulin resistance (Malhotra et al., 2001). Insulin is a vasodilator which increases sodium reabsorption in the kidney when administered intravenously to an individual with normal weight. Thus, in the presence of insulin resistance, the vasodilatory effect of insulin is disabled whereas the renal effect on sodium reabsorption is preserved. Hyperinsulinemia and insulin resistance may result in increased sympathetic nervous system (SNS) activation due to increased sodium reabsorption by the kidney, increased cardiac output by the heart which causes the arteries to respond with vasoconstriction which contribute to the development of hypertension (Morse et al., 2005). Fatty acids themselves can also mediate relative vasoconstriction (Aganović & Dušek, 2007). Hypertension is also frequently associated with several metabolic abnormalities such as obesity, glucose intolerance and dyslipidemia (Kaur, 2014).

2.2.6.5 Genetics

It has been shown that even though individuals might have very similar risk profile, their susceptibility and age of onset of obesity varies greatly. Some non-obese persons by traditional measures are also insulin resistant and have abnormal levels of metabolic risk factors. An example is seen in individuals with 2 diabetic parents or 1 diabetic parent and a first- or second-degree relative with diabetes (Kaur, 2014). In addition, individuals and ethnic variations also exist in the clinical trend of metabolic risk factors in obese or insulin resistant persons (Martin et al., 2003).

This suggests that there is an interaction between genetic and environmental factors (Ordovas, 2007). Thus, the expression of each metabolic risk factor is likely to fall under its own genetic control, which influences the response to different environmental exposures. For example, the worsening of dyslipidaemia among obese people is associated with a variety of polymorphisms in genes that affect lipoprotein metabolism (Laakso, 2004) and also, combination of a genetic predisposition to the malfunctioned insulin secretion with insulin resistance can raise the plasma glucose to abnormal levels (Poulsen et al., 2005).

In 1962, James Neel proposed the "thrifty-gene" hypothesis to explain the high prevalence of obesity, diabetes, MetS and its closely associated co-morbidities in modern times. According to the hypothesis, individuals i.e. obese and overweight individuals who have this "thrifty gene can store surplus energy that will have an evolutionary advantage during periods of harsh environmental conditions with unstable food supply (Neel, 1962). Thus, genetic selection would favour the energy-conserving genotypes during famine or unfavourable environmental conditions. However, the selected genetic variations that will be favoured during malnutrition will be vulnerable when there is excess food supply. This hypothesis assumes that the common genetic variants of thrifty genes predispose one to developing MetS.

Hales and Barker (1992) also introduced another thrifty phenotype hypothesis in 1992 which postulates that babies who experienced an intrauterine malnutrition may have adapted to a poor nutrition by reducing energy expenditure and becoming "thrifty." These metabolic adaptations increase their survival rate even if they are poorly nourished during childhood and adulthood. In the presence of an increased food intake, these adaptations are no longer beneficial but leads to an increased risk of MetS in the future. The associations between low birth weight and insulin

resistance and T2DM development later in life has been observed in several populations which supports this theory (Hales, Desai, & Ozanne, 1997).

2.2.6.6 Glucose Intolerance

The failure of insulin to suppress gluconeogenesis in the liver and to mediate glucose uptake in the muscle and adipose tissues during glucose metabolism causes an increase in insulin secretion to ensure euglycaemia. Defects in insulin secretion predominate and hyperglycaemia occurs if this compensation fails (Aganović & Dušek, 2007).

2.2.7 Metabolic Syndrome Prevention

Prevention of a disease is better than cure especially with a condition like MetS where its diagnosis has not been fully unified and also no medication has been found to treat the condition as a whole (Kaur, 2014). Implementing the required lifestyle interventions may prevent the development of MetS and its life-threatening outcomes of stroke, diabetes and/or cardiovascular disease. The introduction of some lifestyle modification plans like weight loss, diet and exercise can effectively prevent and reduce the burden of MetS.

This may include better urban planning to encourage active lifestyle. i.e. parks and pedestrian walkways can be created in urban areas during urban development plan by the governments. Restricting media advertisement of unhealthy food and educating the public about the health benefits of choosing healthy/ wholesome food over junks will also go a long way to prevent MetS. Civil societies groups can help this campaign by disseminating relevant issues (including promoting healthy lifestyle) and the awareness of the major impact of MetS on the overall health

to its communities through discussions, videos, drama, debates/lectures and the use of mass and social media.

Physical fitness and healthy diet culture should be encouraged during childhood to adulthood (Yamaoka & Tango, 2012). The consumption of whole grain product instead of refined carbohydrate will reduce the risk of developing MetS (Damsgaard et al., 2017). Governments should subsidize the consumption of whole grains, institute laws to barn the importation of fatty foods and increase the taxation on high calorie snacks or sugary foods. In New York City, Philadelphia and Mexico, a small tax was put on sugary drinks which effectively lowered the consumption of sugary drinks (Fletcher et al., 2015). Government can also help promote exclusive breastfeeding for every new-born and introduce good cooking practice lessons and basic nutritional knowledge (life skills) into the secondary level education so the future generation can discover the joy of cooking. This will make it easier to promote healthy diet among them.

Clinicians should continuously educate their patients about good eating habits and the need for adequate physical activity during routine visit which can go a long way in changing people's habit. Metformin which is a unique antidiabetic drug and mimics the effect of exercise can be used for MetS prevention especially those at high risk for developing MetS (Ruderman et al., 2013; Wu et al., 2017). As in the control of other epidemics, education of the population about the health hazard of the metabolic syndrome will be very important.

2.2.8 Metabolic Syndrome Treatment/ Management

Metabolic syndrome is currently driving the twin global epidemics of T2DM and CVD thus there is an urgent moral, medical and economic need to identify and manage those with the conditions

early to reduce their risk of subsequent diseases (Wong, 2005). Metabolic syndrome treatment comprises of the appropriate use of pharmacological agents to treat those whose risk factors are not adequately reduced with the preventive measures and lifestyle changes (Deen, 2004). The management of MetS is clinically difficult as there is no recognized method to improve the whole syndrome hence, most physicians treat each component of MetS separately (Kaur, 2014) with more emphasis on those components that are easily responsive to the drug treatment. For instance, it is easier to prescribe a drug to lower blood pressure, blood glucose or triglycerides rather than initiating a long-term strategy to change people's lifestyle hoping that they will eventually lose weight to help lower their blood pressure, blood glucose and triglycerides.

Physicians can follow the current treatment guidelines of the National Cholesterol Education Programme (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol Treatment in Adults (Adult Treatment Panel III), 2002), the American Diabetes Association (American Diabetes Association, 2005), the American Heart Association (Grundy et al., 2006), and the National Institute of Health Obesity Initiative (National Heart Lung and Blood Institute & National Institutes of Health, National Heart, Lung, and Blood Institute, 1998) for the treatment of MetS risk factors. They can also use the seventh Joint National Commission (JNC-VII) for blood pressure treatment to help lower the blood pressure aspect (Chobanian et al., 2003).

According to the Framingham score, all HIV positive patients should have their cardiovascular risk factors evaluated or non-invasive investigations of their cardiovascular risk be assessed before they are administered with the antiretrovirals. Blood tests for preventive cardiology (e.g. complete blood count to determine anaemia and/or other haematologic abnormalities, determination of serum electrolytes, assessment of renal and hepatic function, assessment of thyroid function)

should be routine before and during ART (every 3-6 months). Routine assessment of blood pressure in HIV-infected patients is important because these patients seem to be at higher risk of developing hypertension than the general population. Predisposing conditions including vasculitis, acquired glucocorticoid resistance, acute and chronic renal failure, and drug interactions should be carefully assessed. Before ART is started, lipid profiles should be measured after an 8-12 hour fast to establish a baseline, and the measurements should be repeated routinely during the ART therapy. Serum glucose and haemoglobin A1C measurements are especially indicated for patients on ART. Fasting lipids and glucose should be measured before the initiation of ART and at regular 3-6 months intervals thereafter (Ghana Health Service & National AIDS/STI Control Programme, 2019). For patients with elevated triglyceride levels at baseline, lipid measurements should be repeated within 1-2 months of starting ART (Barbaro & Iacobellis, 2009).

2.3 Metabolic Syndrome in PLHIV

As a result of the ART, HIV is now considered as a controllable chronic disease with HIV-infected individuals living longer. This has increased the risk of aging-related diseases like CVDs and T2DM in PLHIV including those with well controlled infection (Akl et al., 2017). These antiretroviral medications have been found to be associated with metabolic abnormalities including abnormal cholesterol, high blood sugar, insulin resistance and lactic acidosis. They also cause body shape changes as a result of abnormal distribution of fat (Montessori et al., 2004). The NRTIs are independently also associated with mitochondrial toxicity (Quercia et al., 2015).

2.3.1 Global Prevalence of Metabolic Syndrome in PLHIV

The global prevalence of MetS is not definite due to country-specific variations in MetS prevalence. This is as a result of the population and diagnostic criteria used. A meta-analysis of MetS prevalence involving 65 studies (Europe: 23, the Americas: 26, Africa: 9, Asia: 4, intercontinental: 3) across five continents comprising 55094 HIV-infected participants was conducted to estimate the global prevalence. The pooled prevalence of MetS was found to range from 16.7% to 31.3% which differed significantly by the various diagnostic criteria used (Kim A. Nguyen et al., 2016). The diagnostic criteria used to determine the MetS prevalence in this study was the NCEP-ATP III-2001, IDF-2005 and NCEP-ATP III-2004-2005 with overall prevalence rates of 16.7%, 18.0% and 24.6% respectively. The prevalence of MetS using the IDF criteria was significantly higher in women than in men and among those on ART than the ART naïve patients. There were also significant prevalence variations among the various age groups, smoking habits, duration of HIV diagnosis, severity of infection, NNRTIs use, regional studies and date of study publication (Kim A. Nguyen et al., 2016).

2.3.2 Prevalence of Metabolic Syndrome in PLHIV in sub-Saharan Africa

Sub-Saharan Africa bears an inordinate burden of HIV hence with improved ART coverage and treatment outcomes, the life expectancy of PLHIV has increased drastically hence increasing the number of PLHIV over time (UNAIDS, 2019). This longevity also exposes them to the risk of developing these lifestyles and age-related conditions like MetS. The prevalence of MetS have been reported by several studies in Africa to be higher among PLHIV (10.1%–45.4%) compared to those found in the general population (Ayodele et al., 2012; Bosho et al., 2018; O'Neill & O'Driscoll, 2015; Worm et al., 2010) depending on the sampled population and diagnostic criteria

used. Despite these disparities, PLHIV on the ART have been identified to have a higher prevalence of MetS compared to ART naive counterparts (Gooneratne et al., 2018).

A systematic review conducted in 2019 showed that MetS prevalence among PLHIV estimates in SSA ranged from 6.23% in Abidjan to 58% in south-western Uganda (Todowede et al., 2019). Metabolic syndrome was also shown to be more prevalent in females than males using both the IDF and NCEP-ATP III diagnostic criteria. The estimated MetS prevalence was 12.7% among the females against 3.6% among the males using IDF diagnosis, and 19.7% among females and 15.7% among males when the NCEP-ATP III diagnosis was used. The prevalence of MetS among PLHIV measured irrespective of the MetS diagnosis used in a meta-analysis was 21.5% even though using the IDF diagnostic criteria measured a higher prevalence (25.7%) than that of NCEP-ATP III (19.9%). The overall relative risk of MetS prevalence among PLHIV in the reviewed population compared with the HIV-negative population was 1.83 with an estimated predictive interval of 0.15 to 22.43 (Todowede et al., 2019).

2.3.3 Prevalence of Metabolic Syndrome in PLHIV in Ghana

A study conducted by Obirikorang, Osei-Yeboah, Asare, Quaye & Odame (2016) among HIV-infected patients receiving ART found the prevalence of MetS to be 24.5%, 48.3% and 42.3% using the WHO, NCEP-ATP III and IDF diagnostic criteria respectively. It also showed that irrespective of the diagnostic criteria used, participants who were on ART had significantly higher prevalence of MetS as compared to the ART naïve participants. These findings were higher as compared to studies in other countries including SSA countries (Ayodele et al., 2012; Carr et al., 2006; Jeric´o et al., 2005; Samaras et al., 2007).

2.3.4 Prevalence of Metabolic Syndrome Subcomponents in PLHIV

The prevalence rate of the subcomponents of MetS varies among various studies. A systematic review of the studies conducted in SSA reported prevalence of 77.8% and 83.3% for hypertension and diabetes respectively among PLHIV. Similarly, high triglycerides, visceral obesity and low HDL cholesterol (HDL-C) prevalence were found to be 67.0%, 39.0% and 39.0% respectively. Females have been found to have significantly higher low HDL-C as compared with the males (Todowede et al., 2019). High blood pressure, hypertriglyceridemia, hypercholesterolemia and low HDL-C has also be found by most studies to be the most predominant components accounting for MetS (Bonfanti et al., 2007; Jacobson et al., 2006; Jeric´o et al., 2005; Obirikorang et al., 2016).

2.3.5 Risk factors Associated with Metabolic Syndrome in PLHIV

The pathogenesis of MetS can be attributed to the HIV infection itself, ART, clinical, anthropometric, biochemical and demographic features as well as the complex interaction with the environment and genetics. Factors previously reported to be associated with MetS among PLHIV include tobacco use, physical inactivity, harmful use of alcohol, high body mass index (BMI), high proportion of central body fat, older age and unhealthy diet (high calorie intake, high carbohydrate and high overall sugar intake). With respect to HIV-related factors, high viral load, duration of infection, $CD4^+$ counts and use of ARTs have been associated with increased prevalence of MetS (Akl et al., 2017). Some findings indicates that HIV infection and the ART use confer a significant excess burden of MetS over the traditional lifestyle-related factors (Ayodele et al., 2012; Jeric´o et al., 2005; Moreira et al., 2014; Okafor, 2012; Paula et al., 2013; Todowede et al., 2019) whiles others have reported otherwise (David et al., 2002; Hsue et al., 2004; Maggi et al., 2000; Mondy et al., 2007).

2.3.5.1 Socio-demographic related factors

Several socio-demographic characteristics including sex, age, marital status, education and employment status have been investigated to determine its association with MetS among PLHIV. Increasing age has been shown to be a risk factor for MetS. A study reported by Nguyen et al., (2016) indicated that PLHIV above the age of 40 years have a higher risk of developing MetS as compared with those <40 years. Other studies have also reported an association between increasing age and MetS in PLHIV in SSA (Akl et al., 2017; Guira et al., 2016; Hirigo & Tesfaye, 2016; Mbunkah et al., 2014a; W. et al., 2013; Zannou DM et al., 2009).

Many studies have reported women being at a greater risk of MetS than men even though men have been shown to have a higher blood pressure (Akl et al., 2017; Ayodele et al., 2012; Guira et al., 2016; Hirigo & Tesfaye, 2016; Mashinya et al., 2015; Kim A. Nguyen et al., 2016; Obirikorang et al., 2016; Zannou DM et al., 2009). Although most study results are in this direction, Pan & Pratt (2008) reported that males were at a higher risk of developing MetS than females. Thus, more research is required to understand the differences in MetS prevalence by gender which is usually driven by higher rates of obesity (Kim A. Nguyen et al., 2016). There may also be HIV specific factors that contribute to greater metabolic abnormalities in women compared to men that require further investigation.

Studies, which have determined the association between marital status and MetS have reported married individuals having elevated blood pressure and higher risk of MetS than single, widowed or divorced (Akl et al., 2017) whiles others found no association (Berhane et al., 2012).

Few studies have determined the association between education and MetS in PLHIV where they found formal education to be an independent predictor of MetS (Bosho et al., 2018; Hirigo & Tesfaye, 2016; Kaduka et al., 2012). Other studies have also reported of no association between

educational level attained and MetS in PLHIV (Mondy et al., 2007; Obirikorang et al., 2016; Zannou DM et al., 2009).

In terms of employment/ income level, a study by Bosho et al. (2018) found an association between higher income level and MetS whiles Berhane et al. (2012) reports otherwise.

2.3.5.2 Lifestyle and Other related factors

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

Body mass index measures the general body obesity in terms of being underweight (BMI<18.5kg/m^2), normal (BMI:18.5-24.9kg/m^2), overweight (BMI:25-29.9kg/m^2) or obese (BMI:≥30kg/m^2). This is calculated by the division of body weight (in kilograms) by the square of the height (in metres) (Centers for Disease Control and Prevention, n.d.). Obesity which is one of the most serious risk factors for MetS is no longer a disease of affluence. Most studies have established BMI (obesity) as a known risk factor for MetS among PLHIV (Bosho et al., 2018; Hirigo & Tesfaye, 2016; Idiculla et al., 2018; Maseko & Masuku, 2017; Mondy et al., 2007) and clinical trials have also shown lowering in blood pressure to be associated with reduction in weight (Stevens et al., 2001). A Framingham heart study report indicated that people have about 45% increased risk of developing MetS with a weight gain of ≥2.25 kg over a period of 16 years (Wilson et al., 1999), and also each 11cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing MetS within 5 years (Palaniappan et al., 2004).

Although other groups consider abdominal obesity in their definition for MetS, the IDF definition considers abdominal obesity as the key causative factor. Obesity which may occur as a result of increased energy intake above energy expenditure over a prolonged period of time is now a major risk factor for most non-communicable diseases. Over the years, there has been a global epidemic of overweight and obesity suggesting a major change in environmental, diet and lifestyle factors (Finucane et al., 2011).

In 2015, a global survey of obesity conducted in 195 countries found 603.7 million adults and 107.7 million children to be obese. The prevalence of obesity has doubled in more than 70 countries and even continued to increase in most countries from 1.1% in 1980 to 3.85% in 2015 especially childhood obesity (GBD 2015 Obesity Collaborators et al., 2017). The global rate of death related to high BMI also increased by 28.3% between 1990 and 2015 with obesity contributing to 120 million disability adjusted life-years (Saklayen, 2018). Epidemiological survey also suggests that, metabolically healthy obese (individuals who have high level of insulin sensitivity but do not have hypertension and hyperlipidemia and other features of MetS) accounts for a significant percentage of obese population globally (Wildman et al., 2008).

Even though smoking habit, alcohol consumption, fruits and vegetable intake and physical activity has been found to be associated with MetS (Alberti, Zimmet, & Shaw, 2005; Alvarez et al., 2010; Hirigo & Tesfaye, 2016; Husain et al., 2017; Kingery et al., 2016; Pan & Pratt, 2008; Todowede & Sartorius, 2017 Samaras et al., 2007), other studies found no significant association between them (Bosho et al., 2018; Tesfaye et al., 2014). Regular physical activity is found to reduce the incidence of MetS through several mechanisms including decrease in oxidative stress (and reactive oxygen species), decrease in inflammation and body weight and increase in endothelial function (Montesi et al., 2013).

Family history of diabetes and CVD have also been shown to be significant risk factors for MetS among PLHIV (Hamooya et al., 2021; Mondy et al., 2007; Sobieszczyk et al., 2016).

2.3.5.3 HIV related factors

HIV infection can promote atherosclerosis through immune activation, chronic inflammation, coagulation disorders and lipid disturbances (Baker & Lundgren, 2011; Boccara et al., 2013). The virus has been found to enhance endothelial injury which leads to endothelial dysfunction through the production of molecules. This enhances angiogenesis like adhesion molecules and HIV Tat protein (Kline & Sutliff, 2008). The virus also stimulates the production of human vascular smooth muscle cells which is implicated in the development of atherosclerosis (Eugenin et al., 2008). The onset of coagulation disorders (a "prothrombic state") which is associated with HIV leads to increased levels of abnormal platelet reactivity (Baker & Lundgren, 2011; Kline & Sutliff, 2008). HIV infection is also associated with high levels of triglycerides (results of impaired lipase activity) and decreased levels of HDL-C and correlated high concentration of cytokines which may lead to development of MetS (Pan & Pratt, 2008).

Studies have implicated HIV status to be associated with MetS. HIV-positive patients have been found to have a higher odds of MetS compared with HIV-negative patients (Moreira et al., 2014; Okafor, 2012; Paula et al., 2013; Todowede et al., 2019). Although most of the studies conducted in SSA were among HIV-positive individuals, the few that conducted among HIV-positive and HIV-negative people reported significantly higher MetS risk among the HIV-positives than the HIV-negatives (Mbunkah et al., 2014a; Sani et al., 2014; W. et al., 2013). A study by Fourie, Van Rooyen, Kruger & Schutte (2010) found no significant association between HIV and MetS which is similar to one conducted by Mondy et al. (2007).

In terms of the HIV-infection duration on the risk of MetS, researchers have reported an increased risk of MetS in PLHIV as the duration of the HIV-infection increases (De Socio et al., 2014; Krauskopf et al., 2013; Manner et al., 2013). On the other hand, a study have reported of no association between HIV- infection duration and the risk of MetS among PLHIV (Mondy et al., 2007). Also, even though viral load is used as a marker of immune suppression in PLHIV, a study which assessed the relationship between viral load and MetS reported no association between them (Sobieszczyk et al., 2016).

Several studies have been conducted to determine the association between $CD4^+$ count and the incidence of MetS. Although a higher $CD4^+$ count has been found to be an independent predictor for MetS (Ayodele et al., 2012; Husain, Noor, Elmadhoun, Almobarak, Awadalla, Woodward, Mital, & Ahmed, 2017; Mondy et al., 2007), low $CD4^+$ count has also been associated with higher risk of MetS by other studies (David et al., 2002; Ho et al., 2012; Hsue et al., 2004; Jeric´o et al., 2005; Maggi et al., 2000).

2.3.5.4 ART related factors

Despite the viral suppression and immune recovery promoted by the ART in reducing the burden of HIV-related morbidity and mortality, aging together with prolonged exposure to the ART may increase the risk of MetS among PLHIV (Akl et al., 2017). Accumulated evidence indicates that MetS could be associated with different ART use even though other studies show otherwise (Alvarez et al., 2010; Ayodele et al., 2012; S. Krishnan et al., 2012; Mondy et al., 2007). Although it remains debatable due to conflicting results, several studies have reported the association between ART and MetS in PLHIV. PLHIV and are on the ART have been shown to have a higher risk of MetS than their ART naïve counterparts (Alvarez et al., 2010; Hansen et al., 2009;

Obirikorang et al., 2016; Samaras et al., 2007; Tesfaye et al., 2014; Todowede et al., 2019). A systematic review conducted in SSA found a two-fold higher risk of MetS among PLHIV than HIV-negative people (Todowede et al., 2019). Even though this ratio was not statistically significant as a result of limited studies, the findings suggests that HIV infection and ART appear to contribute to a significant excess burden of MetS. The findings of this review are also similar to ones reported in other studies (Moreira et al., 2014; Okafor, 2012; Paula et al., 2013).

The use of ART leads to immune activation and may lead to low-grade inflammation, which can promote atherosclerosis (Fisher et al., 2006; Coll et al., 2007; Boccara et al., 2013). During immune activation there is an increased levels of TNF-α, which, in turn, impairs metabolism of fatty acids and lipid oxidation, resulting in suppressed lipolysis (Maseko & Masuku, 2017). This alters fat distribution and changes in lipid profile which causes an increase in the levels of triglycerides and low density lipoprotein cholesterol (LDL-C), and a decrease in HDL-C resulting in the risk of MetS (Thorogood et al., 2007). This has been shown by Husain et al. (2017) where PLHIV receiving ART were found to have significantly elevated cholesterol, triglyceride glucose and low-density lipoprotein cholesterol (LDL-c) levels but lower $CD4^+$ cell counts than the ART-naïve people.

Several studies have implicated ART especially the PIs, NNRTIs and NRTIs in inhibiting lipid and glucose metabolism leading to adipocyte and mitochondria dysfunction which results in lipodystrophy, dyslipidemia and mitochondrial toxicity (Boccara et al., 2013; Grinspoon, 2005; Samaras et al., 2007). Both mitochondria dysfunction and adipogenesis result in insulin resistance and subsequent development of MetS (Maseko & Masuku, 2017). Zidovudine, efavirenz and indinavir have been shown to induce toxicity through induction of cardiomyocyte and endothelial

cell apoptosis leading to endothelial dysfunction and vascular damage and hence MetS (Fiala et al., 2004).

The duration of NRTIs usage have been shown with increased adiponectin production which is significantly correlated with triglycerides, abdominal visceral fat, extremity fat, insulin resistance and high density lipoprotein (HDL) cholesterol which are all subcomponents of MetS (Hansen et al., 2009; Jemsek et al., 2006; Jeric´o et al., 2005). Adiponectin is also related to lipodystrophy, insulin resistance and metabolic alterations among PLHIV under PIs-based ART which increases their risk of MetS and CVD as shown by most studies (Hadigan et al., 2002; Hsue et al., 2004; Husain et al., 2017; Maggi et al., 2000; Tesfaye et al., 2014). Patients who had a history of stavudine use were also more likely to have higher triglyceride levels than those who had no history of stavudine use (Tesfaye et al., 2014).

Most ARVs such as nevirapine, lamuvidine (Gabriel L. et al., 2006) efavirenz, indinavir, saquinavir, didanosine (Maseko & Masuku, 2017) and zidovudine (Tang et al., 2003) have been found to be associated with dysfunctional metabolism. Ritonavir have also been reported to cause a striking increase of triglycerides in less than 6 months after ART initiation (Lewington et al., 2002). A study by Lassègue & Clempus (2003) have reported that regardless of ART regimen both hyper triglyceridaemia and hypercholesterolemia have been observed among PLHIV on ART. This implies that all ART regimens may increase the risk of metabolic disorders and the subsequent risk of diabetes and CVD.

Weight gain in the early ART era, was often seen as evidence of nutritional rehabilitation and improved survival and immunologic recovery (Madec et al., 2009; Yuh et al., 2015). However, weight gain and obesity after ART initiation are steadily increasingly thus becoming recognized problems in modern HIV treatment paradigm. Among patients on ART, a high BMI or weight gain

confers an increased risk of developing associate comorbidities like diabetes, neurocognitive impairment, and other metabolic disorders (Herrin et al., 2016; Sattler et al., 2015; Sax et al., 2019). Even though almost all classes of antiretrovirals have been found to cause an increased weight gain after initiation, there is mounting evidence that the integrase strand transfer inhibitors, particularly dolutegravir is associated with more weight gain (Calza et al., 2019; Phillips et al., 2020; Venter et al., 2019a). The use of dolutegravir has been shown to cause some side effects including headaches, diarrhoea, nausea, rash, itching, increase in the level of liver enzymes and increase in the level of enzymes produced in the muscles (creatine phosphokinase) (NAM AIDSMAP, 2022).

Recently, clinicians at the Vanderbilt Comprehensive Care Clinic, a large, urban HIV clinic, noted substantial weight gain in several patients with long-term viral suppression who switched from daily, fixed-dose efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to daily fixed-dose DTG/ABC/3TC. Patients who switched to an INSTI containing regimen gained an average of 2.9 kg at 18 months compared to 0.9 kg among those continued on EFV/TDF/FTC (Norwood et al., 2017). Since the introduction of dolutegravir as the approved and preferred first-line drug regimen, only a handful of research have assessed weight gain in patients with effective virologic suppression who switch to an INSTI-containing regimen and also the effect of DTG on weight gain (Cahn et al., 2019; Calza et al., 2019; Clayden & HIV i-Base, 2019; Eckard & McComsey, 2020; Raffi et al., 2013; S. A. Ruderman et al., 2019). Given the increased cardiometabolic disease risk associated with higher BMI in HIV-infected persons, it is important to assess whether a change from EFV/TDF/FTC to an INSTI-containing regimen among PLHIV is accompanied by an increase in body weight and other metabolic parameters. This excess weight gain increases their risk of MetS. The ADVANCE trial conducted in South Africa found high

treatment-emergent metabolic syndrome (using IDF diagnosis) at week 96 among participants on TAF/FTC/DTG (9%) and TDF/FTC/DTG (5%) as compared to 3% among those on TDF/FTC/EFV (Clayden & HIV i-Base, 2019). Therefore, with the reviewed ART regimens, there is the need to monitor patients on ART for development of MetS and its components.

Generally, the adverse effects of ART and long-term use of ART triggers body mechanisms that lead to development of MetS (Maseko & Masuku, 2017). Studies have shown that the earliest time to develop MetS among PLHIV was 6 weeks of initiation of ART (Macdonald, 2008) whiles others have shown to be more than 6 months (Bonfanti et al., 2007) and a year of ART initiation (Berhane et al., 2012; Estrada et al., 2006). A study conducted by Berhane et al. (2012) found MetS prevalence of 21.1% after 1 year of ART initiation. A prospective cohort study conducted in Ivory Coast among PLHIV found the incidence of metabolic syndrome to be 5.5per 100 person-years of follow-up with a cumulative incidence of 14.4%. The main contributing risk factors were sex and overweight (Tchounga et al., 2016). Sobieszczyk et al. (2016) also reported MetS incidence of 9.13 per 100 person-years with the commonest MetS components being low HDL-C, weight circumference >88cm and elevated blood pressure. It also recorded incidence from 8.7% to 10.4%, 16.7% and 19.2% within 12, 24 and 36 months. Other prevalence studies have also reported similar and higher findings after 12 months post ART initiation (Ayodele et al., 2012; Eholié et al., 2015; Fourie et al., 2010; Jacobson et al., 2006; S. Krishnan et al., 2012; Samaras et al., 2007; Zannou DM et al., 2009).

2.3.6 Metabolic Syndrome Complications among PLHIV

Metabolic syndrome increases the risk of other non-communicable diseases especially type 2 diabetes mellitus (T2DM) and cardiovascular diseases which directly contribute to morbidity and

mortality among PLHIV (Esser et al., 2014). The presence of MetS among PLHIV can also be used to identify those who at a higher risk of dying from CVD and diabetes (Akl et al., 2017).

The presence of more than one metabolic abnormalities in the same individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality (Sattar et al., 2003). This means the more metabolic syndrome components evident in an individual, the higher the risk of cardiovascular mortality (IDF, 2006).

Diabetes mellitus is the most dominant metabolic disease in the world which is the leading cause of blindness, amputation and kidney failure accounting for much of the social and financial burden in all countries especially the developing countries where resource is limited. Diabetes is characterised by insulin secretion defects and peripheral insulin resistance in the skeletal muscle, the adipose tissue and the liver (Esser et al., 2014). The failure of pancreatic β-cells to compensate for insulin resistance leads to chronic hyperglycaemia. It has been predicted that the incidence of diabetes will double by 2025 which indicates a parallel rise in cardiovascular and metabolic related illness and death, with an inevitable and profound impact on global healthcare systems (IDF, 2006). With PLHIV living longer, this burden of diabetes conferred by the presence of MetS will add to the already escalating incidence of diabetes.

Chronic inflammation in PLHIV has been shown to destabilize atherosclerotic plaques which can lead to high blood which is a component of MetS thus resulting to CVDs over time (Ho et al., 2012; Kaplan, 2008).

2.4 Cardiovascular Risk Scoring Systems

HIV-infected patients with pre-existing additional risk factors (e.g. hypertension, diabetes or increased plasma homocysteine levels) might be at raised risk of developing coronary heart disease because of accelerated atherosclerosis. Additionally, longer exposure to ART also seems to increase the risk of myocardial infarction. The results of the Data Collection on Adverse Events of Anti-HIV Drugs study showed that ART is associated with a 26% relative risk increase in the rate of CVD per year of ART exposure (Mashinya et al., 2015).

Cardiovascular disease affects most adults and is common in the general population. Cardiovascular disease includes diseases like coronary heart disease, peripheral arterial disease and aortic disease. Cardiovascular risk scoring systems give an estimate of the probability that an individual will develop CVD within a specified length of time. Although the risk of CVDs increases with age, predicting the risk of CVD in an individual allows the identification of individuals at high risk of CVD so that early interventions can be put in place to reduce the occurrence of future events (Batsis & Lopez-Jimenez, 2010).

Several CVD risk prediction models are used in clinical practice and research worldwide. The modified Framingham Risk Score (FRS) is the most commonly used tool (Wilson et al., 1998), and has been adapted for use in diverse populations in other parts of the world. Other tools include the Prospective Cardiovascular Munster Heart Study (PROCAM) (Assmann et al., 2002), the Systematic Coronary Risk Evaluation system (SCORE) (Conroy et al., 2003), United Kingdom Prospective Diabetes Study (UKPDS) tool for diabetics (Stevens, Kothari, Adler, Stratton, & Holman, 2001), the Reynolds Risk Score (Ridker et al., 2007, 2008), the National Health and Nutrition Examination Survey (NHANES) which includes obesity as a variable (Batsis et al., 2007) and more recently the Jackson heart study cohort among blacks (Fox et al., 2016). The MESA risk

score, China-PAR risk predictor, the pooled cohort equations, the WHO/ISH risk prediction chart and the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) risk score are also used to assess the risk of CVD. All these predictions models were designed to be used in the general population until the D:A:D 5-year risk score was developed purposely to be used among PLHIV which addresses the effect of HIV and the ART. The Framingham 10-year risk score was previously used to estimate the risk of CVD among PLHIV as well (D'Agostino, 2012).

Even though studies have shown that the FRS can be used to estimate CVD risk among PLHIV, the D:A:D gives a better estimate. Mashinya et al. in 2015 also found a 73.8% level of agreement between the Framingham and D:A:D risk estimation equations which was similar to findings of a study conducted in Brazil (Nery et al., 2013). Despite the level of agreement observed in the study, the Framingham equation underestimated the risk for CVD in 26% of the study participants when compared to the D:A:D equation. This suggests that the use of the Framingham equation in PLHIV receiving ART may lead to the exclusion of some individuals to benefit from more aggressive CVD prevention which has also been reported by another study (Klug et al., 2015). Contrary to these findings, other studies have also reported that the use of the Framingham equation overestimated the 10-year CVD risk among PLHIV when compared to D:A:D equation (Edwards-Jackson et al., 2011; Nery et al., 2013).

2.4.1 Framingham 10-year General Cardiovascular Disease Risk Score

The FRS was modelled from the Framingham Heart Study (Wilkins, Wickramasinghe & 2017). People with MetS have a higher lifetime risk of developing atherosclerotic cardiovascular disease (ASCVD). The main aim for MetS treatment is to reduce both the short-term and lifetime risk of other co-morbidities. The standard Framingham 10-year risk score is the practical approach used

to estimate absolute, short-term CVD risk in patients with the MetS without ASCVD or diabetes (National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol Treatment in Adults (Adult Treatment Panel III), 2002). The standard Framingham risk equations capture most of the risk factors of CVD in patients with MetS including cigarette smoking, blood pressure, total cholesterol, HDL-C and age. Patients with ASCVD or diabetes are excluded because they are already in a high-risk category hence there is no need for Framingham risk scoring (D'Agostino, 2012).

A study conducted in Uganda among PLHIV found 58% of the participants with metabolic syndrome of which 17% had a Framingham risk correlating to a 5% or greater risk for CVD within 10 years with males having elevated cardiovascular disease risk scores (Muyanja et al., 2016). A similar study conducted in Uganda by Mateen et al. (2013) reported 20% of the men with at least 10% or more long-term risk of acute cardiovascular disease. The FRS also underestimates the risk of CVD among PLHIV (Eholié et al.). Thus, classifies study participants as having low risk of CVD. Studies conducted among Nigerians using the FRS classified 88.3% as low risk (Edward et al., 2013), 93.3% among South Africans (Mashinya et al., 2015), 72.3% among Slovenians (Pirs et al., 2014) and 60.3% among Germans (Reinsch et al., 2012).

2.4.2 D:A:D 5-year Cardiovascular Risk Score

The Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) cardiovascular risk scoring system is a specific cardiovascular risk score developed from a cohort of HIV- positive patients taking into consideration the type and duration of ARVs administered. This was developed in 2010 from the D:A:D study (Friis-Møller et al., 2010) and subsequently updated in 2016 (Friis-Møller et al., 2016). The D:A:D study used a 5-year prediction model based on the assumption that models

based on time-updated data may more accurately capture and predict individual's current risk. This model takes into account the age, sex, family history of CVD, smoking status, diabetes status, total cholesterol levels, HDL-C, blood pressure, $CD4^+$ counts, years of exposure to a PI (lopinavir), years of exposure to NRTIs and exposure to abacavir or not of the patients (Friis-Møller et al., 2016). A study by Mashinya et al. (2015) using the D:A:D risk model equation showed that 31.1% of participants (PLHIV) had a moderate to high 5-year risk of CVD. The D.A.D is the most appropriate risk scoring model to be used among people living with HIV as it estimates the actual risk among PLHIV (Mashinya et al., 2015; Pirs et al., 2014).

2.4.3 WHO/ISH Risk Prediction Charts

The World Health Organisation/International Society of Hypertension (WHO/ISH) risk prediction chart is a cardiovascular risk scoring system tool developed for assessment and prediction of cardiovascular risk in different populations based on a 10-year modelling approach from the WHO comparative risk assessment study (Mendis et al., 2007). It incorporates the age, sex, diabetes status, systolic blood pressure, smoking status and total serum cholesterol to estimate the risk (Ezzati et al., 2003).

The WHO/ISH prediction chart uses information on the relative risk of each risk factor and the population level estimate of absolute risk to develop a risk prediction chart which is regionally based and thus can be used to estimate the risk of CVD among individuals in resource limited countries. The a risk prediction charts are divided into the 14 WHO epidemiological sub-regions; Africa (AFR D and E), The Americas (AMR A, B and D), Eastern Mediterranean (EMR B and D), Europe (EUR A, B and C), South-East Asia (SEAR B and D) and Western pacific (WP A and B) (World Health Organization, 2007). Even though the WHO/ISH can be used among various

populations, it is not recommended to be used among PLHIV as it does not take into consideration the type of ART used and the duration of ART usage (Edward et al., 2013; Eholié et al., 2015)

2.5 Summary of MetS

The use of different criteria in MetS diagnosis have been a source of confusion for most clinicians and researchers thereby making the estimating of its true prevalence in any setting a challenge. This prevalence varies greatly across countries depending on several factors such as region, area of residence, ethnicity, gender, age and race of the population been studied.

The prevalence rates of metabolic syndrome using various diagnosis among PLHIV from published studies in SSA compared with most developed countries has been shown to be high. However, there is a dearth of publications on metabolic syndrome in PLHIV. Also, the reported high rate of MetS, irrespective of HIV status and diagnosis used, indicates a major metabolic disorder epidemic that requires urgent prevention and management programs in SSA. Similarly, in the era of universal test, treat and track strategy among PLHIV, routine check-up of MetS subcomponents is required in HIV management as biomarkers for MetS.

Most of the studies conducted in SSA were cross-sectional which were used to determine the association of MetS and other risk factors including the ART. In Ghana, only one study has looked at the prevalence of MetS among PLHIV without looking at the risk factors. With the introduction of the new ARV drug regimen (dolutegravir-based regimen), there is the need to assess the effect of this drug combination on MetS and its subcomponents. Also, given the relative paucity of health systems infrastructure targeted to NCDs prevention and treatment in the country (Peck et al., 2014) there is an important need to expand the focus of HIV care. Thus, this study will determine the

prevalence, incidence and clinical correlates of MetS and its subcomponents among a cohort. In addition, it will determine if dolutegravir-based regimen is associated with MetS and estimate the risk of CVD among PLHIV with MetS.

CHAPTER THREE

3.0 METHODS

3.1 Study Design

3.1.1 Objectives 1-4

This study is to determine whether dolutegravir-based regimen increases the risk of developing metabolic syndrome, identify the risk factors associated with metabolic syndrome and also to determine and classify cardiovascular disease risk score for HIV-infected patients. A prospective cohort study was conducted at the HIV Clinic of the Tema General Hospital. The cohort study was conducted to know the time to occurrence of metabolic syndrome and its subcomponents. Two cohorts [Cohort 1: 150 existing HIV-positive patients who switched from TDF+3TC+EFV to TDF+3TC+DTG; Cohort 2: 150 newly diagnosed HIV-positive patients who started on TDF+3TC+DTG] without MetS (NCEP-ATPIII diagnosis). They were then followed up for 1 year to measure the incidence of MetS and its subcomponents among them. All consenting PLHIV aged 18 years and above, non-pregnant (for females) and who were about to switch or start the DTG-based regimen were screened for MetS using the NCEP-ATPIII diagnosis and those without MetS were recruited into the study. Data on demographic, lifestyle, family history of cardiovascular disease, HIV/AIDS, ART and chronic disease were collected using the World Health Organization Stepwise approach to chronic disease risk factor surveillance questionnaire. Blood pressure and anthropometric measurements were carried out and blood samples were also taken for metabolic/biochemical parameters. This was done at the beginning of the follow-up period, 6 months (middle) into the follow-up and at the end of the follow-up period (1 year) for the cohort. Clinical folders of the participants were reviewed for HIV and ART-related data and baseline variables. The cardiovascular risk score assessment tools (10-year Framingham risk score; 10-year

WHO/ISH risk prediction chart and the 5-year D:A:D CVD risk score) were used to estimate the risk level of CVD among the cohort. The cohort study showed the time to occurrence of metabolic syndrome and its subcomponents. Thus, this study will help targeted interventions to be applied before they start developing any co-morbidities.

3.1.2 Objective 5

To assess the level of adherence to HIV treatment and challenges to the baseline assessments before the ART initiation and routine checks, in-depth interviews were conducted in 10 of the 41 HIV clinics providing comprehensive HIV care (HIV testing and counselling, Early infant diagnosis, Prevention of mother-to-child transmission and antiretroviral therapy) in the Greater Accra Region. HIV-positive patients about to start ART and heads at the selected HIV clinics providing comprehensive HIV care were interviewed after an informed consent had been sought. Also, 5 patient's folders were randomly selected from the clinics and reviewed to ascertain the tests (HIV status, HIV type, viral load, pregnancy test, full blood count, blood urea, electrolytes, creatinine, liver function test, fasting blood sugar, cholesterol, lipid profile, Tuberculosis screening, Hepatitis B test, $CD4^+$ count), physical examination (weight, height, skin) and information on medical and social history collected at baseline before ART initiation. MetS can be prevented if the baseline and routine checks are done for patients whenever they visit the facility. Thus, conducting this study will help understand some of the barriers to ensuring these tests are done and also help to explain some of the results.

3.2 Study Location

3.2.1 Objectives 1-4

This aspect of the study was conducted at the Tema General Hospital (TGH) located in the Tema as shown in Figure 3.1. The hospital was built by the colonial administration in 1954 to provide healthcare for workers who constructed the Tema Harbour. This was handed over to the government for public use later. With the hospital's geographical location, surrounding road network and commercial nature of the Metropolis, it has become one of the busiest in the country. The facility is a major referral centre for private and government facilities in the Tema Metropolis with its catchment area extending to Afienya, Dawhenya and Prampram in the Dangme East and West, Sakumono, Teshie, Nungua, Kpone, Ashaiman, Kakasunanka, Appolonia, Lashibi, Community 25 among others, with an estimated population of over 1,000,000. TGH is also situated in a highly industrialised city close to three major highways, namely Accra-Tema, Tema-Aflao and Tema-Akosombo roads providing emergency services to both victims of industrial and road traffic accidents, especially on the Tema-Accra Motorway.

Tema General Hospital provides both in-patient and out-patients services with about 300 bed capacity. The introduction of the NHIS has caused a drastic increase in attendance at the hospital over the years. It has various supporting services such as laboratory, blood bank, radiology, optometry, ultrasound scan, pharmacy and physiotherapy. The facility has 21 various units which include internal medicine, general surgery, paediatrics, theatre, obstetrics and gynaecological care as well as accident and emergency services. It also has specialised clinics and units including the eye, dental, diabetic, sickle cell, dermatology, anaesthetic, chest, hypertensive and ear-nose-throat clinics and fevers Unit. The fevers unit houses the HIV clinic which serves over 200 patients on clinic days. It also has over 5300 PLHIV on the ART. The HIV clinic runs two days in a week

(Tuesdays and Thursdays) through appointment and attends to about 200 patients a day. It operates both institutionalised electronic and manual database which stores all clinic visits as well as medications, laboratory investigations and other patients' data. Currently the staff strength at the clinic is 2 clinicians, 2 nurses, 2 public health nurses, 2 pharmacists, 1 biomedical scientist, 4 volunteers, 6 counsellors and 1 data room staff.

3.2.2 Objective 5

The study was conducted in the Greater Accra Region (GAR) of Ghana. The region is served by both public and private facilities. The public sector comprises of a teaching hospital, regional hospital with about 5 quasi government hospitals. The region also has several districts and sub-metropolitan hospitals, polyclinics, health centers, community clinics and functioning Community-Based Health Planning and Services (CHPS) compounds. Almost all the health facilities in the region provide at least one HIV service (HIV testing and counselling, Early infant diagnosis, Prevention of mother-to-child transmission and Antiretroviral therapy). As at 2018, there were about 359 health facilities in GAR providing various HIV services with 156 providing only Prevention of Mother-To-Child Transmission (PMTCT) service, 24 offering only HIV Testing and Counselling (HTC), and one facility providing just antiretroviral therapy (ART). Early Infant Diagnosis (EID) service is always performed in combination with other services. Some HIV clinics provides more than one service (127 provide both HTC and PMTCT; 1 provide ART and EID; 1 provide ART and PMTCT; 2 provide HTC, PMTCT and ART; 2 provide PMTCT, ART and EID; 4 provide HTC, ART and EID; and 41 provide all four services).

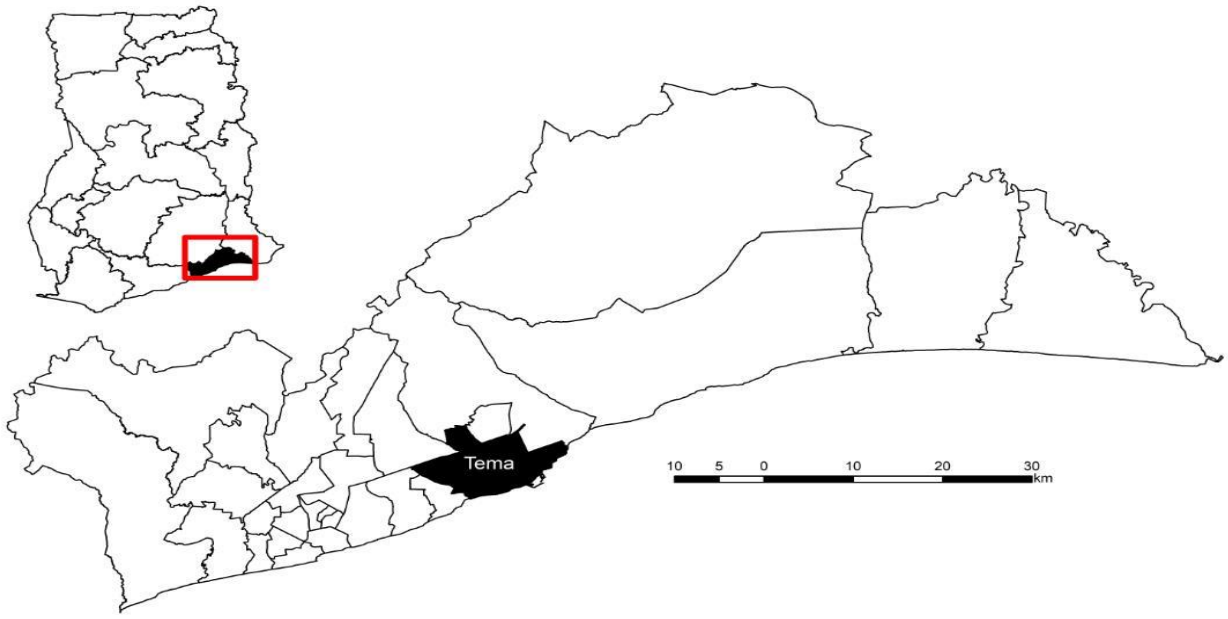


Figure 3. 1: Map of Greater Accra region showing study location

3.3 Study Population

3.3.1 Objective 1-4

The study population were PLHIV who attended the HIV clinic and the sampling frame was the electronic register of patients. PLHIV aged 18 years and above, non-pregnant (for females) who were about to switch and HIV positive patients about to start ART treatment on the first-line dolutegravir-based regimen who attended the clinic for both clinical assessment and dispensing of ARVs were screened for MetS and those who were negative based on the NCEP-ATPIII diagnosis were enrolled into the study. PLHIV without MetS who were about to switch from TDF+3TC+EFV to the new preferred drug regimen (TDF+3TC+DTG) were selected as one cohort (exposed) and HIV positive patients who were about to start the 1st line treatment (TDF+3TC+DTG) were also selected as the second cohort (unexposed).

3.3.2 Objective 5

HIV-positive patients about to start the ART and heads of 10 selected HIV clinics providing comprehensive HIV care were interviewed.

3.4 Sample Size Calculation (Objectives 1-4)

The sample size was estimated using command stpower cox in STATA version 14 under the assumptions for sample size, power and effect size for cohort study using the Cox proportional hazards model [stpower cox, hratio(#) failprob(#)] (Schoenfeld, 1983) based on the following assumptions:

- Probability of detecting a difference when none exists will be 0.05 (alpha-two sided).
- Power of 80% was estimated
- Incidence of metabolic syndrome among those starting the dolutegravir-based regimen will be 5% based on the estimate in the study by (Clayden & HIV i-Base, 2019).
- 17.2% of those who switch from EFV to DTG-based regimen have been shown to gain weight (Kuo et al., 2020) and 25% of overweight people is estimated to develop MetS (Park et al., 2003).

Ha: Metabolic Syndrome occurs less among those who are now starting the dolutegravir-based regimen than those switching to the dolutegravir-based regimen.

hratio= Hazard Ratio of 5.0, based on ratio of 0.25 among those switching (exposed) to 0.05 among those starting on dolutegravir-based regimen (unexposed)

Pr(fail)= Probability of failure event () = 0.05

Estimated sample size was 243

Adjusting for non-response and lost to follow-up at an oversampling estimate of 20%, the total sample size required for this study was 292. Thus, the estimated sample size per group was 146. In all, 300 participants were enrolled into the study with 150 participants in each group.

3.5 Sampling Procedure

3.5.1 Objectives 1-4

3.5.1.1 Inclusion Criteria

PLHIV aged 18 years and above, non-pregnant (for females) who were about to switch to DTG-based regimen and HIV positive patients about to start ART treatment on the first-line dolutegravir-based regimen who attended the clinic for both clinical assessment and dispensing of ARVs.

- **Cohort 1:** Cohort 1: HIV-positive patients who were about to switched to the new preferred drug regimen (TDF+3TC+DTG)
- **Cohort 2:** HIV-positive patients who were about to start the new preferred drug regimen (TDF+3TC+DTG).

3.5.1.2 Exclusion Criteria

PLHIV with previously documented hypertension, diabetes, dyslipidemia, current use of antidiabetics, antihypertensives, lipid-lowering drugs, or any others CV drugs, MetS and those who had given birth in the last 6 months as at the time of study and patients with clinical AIDS or hospitalized. PLHIV with sub-optimal adherence to follow-up visits to HIV clinic (<95%). Adherence was measured using proportion of days covered (PDC).

3.5.2 Objectives 5

3.5.2.1 Inclusion Criteria

Heads of the selected HIV Clinics and newly diagnosed HIV positive patients aged 18 years and above who are about to start the ART.

3.5.2.2 Exclusion Criteria

HIV positive patients who refuse to start the ART

3.6 Selection of Study Participants

3.6.1 Objectives 1-4

- **Cohort 1:** A systematic sampling method was used to select the 150 participants required for this cohort. The list of all the patients on TDF+3TC+EFV who have not started the new drug regimen (TDF+3TC+DTG), are 18 years and above and have adhered to the treatment were compiled and numbered. There were about 1900 compliant patients left to be switched to the DTG based regimen. This number was divided by the 150 participants required for the study to get the sampling interval which was 13. A random number was generated between 1 to 13 using Microsoft Excel to select the first number (participant). The numbers 1 to 13 were entered into a column in an EXCEL spreadsheet and at the column right next to it, one column was selected. The function =RAND() was entered in the formular bar, and F9 function was pressed to change the formular to a random number. Thus, the patient with the number 4 was selected as the first participant and every 13th patient was selected and screened for eligibility via mobile phone and those who were

eligible and consented to join the study were asked to come to the facility to start the new regimen on specific clinic days based on the number of new registrants recruited. They were all asked not to eat when coming. These eligible participants were screened based on the NCEP-ATPIII diagnosis and those without MetS were included in the study. This was done till the 150 participants were reached.

- **Cohort 2:** All the HIV-positive patients (about to start the new first-line drug regimen) who attended the clinic during the six months data collection period were recruited into the study. The hospital clinic days were on Tuesdays and Thursday, thus those who were eligible and consented to participate in the study were asked to come to the facility the next clinic day to start their medication (i.e. those recruited on Tuesdays were asked to come on Thursdays to start their treatment and vice versa). They were asked not to eat before coming. These eligible participants were screened based on the NCEP-ATPIII diagnosis and those without MetS were included in the study. The screening was done at each clinic day till the 150 participants required for the study were gotten. About 3 people were recruited averagely on a clinic day.

The same number of participants per each cohort started the DTG-based regimen at the same time (i.e. if 3 participants are recruited on Tuesday to start the ART on Thursday from cohort 2, the same number of participants in cohort 1 were asked to also come and start the ART on the Thursday).

3.6.2 Objective 5

All the 41 HIV clinics providing comprehensive HIV care were listed and numbered after which 10 were selected randomly using the lottery process. By this process, the numbers 1-41 were

written on a piece of paper, folded and put in a box. After shuffling by an independent person, ten numbers corresponding to ten clinics were picked one at a time without replacement. Twenty (20) HIV-positive patients (2 from each facility) who attended the clinic on the day of the study to start the ART were randomly selected. All the new registrants on that day were given numbers. These numbers were written on a piece of paper, folded and put in a box. After shuffling by an independent person, two patients were picked one at a time without replacement in each of the 10 facilities. The heads of the 10 HIV clinics were selected purposively. Five folders of patients who have been on treatment for the past 3 months were also picked randomly. This was done by compiling the list of all the newly diagnosed HIV positive patients for the past 3 months in each facility. They were then numbered and random numbers were generated using Microsoft excel. Folders of patients whose numbers were generated were picked from the shelves in all the selected facilities. The folders were reviewed until saturation was reached.

3.7 Study Variables

3.7.1 Objectives 1-4

- Primary outcomes: Metabolic syndrome based on the NCEP-ATPIII diagnosis and CVD risk.
- Secondary outcomes: Obesity, High blood Pressure, High blood glucose, High Cholesterol
- Primary explanatory variable: DTG-based regimen (TDF+3TC+DTG) only and switching from EFV-based regimen (TDF+3TC+EFV) to DTG-based regimen.
- Other explanatory variables: age, sex, religion, educational level, employment level, marital status, ethnicity, duration since HIV diagnosis, current ART use and duration, family history of diabetes or hypertension, viral load, smoking habit, alcohol use, fruit and vegetable intake,

physical activity level, weight, height, hip circumference, waist circumference, arm circumference, blood pressure, creatinine level, plasma glucose, lipid levels, body mass index and co-morbid conditions.

3.7.2 Objective 5

Patients' folders were reviewed to ascertain the following information:

- Laboratory tests (HIV type, viral load, pregnancy test, full blood count, blood urea, electrolytes, creatinine, liver function test, fasting blood sugar, cholesterol, lipid profile, Tuberculosis screening, Hepatitis B test, $CD4^+$ count)
- Physical examination (weight, height, skin, mouth, lymphadenitis/lymphadenopathy, respiratory, cardiovascular system, genito-urinary system, gastrointestinal system, anorectal area, nervous and musculo-skeletal systems, mental status, genital tract)
- Information on medical history (date of initial HIV diagnosis and type of HIV infection; current symptoms screen for tuberculosis, Hepatitis B and C; past diagnosis of tuberculosis, diabetes, hypertension; drug history including treatment for TB and Hepatitis B; previous ARV exposure; sexual history and past symptoms of STI; Obstetrics and Gynaecological history including family planning; history of drug use)
- Information on social history (family support systems, income).

3.8 Data Collection

3.8.1 Objectives 1-4

The World Health Organization stepwise approach [WHO STEPS] (WHO, 2020) to chronic disease risk-factor surveillance was adapted and used to develop a questionnaire. The questionnaire was transferred into KoboToolbox Software for the data collection. A tablet with the software was used to administer the questionnaire to the study participants after an informed consent has been sought. Information on dietary intake, physical activity, socio-demographic, tobacco use, alcohol consumption, family and medical history were obtained. The chart records of the study participants were reviewed to extract data on HIV diagnosis date, clinic enrolment date, ART initiation date, ART regimen history, $CD4^+$ count history and other information. Blood pressure and anthropometric measurements were taken and blood samples were also drawn for metabolic and biochemical analysis. After the cohorts have been selected, they were all followed up separately for one year. During this period, the incidence of MetS and time varying co-variates were measured at 6 months and at one year. All the anthropometric and biochemical analysis were done at baseline (0), midline (6 months) and endpoint (12 months) for all participants. We were in contact with the participants 3 consecutive times. All the study participants (cohorts) were contacted prior to the next data collection to remind them of their appointments and not to eat before coming. Those who could not make it were visited at home for data and sample collection.

3.8.1.1 Anthropometric and blood pressure measurements

All study participants underwent physical examination by a trained nurse who measured their weight, height, waist circumference (as proxy for visceral fat) and hip circumference. Their blood pressure was also measured using Omron HEM-8712 Fully Automatic Blood Pressure Monitor.

The weight of the study participants was measured to the nearest 0.1kg using a calibrated digital electronic weighing scale. To ensure quality results, the scale was placed on an even surface and study participants were made to stand in the centre of the scale's platform bare footed with their weight distributed evenly to both feet.

The height of the study participants was measured using a wall mounted stadiometer to the nearest 0.1cm. For quality control, the study participants were asked to remove their footwear and stand in an upright position with their back to the height rule and head in a Frankfurt horizontal plane.

The waist and hip circumferences of study participants were measured with an inelastic but flexible standard tape measure to the nearest 0.1cm. The waist circumference was measured at a level midway between the lower rib margin and iliac crest with the tape around the body in a horizontal position. Hip circumference was measured as the maximal circumference over the buttocks. Quality control was ensured by taking two measurements and the average estimated. Also, study participants were made to stand with their feet close together for even distribution of weight to each leg.

Blood pressure readings were taken using an automated sphygmomanometer with an inflatable cuff. This was done after study participants have rested for at least 10 minutes. They were then asked to sit in an upright position and relax. To ensure quality readings, three measurements were taken 3 minutes apart on alternating arms and the average of these three readings were estimated. Only estimated measurements were used in analysis.

3.8.1.2 Sample collection for biochemical and metabolic parameters

Blood was collected using standard laboratory procedures from participants by a laboratory technologist from TGH laboratory. A 6mL venous blood sample was drawn via venipuncture from

the antecubital fossa or dorsum of hand of study participant's choice or their non-dominant hand after an overnight fast (12 hours minimum). This is the minimum amount of blood required by the laboratory for their automated analyzers to perform the requested laboratory test and give accurate and consistent results.

In drawing the blood, participants' arm was placed in an extended position while he/she was comfortably seated and an appropriate vein was located (commonly use veins include the cubital, basilic of cephalic vein). The puncture site was cleaned with a cotton swab containing 70% isopropyl alcohol after a tourniquet have been applied 3-4 inches above the collection site. With the appropriate needle (18 gauge) attached to the hub, the plastic cover over the needle was removed and the skin held tight, the needle was inserted into the vein followed by attaching the vacutainer tubes to draw blood while the hub was held securely. The tourniquet was removed immediately blood started to flow.

Blood samples were aliquot into EDTA tube and gel separator tube which were labelled immediately with participants' identity code. The tube containing EDTA was used to run the haematologic tests (Full blood count: Hb, total WBC and differential, platelet count). The blood samples in the gel separator tubes were allowed to clot for 30 minutes and then centrifuged at 3000 rpm for 2 minutes at room temperature. The serum was then separated and analysed for creatinine concentration, total cholesterol concentration, HDL-cholesterol concentration, triglycerides concentration and liver function tests. The remaining samples were stored at −80 °C until analysis. All samples were analyzed at the central biochemical laboratory of the TGH.

3.8.2 Objective 5

A record review of HIV-positive patient on ART for the past 3 months' folders were carried out using a checklist that was developed based on the WHO and NACP recommended assessment before ART initiation. It was assumed that any information on history, physical examination, laboratory examination and treatment is what is recorded in the patients' folder. Information on any service not recorded, was deemed not to have been delivered. Heads of the HIV clinics were interviewed using a structured interview guide to determine some of the challenges they are encountering in adhering to the assessment to be done before ART initiation including availability of personnel, services, infrastructure, logistics and supplies (availability of drugs) that are required to support their work. They were also asked if their HIV clinic is equipped enough to treat patients with other co-morbidities especially MetS. HIV-positive patients who were about to start ART were interviewed to determine the type of counselling or guidance given to them before the ART initiation and the challenges they encountered.

3.8.2.1 In-depth Interviews

In-depth interviews were conducted by 2 researchers (moderator/recorder and a note taker) who have experience in qualitative methods and in-depth interviewing. Interview guides were used to facilitate discussion around barriers and facilitators related to baseline assessments to be done before the ART initiation and the ability of the HIV clinic to treat patients with other co-morbidities especially MetS. The in-depth interviews lasted between 20 minutes and 40 minutes.

3.9 Quality Control

Research assistants who can read and write English and are also fluent in Ga, Twi and/ or Ewe were trained. Training entailed explanation of the questionnaire, interview guide, ethics and how to seek informed consent from study participants. Questions in the questionnaire and interview guide were explained to research assistants to prevent interviewer bias. They were also trained to conform to the ethical guidelines of the study. A pre-test of the study questionnaire was done with 20 volunteers at the HIV clinic at Achimota Hospital and all challenges were addressed appropriately. All laboratory analysis were conducted to follow standard operating procedures and all equipment calibrated according to manufacturer's specification. The same person took the anthropometric measures and blood pressure to ensure consistencies and also only one interviewer was trained to conduct the in-depth interviews.

3.10 Data analysis

3.10.1 Objectives 1 to 4

The pre-coded questionnaires were serialised at the time of entry in KoboToolbox and checked for completeness. All the information gathered in the KoboToolbox were exported to Stata/SE 14 (STATA Corp LP, Texas, USA) for statistical analysis. Missing data, inconsistencies and outliers were checked by using the codebook command. Frequency, histogram and line graph were used to check normality of continuous variables. Continuous variables were reported as mean ± Standard Deviation (SD) and all the continuous variables which were found not to be normally distributed were reported as medians and interquartile ranges (IQR). Categorical variables were reported as percentages. The Pearson chi-square test was used to test for statistically significant

associations between categorical variables. For continuous variables, the independent student t-test was used and Wilcoxon rank sum test was used to ascertain statistical difference between 2 medians for metabolic syndrome and non-metabolic syndrome groups. Some continuous variables like triglyceride, fasting blood glucose, LDL cholesterol and HDL Cholesterol values were log-transformed prior to statistical analysis.

Waist-to-height ratio (WHR) (waist/height) and waist-to-hip ratio (WHR) (waist/hip) were calculated. Abdominal obesity was defined as WHR of ≥0.85 for women and WHR of ≥0.90 for men (WHO, 2020). Body Mass Index (BMI) was calculated as weight (kg)/height (m^2). BMI <25.0kg/m^2 was considered as underweight/normal and ≥25.0kg/m^2 was considered as overweight/obese.

All the MetS subcomponents were categorized using the NCEP-ATPIII diagnosis (abdominal obesity (waist circumference ≥88 cm for females and ≥102 cm for males), high TG concentration (≥1.7 mmol/l), low HDL-C concentration (≤1.3 for females and ≤1.1 for males), high Blood pressure (systolic blood pressure (SBP) ≥130mmHg and/or a diastolic blood pressure (DBP) ≥85mmHg) and elevated fasting plasma glucose concentration (>6.1 mmol/l)). MetS based on NCEP-ATPIII diagnosis was defined by the presence of any three of the subcomponents and IDF diagnosis was defined by the presence of abdominal obesity plus any two of the subcomponents.

Prevalence of MetS at screening was calculated as the number of cases at baseline divided by the total screened population using the NCEP-ATPIII diagnosis. The frequencies of all metabolic subcomponents at screening were also determined. Logistic regression was used to estimate the odds ratios and 95% confidence intervals for associations between potential risk factors and MetS with and without adjustment for sociodemographic, clinical and laboratory factors. Univariate models were used to examine the unadjusted associations between covariates and MetS. For the

final multivariable model, only those that were statistically significant ($p \leq 0.05$) were retained in the model.

Incidence of MetS and its subcomponents were evaluated among the cohorts. Person months at risk was calculated from baseline until first MetS diagnosis, death, lost to follow-up and end of follow-up. The incidence rate of MetS and its subcomponents were calculated as the number of incident cases divided by the total person-months at risk. Exact 95% confidence intervals (CI) were calculated under a Poisson distribution.

Independent sample t-test was also used to compare mean age among participants who developed MetS. Kaplan meier curves were used to estimate failure probabilities of the covariates under study and MetS. Bivariate analysis using Chi-squared test was used to identify associations between drug and HIV related factors, socio-demographic, dietary intake, physical activity, tobacco use, alcohol consumption, family and medical history, biochemical and physical measures, and the main outcomes of interest (MetS). The Kaplan Meier failure curves and log rank test statistic was also used to test for equality of survival by background, drug and HIV related factors and MetS. In all statistical analysis that was performed, a p-value of 0.05 was used to determine statistical significance. To determine the relationship between MetS with dolutegravir-based regimen intake and background factors, Cox proportional hazard models (Hazard Ratios) were used to estimate the hazard of MetS. Crude hazards were derived and the strength of their influence on the hazard of MetS using hazard ratios (HR) and their 95% confidence intervals was used for comparisons of their effect on MetS. To examine the contribution of dolutegravir-based regimen on MetS, hazard ratios and their 95% confidence intervals were used for comparisons to determine effect of MetS by the drug intake adjusting for all possible confounders. The Log-Rank test was used to determine whether differences identified in survival between groups was statistically significant.

Data were prepared for survival analysis by creating a time variable for which the event of interest was measured against. The events of interest were captured on a 6-month interval. The time variable was thus generated in 6-months for the 12 months period. This time variable was created in two forms – start date and end time. The start date variable was created to identify the month and year within which dolutegravir-based regimen intake begun. This variable was thus generated for all 300 participants. The end time variable was created to identify the period when one develops MetS or is censored. Data were set to survival time data using STATA command stset and analysis of the data was performed using st commands.

The data was also analysed to estimate the cardiovascular disease risk of the study participants using the 10-year WHO/ISH cardiovascular risk prediction score, 10-year general Framingham cardiovascular risk score (FRS) and the 5-year D:A:D cardiovascular risk score. The variables used in estimating the cardiovascular risk scores were age, sex, blood pressure, systolic blood pressure, FPG level, total cholesterol level, HDL-C level, smoking status, family history of CVD and smoking status. The WHO/ISH cardiovascular risk prediction scores were classified as low risk (<10%), moderate risk (10% to <20%) and high risk (≥20%). Participants were regarded as low risk, moderate risk, or high risk when the risk score for developing CVD in 10 years per the FRS was <10%, 10% to <20% or ≥20 % respectively (Anderson et al., 2013). The risk of developing coronary heart disease in the next 5-years using the D:A:D prediction score was regarded as low (<1 %), moderate (1to <5%) and high/very high risk (≥5 %) (Friis-Møller et al., 2016). The level of agreement between the various risk equations was determined using Cohen's Kappa coefficient with 95% confidence interval. Kappa was interpreted as perfect agreement (>0.80), substantial agreement (0.61-0.80), moderate agreement (0.41-0.60), fair agreement (0.21-0.40) and poor agreement (≤0.20) (Mashinya et al., 2015). It was assumed that the 5-year D:A:D

prediction was constant over a 10-year period for the comparison of the D:A:D 5-year score with the FRS and the WHO/ISH scores.

3.10.2 Objective 5

Qualitative data was transcribed through playing and replaying the voice recorder and also narrating the note taken during interviews. The voice recorder audio was listened to several times in a quiet place. It was then transcribed independently by two research assistants verbatim. The quotes were narrated and cited using participant's code. Thematic areas were identified and arranged based on their themes. Ideas were colour coded and merged. Data was analyzed using Nvivo 12 software.

3.11 Specimen Analysis

3.11.1 Haematologic tests

Two (2)mls to three (3)mls of venus sample was taken into EDTA tube to prevent blood from clotting (2 to 5mins). The sample was then mixed using the sample mixers or roller for about 2 mins. Sample was analysed using the XN-330 analyzer which has a fully integrated IPU (information processing unit) including an LCD color touchscreen that made it easy to operate. The analyzer has a probe that aspirate the sample and measured into different characteristics unit. The results were captured and auto-printed.

3.11.2 Fasting plasma glucose

A glucometer device was used to check the blood sugar levels. A lancet was pierced on the tip of the finger after cleaning with alcohol. A test strip was inserted into the slot provided in the glucometer before pricking the finger which made it easy to add the blood sample to the strip. A small drop of blood was put on the strip so it can be analysed by the glucometer. The glucometer then gave a reading within seconds. This was repeated and the average of the readings was estimated. Glycated Haemoglobin (HbA1c) test was done for those with elevated fasting plasma glucose levels at 12 months.

3.11.3 Total cholesterol

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

3.11.4 High-density lipoprotein cholesterol

High-density lipoprotein cholesterol was measured by the direct enzymatic colorimetric method using Randox RX Monza® chemistry auto analyser (Randox laboratories ltd). A volume of 50µL

of serum was pipetted into the sample well and assayed for high-density lipoprotein cholesterol concentration. The principle behind the method involves the reaction of apoB containing lipoprotein in the sample with a blocking agent, a detergent. This renders them non-reactive and thus the non-HDL lipoprotein LDL, very low-density lipoprotein and chylomicrons are inhibited from reacting with the enzymatic cholesterol reagent. This ensures HDL-cholesterol alone was measured in the reaction assay. The enzymatic endpoint method involves the conversion of esterified HDL-cholesterol to unesterified HDL-cholesterol by the enzyme PEG cholesterol esterase. The resulting unesterified HDL-cholesterol was acted upon by cholesterol oxidase to yield cholestone and H_2O_2. The H_2O_2 produced was then coupled with 4-aminoantipyrine (4-AP) in the presence of peroxidase (POD) to yield a coloured complex quinoneimine, which was measured at 600nm.

3.11.5 Triglycerides

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

quinoneimine, which was measured at 505nm. The intensity of the coloured complex formed was directly proportional to the concentration of total triglycerides in the sample.

3.11.6 Low-density lipoprotein cholesterol (LDL-C)

LDL-C serum concentration was calculated using the Friedewald equation as follows:

[LDL-C] = [Total Cholesterol] - [HDL-C] - ([Triglycerides]/2.2) where all concentrations were in mmol/L (Friedewald et al., 1972).

3.11.7 Creatinine

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

3.11.8 Liver biochemical function test

The Aspartate Transaminase (AST), Alanine Aminotransferase (ALT) and Gamma-glutamyl Transferase (GGT) were run using a Selectra Pro S biochemical analyser (Puteaux, France). This

was an automated biochemical analyser and runs up to 120 photometric tests per hour. Whole blood samples collected in a serum separator tubes (yellow top) were centrifuged at 1000g for 10 minutes to obtain serum. After calibration/ programming, the analyser picked a fixed volume serum from the sample tube for analysis, eliminating all forms of contact with the sample whilst in operation and results were then displayed on the monitor and printed.

3.11.9 Hepatitis B and C

Hepatitis B screening (hepatitis B surface antigen (HBsAg) test) and Hepatitis C screening (HCV antibody test) were performed with a Core technology hepatitis B and C test kits (Beijing, China). This had an accuracy of 99% and sensitivity of 2ng/ml. Following the manufacturers' instructions, drops of whole blood was placed on the sample well of the cassette using a 25µl pipette after which the buffer was added. Results were available in 10-15 minutes. A positive result was indicated by two coloured bands, one in the control region (C) and one in the test region (T). A negative result was also indicated by one coloured band in the control region and no coloured band in the test region.

3.12 Record/specimen storage and protection

Data linked to subjects' identities were collected in anticipation of the need to be able to return laboratory analysis results to those participants who desire it, and also relay significant new knowledge which was obtained. All data and specimens were protected against inappropriate use or disclosure, or malicious or accidental loss in order to protect the confidentiality of subject data. Data were locked with restricted access on a secure laptop which can only be accessed by the Principal investigator.

Specimens of blood were stored for a maximum of 2 weeks during the analysis period to enable us to confirm inconsistent or abnormal results after which they were destroyed as well as the identifiers on their storage containers. Study survey forms (soft copy) were destroyed at the conclusion of the study.

3.13 Return of laboratory results to participants/ Follow-up

Results obtained from the blood samples collected from participants were discussed with them and returned to them after the analysis had been completed. This was done via in-person and phone conversation through the contact numbers they provided and later had copies of the laboratory results given to them in person. Participants with abnormal laboratory results were given the report and the implications of these results explained to them by the principal investigator. These participants were assisted with a referral letter to see the appropriate physician/ specialist for further explanation and medical care.

3.14 Ethical Consideration

Ethical approval (GHS-ERC 005/11/20) was sought from Ghana Health Service Ethics Review Committee. Consent was also taken from the Regional Health Director, Tema Municipal Health Director and the Director of NACP. Permission was also sought from the heads of the selected HIV clinics where the study was conducted. The study was explained to the participants in their own native languages (Twi/Ewe/Ga) if they could not understand the English language. A written informed consent was also sought from the participants. Those who met the inclusion criteria and agreed to participate were made to sign the consent form before they were administered the questionnaire. i.e. participation was voluntary. They were informed of the potential risk in

participating in the study and the benefits with compensation they will receive. The duration of the data collection, sample collection and interview were communicated to them. Declaration of conflict of interest of this study was also communicated to the participants. All responses obtained were kept confidential. Forms for each participant was deleted. The electronic data was locked with a password which is known to the principal investigator to prevent access to unauthorized people.

CHAPTER FOUR

4.0 RESULTS

4.1 Screening

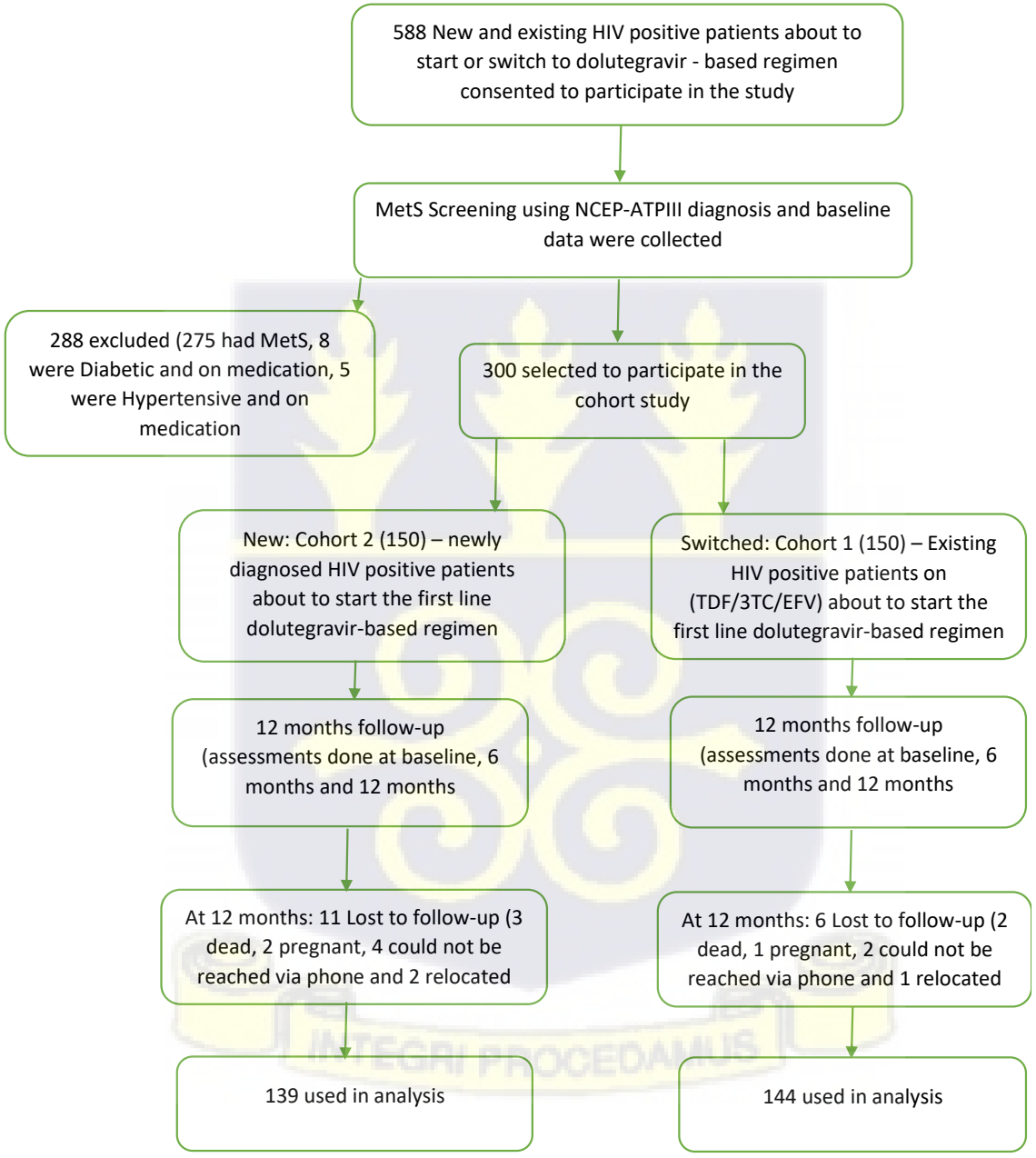


Figure 4. 1: Summary of Cohort study

In all, 588 participants who consented and were eligible to participate in the study were screened for MetS based on the NCEP-ATPIII diagnosis to get the 300 participants needed for the cohort study. Of the 500 participants, 288 were excluded because 275 had MetS, 8 were diabetic and on medication and 5 were hypertensive and were on medication. There were 150 participants in each cohort (newly diagnosed HIV positive patients about to start the first line dolutegravir-based regimen and the Existing HIV positive patients on (TDF/3TC/EFV) about to switch to the first line dolutegravir-based regimen). Each cohort was followed for 12 months at which data was collected at baseline, 6 months, and 12 months. At the end of the follow-up period, 11 were lost to follow-up (3 dead, 2 pregnant, 4 could not be reached via phone and 2 relocated) in the New cohort and 6 were lost to follow-up (2 dead, 1 pregnant, 2 could not be reached via phone and 1 relocated) in the Switched cohort as shown in Figure 4.1. In all 283 participants were used in some of the statistical analysis (New cohort (139) and Switched cohort (144).

4.1.1 Socio-demographic characteristics of screened participants

In all, 588 HIV positive patients were screened of which 64.5% (450) were between 31-50 years. Most have had education to middle or Junior High School (JHS). Majority of the participants were married (45.7%) and also employed (84.1%) as shown in Table 4.1. Using the NCEP-ATPIII criteria for MetS diagnosis, 46.8% had MetS compared with 23.8% when the IDF diagnosis was used. Among those with MetS, the majority (57.5%) were between ages 41-50 while 68.5% of those without MetS were between 18-30 years. The difference among those with MetS and those without MetS in terms of the age groups, sex and employment status were significant ($p<0.001$).

Table 4. 1: Socio-demographic characteristics of screened HIV positive participants for eligibility by MetS status at the Tema General Hospital

Variables (N=588)	N (%)	MetS Status		P-value
		Present	Absent	
Age (Years)				
Age (mean± SD)	40.61 ± 10.73			<0.001*
18-30	111 (18.9)	35 (31.5)	76 (68.5)	
31-40	191 (32.4)	85 (44.5)	106 (55.5)	
41-50	188 (32.0)	108 (57.5)	80 (42.6)	
51-60	71 (12.1)	39 (54.9)	32 (45.1)	
>60	27 (4.6)	8 (29.6)	19 (70.4)	
Sex				<0.001*
Male	177 (30.1)	54 (30.5)	123 (69.5)	
Female	411 (69.9)	221 (53.8)	190 (46.2)	
Highest Education				0.427
No Formal Education	93 (15.8)	51 (54.8)	42 (45.2)	
Primary	104 (17.7)	50 (48.1)	54 (51.9)	
Middle/ JHS	247 (42.0)	113 (45.8)	134 (54.2)	
Secondary/ SHS	99 (16.8)	41 (41.4)	58 (58.6)	
Tertiary	45 (7.7)	20 (44.4)	25 (55.6)	
Ethnicity				0.255
Akan	217 (36.9)	110 (50.7)	107 (49.3)	
Ga Adangbe	98 (16.7)	38 (38.8)	60 (61.2)	
Ewe	192 (32.7)	91 (47.4)	101 (52.6)	
Northern	81 (13.8)	36 (44.4)	45 (55.6)	
Marital Status				0.054
Single	194 (33.0)	79 (40.7)	115 (59.3)	
Married/Co-Habiting	269 (45.7)	128 (47.6)	141 (52.4)	
separated/Divorced/Widowed	125 (21.3)	68 (54.4)	57 (45.6)	
Employment Status				<0.001*
Student	24 (4.1)	2 (8.3)	22 (91.7)	
Employed	493 (84.1)	229 (46.5)	264 (53.5)	
Unemployed	69 (11.8)	42 (60.9)	27 (39.1)	
Smoking Habit				0.856
Smokes	44 (7.5)	20 (45.50)	24 (54.5)	
Does not smoke	544 (95.5)	255 (46.9)	289 (53.1)	
Alcohol Intake				0.430
Takes in alcohol	115 (19.6)	50 (43.5)	65 (56.5)	
Does not take alcohol	473 (80.4)	225 (47.6)	248 (52.4)	
Total	**588**	**275 (46.8)**	**313 (53.2)**	

*Statistically significant using a chi square test

4.1.2 Clinical characteristics of screened participants

Of the 588 people screened, 61.7% had changed their medication from the Efavirenz-based combination to Dolutegravir-based combination. Majority started the ARVs in Stage 1 of HIV. Those with MetS had abnormal and elevated levels of the MetS components (Fasting blood Glucose, Blood Pressure, Triglyceride, Waist Circumference and HDL-Cholesterol) as compared with those without MetS and this difference was statistically significant (Table 4.2). Most of those without MetS had abnormal HDL-C (56%). Those on ART had a statistically significant higher prevalence of MetS (56.5%) as compared to the ART naïve participants (31.1%).

Table 4. 2: Clinical characteristics of screened HIV positive participants for eligibility by MetS status at the Tema General Hospital

Variables (N=588)	N (%)	MetS Status		P-value
		Present	Absent	
ART Status				<0.001*
ART Naïve	225 (38.3)	70 (31.1)	155 (68.9)	
On ART	363 (61.7)	205 (56.5)	158 (43.5)	
WHO Stage at Diagnosis				0.370
Stage I	458 (77.9)	214 (46.7)	244 (53.3)	
Stage II	57 (9.7)	28 (49.1)	29 (50.9)	
Stage III	50 (8.5)	26 (52.0)	24 (48.0)	
Stage IV	23 (3.9)	7 (30.4)	16 (69.6)	
Blood Pressure (mmHg)				<0.001*
Diastolic – Median (IQR)	77 (68,85)	73 (65,81)	79.5 (71, 89)	
Systolic – Median (IQR)	121 (108, 138)	118.5 (105,134)	125 (112, 144)	
Non Hypertensive	331 (56.3)	99 (29.9)	232 (70.1)	
Hypertensive	257 (43.7)	176 (68.5)	81 (31.5)	
Waist Circumference (cm)				<0.001*
Mean±SD	83.12 ± 13.7			
Abdominal Obesity Absent	397 (67.5)	160 (40.3)	237 (59.7)	
Abdominal Obesity Present	191 (32.5)	115 (60.2)	76 (39.8)	
HDL- Cholesterol (mmol/L)				<0.001*
Median (IQR)	1.27 (1.03, 1.60)	1.16 (0.92, 1.5)	1.39 (1.12, 1.62)	
Normal HDL-C	395 (67.2)	174 (44.0)	221 (56.0)	
Abnormal HDL-C	193 (32.8)	101 (52.3)	92 (47.7)	
Fasting Blood Glucose (mmol/L)				<0.001*
Median (IQR)	6.10 (5.60, 6.80)	6.30 (5.90, 6.80)	5.80 (5.20, 6.80)	
Normal	137 (23.3)	19 (13.9)	118 (86.1)	
Elevated	451 (76.7)	256 (56.8)	195 (43.2)	
Triglyceride (mmol/L)				<0.001*
Median (IQR)	1.12 (0.86, 1.61)	1.47 (0.94, 1.97)	0.99 (0.8, 1.25)	
Normal Triglycerides	451 (76.7)	160 (35.5)	291 (64.5)	
Elevated Triglycerides	137 (23.3)	115 (83.9)	22 (16.1)	

***Statistically significant using a chi square test and wilcoxon rank sum test; **IQR**: Interquartile Range; **ART**: Antiretroviral therapy; **SD**: Standard deviation; **HDL**: High density lipoprotein

4.1.3 Prevalence of MetS syndrome and the subcomponents of screened participants

Figure 4.2 shows the prevalence of MetS syndrome using NCEP-ATPIII diagnosis and the subcomponents of MetS. The prevalence of MetS using the NCEP-ATPIII diagnosis was 46.8% with 93.1% and 64% of those with MetS having elevated fasting blood glucose levels and blood

pressure respectively. Among those screened, those with MetS had abnormal levels of all the MetS components as shown in Figure 4.2.

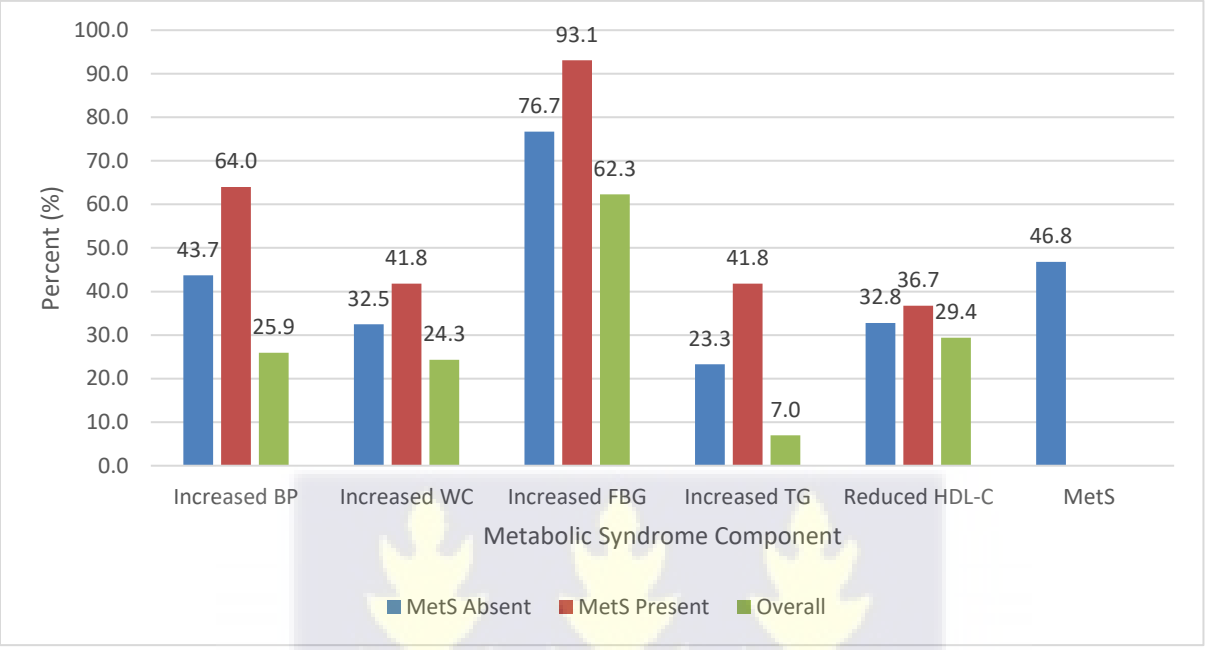


Figure 4. 2: Prevalence of metabolic subcomponents and metabolic syndrome among screened HIV positive participants for eligibility at the Tema General Hospital

4.1.4 Logistic regression modelling of factors associated with MetS of screened participants

4.1.4.1 Univariate analysis of factors associated with MetS

A test of the strength of the association of the socio-demographic characteristics of the screened participants using a univariate logistic model showed that there was strong evidence of association between the age, sex, employment status and MetS ($p<0.001$). Compared with those between ages 18-30 years, the odds of people between ages 41-60 developing MetS was about three times. People who smoke and take in alcohol were 94% and 85% respectively more likely to develop MetS than those who do not smoke or take in alcohol (Table 4.3). The study revealed that marital

status and highest level of education did not influence the development of MetS (p=0.053 & p=0.427 respectively).

Those who were on ART (Efavirenz-based regimen) were about 1.23 more likely to develop MetS as compared to the ART naïve even though the difference was not significant. Participants with hypertension were about 5 times more likely to develop MetS as compared with the non-hypertensives (95% CI: 3.58-7.25) as shown in Table 4.4. Univariate logistic model also showed strong evidence of association (p<0.001) between the metabolic subcomponents (blood pressure, waist circumference, HDL-Cholesterol, blood fasting glucose and triglyceride) and MetS to varying extent (Table 4.4). The odds of developing MetS with abdominal obesity was twice that among those without abnormal obesity. Those with elevated HDL-Cholesterol had lower odds of developing MetS (OR=0.27; 95% CI: 0.16-0.46).

Table 4. 3: Crude analysis of factors associated with MetS among screened HIV positive participants for eligibility at the Tema General Hospital

	Unadjusted		
Variables (N=588)	**OR**	**95% CI**	**P-value**
Age (Years)	1.02	1.01-1.04	
Age groups			<0.001*
18-30	Ref		
31-40	1.74	1.06-2.85	
41-50	2.93	1.79-4.80	
51-60	2.65	1.43-4.90	
>60	0.91	0.37-2.29	
Sex			<0.001*
Male	Ref		
Female	0.38	0.26-0.55	
Highest Education			0.427
No Formal Education	Ref		
Primary	1.44	0.89-2.32	
Middle/ JHS	1.10	0.69-1.74	
Secondary/ SHS	0.84	0.52-1.34	
Tertiary	0.95	0.50-1.80	
Ethnicity			0.252
Akan	Ref		
Ga Adangbe	0.62	0.38-1.00	
Ewe	0.88	0.59-1.29	
Northern	0.78	0.47-1.30	
Marital Status			0.053
Single	Ref		
Married/Co-Habiting	0.76	0.52-1.10	
Separated/Divorced/Widowed	1.31	0.86-2.01	
Employment Status			<0.001*
Student	Ref		
Employed	0.10	0.02-0.45	
Unemployed	1.79	1.07-3.00	
Smoking Habit			0.856
Smokes	Ref		
Does not smoke	0.94	0.51-1.75	
Alcohol Intake			0.430
Takes in alcohol	Ref		
Does not take alcohol	0.85	0.56-1.28	

*Statistically significant; **JHS**: Junior High School; **SHS**: Senior High School

Table 4. 4: Crude analysis of factors associated with MetS among screened HIV positive participants for eligibility at the Tema General Hospital

	Unadjusted		
Variables (N=588)	**OR**	**95% CI**	**P-value**
ART Status			0.210
ART Naïve	Ref		
On ART	1.23	0.88-1.72	
WHO Stage at Diagnosis			0.133
Stage I	Ref		
Stage II	1.10	0.63-1.91	
Stage III	1.24	0.69-2.22	
Stage IV	0.50	0.20-1.24	
Blood Pressure			<0.001*
Non Hypertensive	Ref		
Hypertensive	5.09	3.58-7.25	
Waist Circumference			<0.001*
Abdominal Obesity Absent	Ref		
Abdominal Obesity Present	2.24	1.58-3.19	
HDL- Cholesterol	0.27	0.16-0.46	<0.001*
Fasting Blood Glucose	7.8	3.25-18.74	<0.001*
Triglyceride	4.29	2.92-6.29	<0.001*

***Statistically significant; **ART**: Antiretroviral therapy; **HDL**: High density lipoprotein; **WHO**: World Health Organization

4.1.4.2 Multivariable logistic regression analysis of factors associated with MetS

Multivariable logistic regression analysis which adjusted for the effects of all the possible risk factors which were significantly associated after univariate analysis found sex, hypertension, abnormal waist circumference, low HDL-Cholesterol levels, elevated blood fasting glucose and elevated triglyceride to be independently associated with MetS (p<0.001) [Table 4.5]. The results of this model showed that many of the socio-demographic variables had insignificant P values and, in general, precision about point estimates was low.

Sex and those with low HDL-Cholesterol levels were associated with lower odds of developing MetS (OR 0.66, 95% CI; 0.04-0.13 and OR 0.04, 95% CI; 0.02-0.09 respectively) indicative of

moderate positive relationship (Table 4.5). Those with elevated fasting blood glucose and elevated blood pressure had the highest odds of developing MetS in the presence of other factors as compared with all the independent factors associated with MetS (OR=26.52, 95% CI. 7.56-92.92 and OR=15.57, 95% CI. 8.92-27.15 respectively) [Table 4.5]. In the presence of other factors, the odds of developing MetS increased among all the MetS subcomponents and also there was strong evidence of association between them and having MetS (p<0.001) as shown in Tables 4.4 and 4.5.

Table 4. 5: Risk factors associated with MetS among screened HIV positive participants for eligibility at the Tema General Hospital

	Adjusted		
Variables (N=588)	**OR**	**95% CI**	**P-value**
Age	0.98	0.96-1.01	0.136
Sex			<0.001*
Male	Ref		
Female	0.66	0.04-0.13	
Blood Pressure			<0.001*
Non Hypertensive	Ref		
Hypertensive	15.57	8.92-27.15	
Waist Circumference			<0.001*
Abdominal Obesity Absent	Ref		
Abdominal Obesity Present	4.94	2.76-8.84	
HDL- Cholesterol	0.04	0.02-0.09	<0.001*
Fasting Blood Glucose	26.52	7.56-92.92	<0.001*
Triglyceride	9.95	5.71-17.31	<0.001*

*Statistically significant; **HDL**: High density lipoprotein

4.2 Cohort Study

4.2.1 Follow-up

At the end of the 12-months follow-up, 17 participants were lost to follow-up of which 2 were lost at 6 months. The median follow-up duration was 11.99 months (IQR [11.97,11.99]) with no difference between the two cohorts, and the at-risk period was estimated to 3311.08 person-months and 275.95 person-years of observation. The mean weight was 63.84kg at baseline and increased

to 70.97kg and 73.77kg, at 6 and 12 months respectively. Almost all the metabolic components increased over the 12-months period, with the exception of the median HDL-Cholesterol which reduced at the end of the 12 months and the median Triglyceride level also decreasing at 6 months and increasing at 12 months as evident in Table 4.6. The creatinine levels, ALT and AST levels also increased over the 12-month period as shown in Table 4.6.

Table 4. 6: Changes in anthropometric and biochemical parameters of cohort participants during the follow-up period at the Tema General Hospital

Variables (N=300)	**Follow-up Period**		
	Baseline	**6 months**	**12 months**
Weight (kg)			
Mean ± SD	63.84 ± 12.27	70.97 ± 12.92	73.77 ± 14.20
Waist Circumference (cm)			
Mean ± SD	77.97 ± 11.73	82.17 ± 13.95	87.49 ± 12.95
Blood Pressure (mmHg)			
Diastolic – Median (IQR)	77 (68, 85)	78 (68, 89)	83 (73, 95)
Systolic – Median (IQR)	121 (108,138)	127 (114, 144)	139.5 (120, 157)
HDL- Cholesterol (mmol/L)			
Median (IQR)	1.42 (1.17, 1.64)	1.45 (0.98, 1.75)	1.34 (0.95, 1.98)
Triglyceride (mmol/L)			
Median (IQR)	1.01 (0.80, 1.38)	0.98 (0.70, 1.47)	1.32 (0.95, 1.79)
Fasting Blood Glucose (mmol/L)			
Median (IQR)	5.40 (5.30, 5.50)	5.40 (5.20, 6.10)	5.50 (5.30, 5.90)
Creatinine Level ($\times 10^3/\mu L$)			
Mean ± SD	88.47 ± 41.57	100.04 ± 29.26	116.51 ± 57.60
AST (U/L)			
Mean ± SD	37.10 ± 21.57	43.63 ± 25.24	46.82 ± 25.63
ALT (U/L)			
Mean ± SD	33.50 ± 22.64	36.01 ± 20.95	39.89 ± 22.45

IQR: Interquartile Range; **AST**: Aspartate transaminase; **ALT**: Alanine Aminotransferase; **SD**: Standard deviation; **HDL**: High density lipoprotein

4.2.2 Baseline socio-demographic characteristics of sampled participants

Table 4.7 summarizes the baseline socio-demographic characteristics of the study population. In all, 300 HIV positive patients were sampled (150 per cohort) and followed for one year. At

baseline, those who switched to dolutegravir-based regimen (Switched) were older in mean age (43.50±9.48) than those who had been newly diagnosed with HIV and were initiated on dolutegravir-based regimen (New) [37.80±10.89] and this difference was statistically significant ($p<0.001$). The difference between the age groups among those starting and those switching to dolutegravir-based regimen was statistically significant ($p<0.001$) with 64% and 37% being below 40 years among the New and Switched cohorts respectively. Majority of the participants were females (71%) and also have had education to the Middle/JHS level (43%). Most of the participants were employed (80.7%) with seventy-three percent (73%) earning less than 500 Ghana cedis (GHS500.00) monthly. Even though majority of the participants lived in and around where they receive their medication (75%), some lived as far as 41km away. About 75% of the participants lived with other relatives. With exception of ethnicity and number of adults in the household, there was a statistically significant difference between the New and Switched participants for all the socio-demographic variables ($p<0.05$).

Table 4. 7: Socio-demographic characteristics of sampled participants at baseline by ART Status at the Tema General Hospital

Variables (N=300)	N (%)	Cohort		P-value
		New	Switched	
Age				
Age (mean± SD)	40.65± 10.58	37.80±10.89	43.50±9.48	<0.001*
18-30	56 (18.7)	43 (76.8)	13 (23.2)	
31-40	96 (32.0)	53 (55.2)	43 (44.8)	
41-50	99 (33.0)	36 (36.4)	63 (63.6)	
51-60	36 (12.0)	11 (30.6)	25 (69.4)	
>60	13 (4.3)	7 (53.9)	6 (46.1)	
Sex				0.001*
Male	87 (29.0)	57 (65.5)	30 (34.5)	
Female	213 (71.0)	93 (43.7)	120 (56.3)	
Highest Education				0.016*
No Formal Education	46 (15.3)	19 (41.3)	27 (58.7)	
Primary	52 (17.3)	31 (59.6)	21 (40.4)	
Middle/ JHS	129 (43.0)	54 (41.9)	75 (58.1)	
Secondary/ SHS	50 (16.7)	33 (66.0)	17 (34.0)	
Tertiary	23 (7.7)	13 (56.5)	10 (43.5)	
Ethnicity				0.832
Akan	111 (37.0)	55 (49.5)	56 (50.5)	
Ga Adangbe	47 (15.7)	25 (53.2)	22 (46.8)	
Ewe	99 (33.0)	51 (51.5)	48 (48.5)	
Northern	43 (14.3)	19 (44.2)	24 (55.8)	
Marital Status				0.028*
Single	**135 (45.0)**	**74 (54.8)**	**61 (45.2)**	
Married/Co-Habiting	100 (33.3)	53 (53.0)	47 (47.0)	
separated/Divorced/Widowed	65 (21.7)	23 (35.4)	42 (64.6)	
Employment Status				0.019*
Student	24 (8.0)	18 (75.0)	6 (25.0)	
Employed	242 (80.7)	119 (49.2)	123 (50.8)	
Unemployed	34 (11.3)	13 (38.2)	21 (61.8)	
Monthly Income Level (GHS)				0.003*
<=500	220 (73.3)	97 (44.1)	123(55.9)	
501-1000	54 (18.0)	37 (68.5)	17 (31.5)	
>1000	26 (8.7)	16 (61.5)	10 (38.5)	
Residence in and around Tema Metropolis				<0.001*
Resides in and around Tema	225 (75.0)	94 (41.8)	131 (58.2)	
Does not reside in and around Tema	75 (25.0)	56 (74.7)	19 (25.3)	
Number of Adults in Household				0.142
Living Alone	75 (25.0)	32 (42.7)	43 (57.3)	
Live with Others	225 (75.0)	118 (52.4)	107 (47.6)	

***Statistically significant using chi square test; **JHS**: Junior High School; **SHS**: Senior High School; **SD**: Standard Deviation; **GHS**: Ghana cedis

4.2.3 HIV, ART and Behavioural characteristics of sampled participants at baseline

Majority of participants were diagnosed with HIV at WHO Stage I (77%). Among those who were already receiving ART (Efavirenz-based regimen) and were switched to receive the dolutegravir-based regimen, majority had been on medication between 12-60 months (58.3%) as shown in Table 4.8. At the end of the 1 year follow-up, almost all the participants had their viral loads below 1000copies/µL and there was also no statistically significant difference between the cohorts ($p=0.294$). Some participants (21.9%) reported some drug-related side effects during the follow-up period of which the most predominant complaints were headache (25.8%), Diarrhoea (5%) and lack of sleep (22.6%) as shown in Table 4.8. Eleven (11%) and Six percent (6%) of the participants had family history of hypertension and diabetes respectively. Only few of the participants were current smokers (0.7%) and nineteen percent (19%) were consuming alcohol. Majority were physically active (79.9%). With the exception of WHO stage at diagnosis, family history of hypertension and physical activity, all the other factors were not statistically significant among the two cohorts ($p>0.05$) as shown in Table 4.8.

Table 4. 8: HIV, ART and Behavioural characteristics of sampled participants at baseline by ART Status at the Tema General Hospital

Variables (N=300)	N (%)	Cohort		P-value
		New	Switched	
WHO Stage at Diagnosis				0.006*
Stage I	231 (77.0)	112 (48.5)	119 (51.5)	
Stage II	31 (10.3)	11 (35.5)	20 (64.5)	
Stage III	26 (8.7)	16 (61.5)	10 (38.5)	
Stage IV	12 (4.0)	11 (91.7)	1 (8.3)	
ART Duration (TDF/3TC/EFV) – Months, N=144				
<12			43 (29.9)	
12-60			84 (58.3)	
>60			17 (11.8)	
Viral Load (copies/µL), (N=283)				0.294
<1000	262 (92.6)	131 (50.0)	131 (50.0)	
≥1000	21 (7.4)	8 (49.1)	13 (50.9)	
Drug related side effects (N=62)				0.624
Diarrhoea	14 (22.6)	7 (50.0)	7 (50.0)	
Dizziness/Nausea/Thirsty	11 (17.7)	8 (72.7)	3 (27.3)	
Headache	16 (25.8)	9 (56.3)	7 (43.8)	
Itching	8 (12.9)	4 (50.0)	4 (50.0)	
Lack of Sleep	13 (21.0)	5 (38.5)	8 (61.5)	
None (N=221)	**221 (78.1)**	**106 (48.0)**	**115 (52.0)**	
Family History of Hypertension				0.004*
Family history of hypertension	34 (11.3)	9 (26.5)	25 (73.5)	
No family history of hypertension	266 (88.7)	141 (53.0)	125 (47.0)	
Family History of Diabetes				0.331
Family history of Diabetes	18 (6.0)	7 (38.9)	11 (61.1)	
No family history of Diabetes	282 (94.0)	143 (50.7)	139 (49.3)	
Smoking Habit				0.156
Smokes	2 (0.7)	2 (100.0)	0 (0.0)	
Does not smoke	298 (99.3)	148 (49.7)	150 (50.3)	
Alcohol Intake				0.303
Takes in alcohol	57 (19.0)	32 (56.1)	25 (43.9)	
Does not take alcohol	243 (81.0)	118 (48.6)	125 (51.4)	
Physical Activity				0.015*
Exercises	239 (79.7)	111 (46.4)	128 (53.6)	
Does not exercise	61 (20.3)	39 (63.9)	22 (36.1)	
Fruit Intake (days in a week)				0.418
0-2	157 (52.3)	82 (52.2)	75 (47.8)	
3-7	143 (47.7)	68 (47.6)	75 (52.4)	
Vegetable Intake (days in a week)				0.816
0-2	130 (43.3)	66 (50.8)	64 (49.2)	
3-7	170 (56.7)	84 (49.4)	86 (50.6)	

*Statistically significant using chi square test; **ART**: Antiretroviral therapy; **WHO**: World Health Organization

4.2.4 Haematological, Biochemical, Blood pressure and Anthropometric parameters of sampled participants at baseline

The mean Haemoglobin level among the participants at baseline was 11.83 ± 2.81g/dL with 11.62 ± 2.83g/dL among the New cohort and 12.05 ± 2.78g/dL among the Switched cohort. There was no statistically significant difference between the mean levels of the Haematological parameters among the groups ($p>0.05$) as evident in Table 4.9. Almost 50% of the participants had abnormal lymphocytes levels with more participants in the Switched cohort (63.5%) having abnormal levels compared to the New cohort (36.5%). This difference was statistically significant ($p<0.001$) as shown in Table 4.9. Seventy-three percent (73%) of the New cohort had abnormal Creatinine levels as compared to 27% among the Switched cohort and this difference was statistically significant ($p=0.007$). Liver function test conducted showed that the mean levels of AST (40.32 ± 26.69U/L) and ALT (36.72 ± 27.89U/L) were higher among the New cohort as compared to the Switched cohort (AST (33.89 ± 14.14U/L) and ALT (30.29 ± 15.16U/L)) and the difference was statistically significant ($p=0.005$ and $p=0.007$ respectively). Fifteen percent (15%) and six percent (6%) of the participants tested positive for Hepatitis B and Hepatitis C respectively as shown in Table 4.9. The mean weight of the participants in the two cohorts at baseline were 61.98 ± 12.94kg in the New cohort and 65.69 ± 11.29kg in the Switched cohort. This difference was statistically significant ($p=0.004$). At baseline, 40% of the participants were hypertensive and 31.3% had hypercholesterolemia. The difference between those with abnormal platelets levels, low HDL-C, hypercholesterolemia and abnormal LDL-Cholesterol among the New and Switched cohorts were statistically significant ($p<0.05$) as Shown in Table 4.10.

Table 4. 9: Haematological and Biochemical parameters of sampled participants at baseline by ART Status at the Tema General Hospital

Variables (N=300)	N (%)	Cohort		P-value
		New	Switched	
Haemoglobin level (g/dL)				0.177
Mean± SD	11.83 ± 2.81	11.62 ± 2.83	12.05 ± 2.78	
Normal	141 (47.0)	65 (46.1)	76 (53.9)	
Anaemic	159 (53.0)	85 (53.5)	74 (46.5)	
Platelets ($\times 10^3/\mu L$)				0.017*
Mean± SD	243.96 ± 95.32	236.47 ± 96.89	251.44 ± 93.44	
Normal	219 (73.0)	109 (49.8)	110 (50.2)	
Abnormal	81 (27.0)	41 (50.6)	40 (49.4)	
White blood cell ($\times 10^3/\mu L$)				0.276
Mean± SD	8.18 ± 5.29	8.07 ± 5.56	8.30 ± 5.02	
Normal	195 (65.0)	93 (47.7)	102 (52.3)	
Abnormal	105 (35.0)	57 (54.3)	48 (45.7)	
Red blood cell ($\times 10^3/\mu L$)				0.064
Mean± SD	4.34 ± 1.03	4.23 ± 1.00	4.45 ± 1.04	
Normal	216 (72.0)	105 (48.6)	111 (51.4)	
Abnormal	84 (28.0)	45 (53.6)	39 (46.4)	
Lymphocytes ($\times 10^3/\mu L$)				<0.001*
Mean± SD	47.12 ± 25.10	43.07 ± 21.96	51.18 ± 27.93	
Normal	152 (50.7)	96 (63.2)	56 (36.8)	
Abnormal	148 (49.3)	54 (36.5)	94 (63.5)	
Monocytes ($\times 10^3/\mu L$)				<0.001*
Mean± SD	7.71 ± 6.50	8.97 ± 6.81	6.45 ± 5.92	
Normal	215 (71.7)	103 (47.9)	112 (52.1)	
Abnormal	85 (28.3)	47 (55.3)	38 (44.7)	
Creatinine Level ($\times 10^3/\mu L$)				0.007*
Mean ± SD	88.47 ± 41.57	91.82 ± 54.84	85.12 ± 20.93	
Normal	270 (90.0)	128 (47.4)	142 (52.6)	
Abnormal	30 (10.0)	22 (73.3)	8 (26.7)	
AST (U/L)				0.005*
Mean ± SD	37.10 ± 21.57	40.32 ± 26.69	33.89 ± 14.14	
Elevated levels (>40)	148 (49.3)	78 (52.7)	70 (47.3)	
ALT (U/L)				0.001*
Mean ± SD	33.50 ± 22.64	36.72 ± 27.89	30.29 ± 15.16	
Elevated levels (>40)	86 (28.7)	56 (65.1)	30 (34.9)	
Hepatitis B				0.258
Negative	255 (85.0)	124 (48.6)	131 (51.4)	
Positive	45 (15.0)	26 (57.8)	19 (42.2)	
Hepatitis C				0.145
Negative	282 (94.0)	138 (48.9)	144 (51.1)	
Positive	18 (6.0)	12 (66.7)	6 (33.3)	

***Statistically significant using chi square test; **SD**: Standard Deviation

Table 4. 10: Anthropometric and Biochemical parameters of cohort participants at baseline by ART Status at the Tema General Hospital

Variables (N=300)	**N (%)**	**Cohort**		**P-value**
		New	**Switched**	
Height (cm) – Mean ± SD	163.91 ± 8.28	164.46 ± 8.80	163.37 ± 7.72	0.254
Weight (cm) – Mean ± SD	63.84 ± 12.27	61.98 ± 12.94	65.69 ± 11.29	0.004*
Hip Circumference (cm) – Mean ± SD	93.96 ± 15.66	86.94 ± 15.09	100.98 ± 12.85	<0.001*
BMI (kg/m^2)				0.004*
Underweight (<18.5)	36 (12.0)	27 (75.0)	9 (25.0)	
Healthy Weight (18.5-24)	155 (51.7)	79 (51.0)	76 (49.0)	
Overweight (25-29)	79 (26.3)	32 (40.5)	47 (59.5)	
Obese (>30)	30 (10.0)	12 (40.0)	18 (60.0)	
WHR				0.288
Abdominal Obesity Absent	181 (60.3)	86 (47.5)	95 (52.5)	
Abdominal Obesity Present	119 (39.7)	64 (53.8)	55 (46.2)	
Waist Circumference (cm)				<0.001*
Mean ± SD	77.97 ± 11.73	73.64 ± 11.59	82.31 ± 10.19	
Abdominal Obesity Absent	267 (89.0)	139 (52.1)	128 (47.9)	
Abdominal Obesity Present	33 (11.0)	11 (33.3)	22 (66.7)	
Blood Pressure (mmHg)				0.001*
Diastolic – Median (IQR)	77 (68, 85)	78 (68, 89)	83 (73, 95)	
Systolic – Median (IQR)	121 (108,138)	127 (114, 144)	139.5 (120, 157)	
Non Hypertensive	180 (60.0)	97 (53.9)	83 (46.1)	
Hypertensive	120 (40.0)	53 (44.2)	67 (55.8)	
Total cholesterol (mmol/L)				<0.001*
Mean ± SD	4.73 ± 1.24	4.41 ± 1.13	5.05 ± 1.26	
Normal	206 (68.7)	115 (55.8)	91 (44.2)	
Hypercholesterolemia	94 (31.3)	35 (37.2)	59 (62.8)	
HDL- Cholesterol (mmol/L)				<0.001*
Median (IQR)	1.42 (1.17, 1.64)	1.36 (1.12, 1.58)	1.43 (1.28, 1.73)	
Normal	240 (80.0)	104 (43.3)	136 (56.7)	
Abnormal	60 (20.0)	46 (76.7)	14 (23.3)	
LDL- Cholesterol (mmol/L)				<0.001*
Mean ± SD	2.83 ± 0.93	2.60 ± 0.88	3.06 ± 0.92	
Normal	218 (72.7)	119 (54.6)	99 (45.4)	
Abnormal	82 (27.3)	31 (37.8)	51 (62.2)	
Triglyceride (mmol/L)				0.148
Median (IQR)	1.01 (0.80, 1.38)	1.03 (0.84, 1.38)	1.00 (0.79, 1.35)	
Normal Triglycerides	270 (90.0)	136 (50.4)	134 (49.6)	
Elevated Triglycerides	30 (10.0)	14 (46.7)	16 (53.3)	
Fasting Blood Glucose (mmol/L)				0.019*
Median (IQR)	5.40 (5.30, 5.50)	5.40 (5.20, 5.50)	5.40 (5.30, 5.50)	
Normal	242 (80.7)	125 (51.7)	117 (48.3)	
Elevated	58 (19.3)	25 (43.1)	33 (56.9)	

***Statistically Significant; **IQR**: Interquartile Range; **SD**: Standard deviation; **HDL**: High density lipoprotein; **LDL**: Low density lipoprotein; **BMI**: Body Mass Index; **WHR**: Waist-to-hip-ratio

4.2.5 Objective 1: Incidence of MetS and its subcomponents among sampled participants

The overall incidence rate of MetS per 100 person-months (pmo) on dolutegravir based-regimen using the NCEP-ATPIII diagnosis at the end of the 12 months follow-up was 3.47 (CI:2.89-4.17) and incidence rate of 41.68 (34.71-50.03) per 100 person-years with an incidence of 115. At 6 months, the incidence of MetS was 28 with an incidence rate of 1.56 (CI: 1.07-2.25) per 100 person-months and incidence of 87 between 6-12 months at an incidence rate of 5.75 (CI: 4.66-7.10) per 100 person-months.

Also, the incidence rate of MetS per 100 person-months after 12 months on dolutegravir based-regimen was higher among the Switched cohort (4.72, CI: 3.78 – 5.89) at an incidence of 78 compared with the New cohort (2.23, CI: 1.62 – 3.08) at an incidence of 37. Among the metabolic subcomponents, Waist circumference recorded the highest incidence (100) with an incidence rate of 3.31 (CI: 2.72 – 4.02) per 100 person-months with blood pressure having the lowest incidence (73) with an incidence rate of 3.54 (CI: 2.82 – 4.46) per 100 person-months as shown in Table 4.11.

Table 4. 11: Estimated incidence rate per 100 person-months of sampled participants at the Tema General Hospital

Variables (N=300)	Person-months	Failure (Incidence)	Incidence Rate per 100 pmo	95% Confidence Interval
MetS (NCEP-ATPIII)	3311.08	115	3.47	2.89 – 4.17
DTG-based Regimen Duration (Months)				
0-6	1798.74	28	1.56	1.07 – 2.25
6-12	1512.34	87	5.75	4.66 – 7.10
Cohort				
New	1658.37	37	2.23	1.62 – 3.08
Switched	1652.71	78	4.72	3.78 – 5.89
MetS Components				
Abdominal Waist Circumference	3023.97	100	3.31	2.72 – 4.02
High Blood Pressure	2060.06	73	3.54	2.82 – 4.46
Low HDL- Cholesterol	2790.41	82	2.94	2.37 – 3.65
Elevated Triglyceride Levels	3089.77	75	2.42	1.94 – 3.04
Elevated Fasting Blood Glucose	2760.04	79	2.86	2.30 – 3.57

MetS: Metabolic Syndrome; **DTG**: Dolutegravir; **NCEP-ATPIII**: National Cholesterol Education Program Adult Treatment Panel III; **HDL**: High Density Lipoprotein; **pmo:** person months

4.2.6 Objective 2: Effect of dolutegravir-based regimen on MetS among sampled participants

After 12 months on dolutegravir based regimen, 115 (38.3%) and 74 (24.7%) of the participants developed MetS based on NCEP-ATPIII and IDF diagnosis respectively. The probability of developing MetS after 12 months on DTG varied significantly according to the two cohorts (log-rank test p-value<0.001), with those initiating ART with dolutegravir-based regimen having lower probability (89%) of developing MetS than those already on ART and are switching to dolutegravir-based regimen (92%) as shown in Figure 4.3. All the cohorts had the same experience of MetS development (100% probability) between 0 to 6 months after ART initiation. Even though some developed MetS at 6 months (28), majority had MetS after 12 months (87) on dolutegravir. Bivariate analysis reported relationships between MetS and ART exposure. In general, the hazard

of developing MetS was 2.76 times higher among the Switch cohort compared to the New cohort which was statistically significant (p<0.001). Also, after controlling all factors in adjusted analysis, the hazard of developing MetS was still high among the Switched cohort compared to the New cohort (HR:2.00, p=0.018). A Log rank test of equality of survival between those who switched compared to those who started with the dolutegravir-based regimen produced a chi-squared value of <0.001. The log rank test clearly rejects the null hypothesis that the hazard of MetS among the switched cohort and the new cohort are the same.

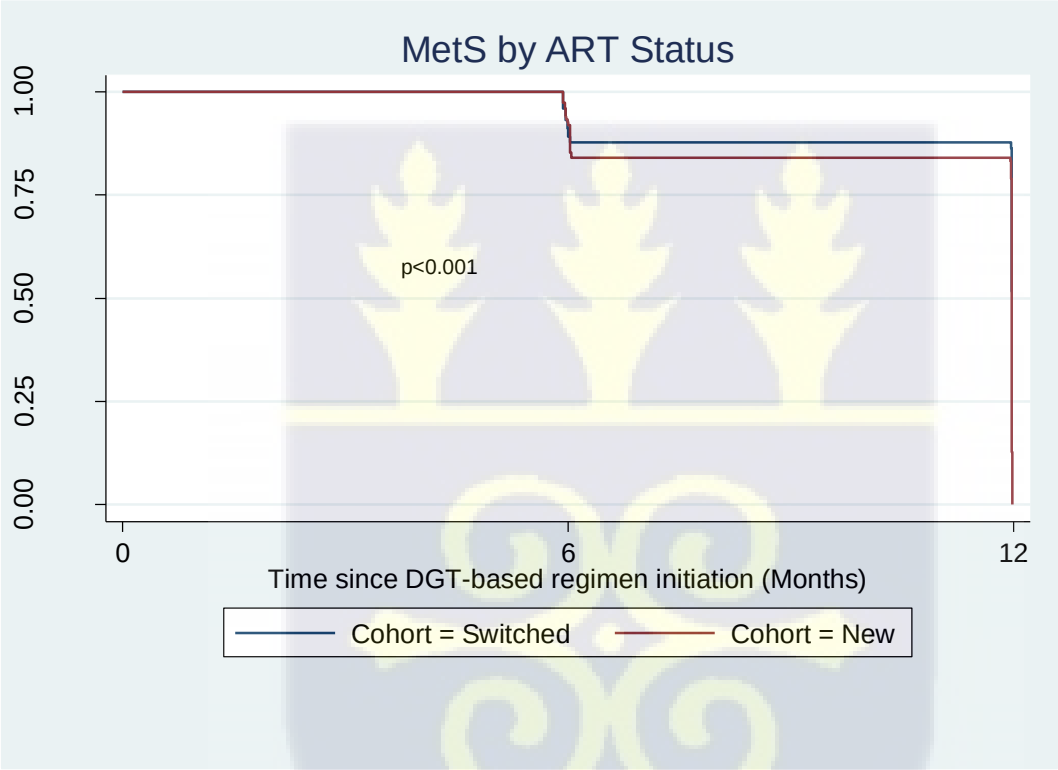


Figure 4. 3: Kaplan Meier failure estimates and Log rank results of associations between MetS and ART status

4.2.7 Objective 3: Risk factors associated with MetS among sampled participants

Bivariate and multivariate analysis reported relationships between MetS and background factors. The hazard of an HIV positive patient on dolutegravir-based regimen developing MetS increased by 0.01 for each yearly increase in age [HR= 1.01, 95% CI (0.95, 0.99)] (Table 4.12). HIV positive patients between the ages of 18-30 years had a reduced hazard of developing MetS as compared to all the older age groups shown in Table 4.12. Females had a significantly reduced hazard of developing MetS [HR=0.38; 95% CI (0.23, 0.62)] compared to the Males. A reduced hazard of developing MetS was also identified among HIV positive patients with Middle/JHS education and higher compared to those without formal education. Additionally, in adjusted analysis, age in years, marital status, and number of adults in household were significantly associated with increased hazard of developing MetS whiles sex and employment status were also significantly associated with reduced hazard of developing MetS (Table 4.12) after controlling for all factors.

Those who were diagnosed with HIV at WHO stage II, III and IV had reduced hazard of developing MetS as compared to those who were diagnosed at Stage I in the bivariate analysis but had increased hazard of MetS development in the adjusted analysis which increased with each Stage as shown in Table 4.13. Among those who had switched ART regimen, the hazard of developing MetS was about 1.59 higher among participants who had been on Efavirenz for more than 5 years as compared to those on medication for less than 1 year. The hazard of developing MetS was significantly high among those with family history of hypertension in the bivariate analysis [HR=2.02; 95% CI (1.22, 3.34)] and even higher in the adjusted analysis [HR=19.9; 95% CI (5.22, 75.9)] as compared with those without any family history of hypertension.

In both bivariate and adjusted analysis, all the components of MetS had increased hazards of developing MetS even though some were not statistically significant as shown in Table 4.14. Even

though those with Hepatitis B and C had reduced hazards of developing MetS in the bivariate analysis compared with those without [HR=0.94; 95% CI (0.55, 1.62) and HR=0.47; 95% CI (0.19, 1.16) respectively], there was an increased hazard of them developing MetS in the presence of other factors [HR=1.85; 95% CI (0.38, 8.98) and HR=1.67; 95% CI (0.14, 19.8) respectively].

In general, the risk factors found to be significantly associated with MetS after adjusting for all covariates include ART intake (cohort), age, sex, employment status, marital status, number of adults in household, WHO Stage, family history of hypertension, platelets counts, creatinine levels, HDL-C, triglyceride levels, fasting blood glucose, body mass index, waist circumference and blood pressure.

Table 4. 12: Hazard of MetS by background characteristics of sampled HIV positive patients at the Tema General Hospital

Variables (N=300)	Unadjusted HR (95%CI)	P-value	Adjusted HR (95%CI)	P-value
Cohort		<0.001*		0.018*
New	Ref		Ref	
Switched	2.76 (1.85-4.11)		2.00 (1.12-3.55)	
Age	1.01 (0.99-1.03)		0.98 (0.95-0.99)	
Age groups		0.171		0.002*
18-30	Ref		Ref	
31-40	1.20 (0.67-2.17)		30.2 (2.49-36.5)	
41-50	1.32 (0.75-2.33)		40.8 (3.05-54.6)	
51-60	1.58 (0.82-3.05)		58.4 (4.27-80.0)	
>60	1.07 (0.40-2.91)		32.8 (0.10-50.5)	
Sex		<0.001*		0.022*
Female	Ref		Ref	
Male	0.38 (0.23-0.62)		0.38 (0.16-0.87)	
Highest Education		0.033*		0.417
No Formal Education	Ref		Ref	
Primary	1.01 (0.62-1.66)		1.30 (0.69-2.45)	
Middle/ JHS	0.74 (0.44-1.26)		0.85 (0.36-2.03)	
Secondary/ SHS	0.57 (0.32-1.03)		0.80 (0.31-2.06)	
Tertiary	0.33 (0.12-0.91)		0.84 (0.19-3.81)	
Ethnicity		0.563		0.475
Akan	Ref		Ref	
Ga Adangbe	0.88 (0.48-1.60)		1.17 (0.36-3.84)	
Ewe	0.88 (0.57-1.36)		1.19 (0.30-4.76)	
Northern	1.01 (0.58-1.77)		1.55 (0.47-5.14)	
Marital Status		0.066		0.002*
Single	Ref		Ref	
Married/Co-Habiting	0.66 (0.43-1.03)		8.31 (2.22-31.0)	
Separated/Divorced/Widowed	1.03 (0.65-1.65)		0.86 (0.25-2.98)	
Employment Status		0.417		<0.001*
Student	Ref		Ref	
Employed	1.35 (0.65-2.80)		0.01 (0.00-0.60)	
Unemployed	2.24 (0.97-5.11)		0.01 (0.00-0.13)	
Income Level (Monthly GHS)		0.289		0.297
<=500	Ref		Ref	
501-1000	0.83 (0.49-1.38)		0.69 (0.13-3.63)	
>1000	0.68 (0.33-1.39)		0.21 (0.01-3.95)	
Residence in and around Tema Metropolis		0.583		0.492
Does not reside in and around Tema	Ref		Ref	
Resides in and around Tema	1.12 (0.74-1.71)		1.63 (0.40-6.57)	
Number of Adults in Household		0.369		0.021*
Living Alone	Ref		Ref	
Live with Others	1.22 (0.79-1.90)		3.45 (1.20-9.95)	

***Statistically significant; **JHS**: Junior High School; **SHS**: Senior High School; **GHS**: Ghana cedis; **HR**: Hazard ratio

Table 4. 13: Hazard of MetS by behavioural, HIV and ART characteristics of sampled HIV positive patients at the Tema General Hospital

Variables (N=300)	Unadjusted HR (95%CI)	P-value	Adjusted HR (95%CI)	P-value
WHO Stage at Diagnosis		0.123		0.001*
Stage I	Ref		Ref	
Stage II	0.83 (0.44-1.56)		4.04 (0.96-17.0)	
Stage III	0.79 (0.41-1.52)		0.04 (0.01-0.26)	
Stage IV	0.33 (0.08-1.35)		17.9 (0.45-71.0)	
ART Duration (Switched) – Months, N=144		0.039*		0.384
<12	Ref		Ref	
12-60	0.59 (0.36-0.97)		0.76 (0.40-1.42)	
>60	1.11 (0.57-2.16)		1.09 (0.45-2.63)	
Viral Load (copies/µL)		0.067		0.803
<1000	Ref		Ref	
≥1000	1.72 (0.96-3.07)		1.23 (.25-6.11)	
Drug related side effects		0.041*		0.090
None	Ref		Ref	
Diarrhoea	0.48 (0.15-1.54)		0.80 (0.10-6.56)	
Dizziness/ Nausea/Thirsty	0.50 (0.12-2.03)		0.39 (0.02-7.05)	
Headache	1.21 (0.59-2.51)		5.42 (0.61-48.4)	
Itching	2.88 (1.04-7.92)		0.77 (0.03-18.7)	
Lack of Sleep	1.76 (0.81-3.82)		0.19 (0.03-1.29)	
Family History of Hypertension		0.006*		<0.001*
No family history of hypertension	Ref		Ref	
Family history of hypertension	2.02 (1.22-3.34)		19.9 (5.22-75.9)	
Family History of Diabetes		0.332		0.503
No family history of diabetes	Ref		Ref	
Family history of diabetes	1.43 (0.69-2.94)		1.72 (0.36-8.39)	
Smoking Habit		1.000		
Does not smoke	Ref			
Smokes	0.00		-	
Alcohol Intake		0.642		0.064
Does not take alcohol	Ref		Ref	
Takes alcohol	0.89 (0.54-1.46)		2.96 (0.94-9.31)	
Physical Activity		0.149		0.338
Does not exercise	Ref		Ref	
Exercises	1.45 (0.88-2.40)		0.51 (0.13-2.02)	
Fruit Intake (days in a week)		0.871		0.059
0-2	Ref		Ref	
3-7	1.03 (0.71-1.49)		0.41 (0.17-1.03)	
Vegetable Intake (days in a week)		0.771		0.101
0-2	Ref		Ref	
3-7	0.95 (0.66-1.37)		2.38 (0.84-6.72)	

***Statistically significant; **WHO**: World Health Organization

Table 4. 14: Hazard of MetS by Haematological, Biochemical and Anthropometric parameters of sampled HIV positive patients at the Tema General Hospital

Variables (N=300)	**Unadjusted HR (95%CI)**	**P-value**	**Adjusted HR (95%CI)**	**P-value**
Haemoglobin level (g/dL)	0.94 (0.88-1.01)	0.083	1.05 (0.84-1.33)	0.649
Platelets ($\times 10^3/\mu L$)	1.00 (0.99-1.00)	0.422	1.01 (1.01-1.02)	<0.001*
White blood cell ($\times 10^3/\mu L$)	0.98 (0.64-1.50)	0.932	0.58 (0.22-1.51)	0.265
Red blood cell ($\times 10^3/\mu L$)	0.65 (0.29-1.45)	0.295	0.31 (0.14-7.14)	0.466
Lymphocytes ($\times 10^3/\mu L$)	1.00 (0.89-1.13)	0.908	0.85 (0.60-1.20)	0.354
Monocytes ($\times 10^3/\mu L$)	0.86 (0.73-1.01)	0.060	1.09 (0.74-1.61)	0.653
Creatinine Level	1.16 (0.76-1.76)	0.501	9.32 (1.65-52.6)	0.011*
AST (U/L)	1.40 (0.94-2.07)	0.098	1.65 (0.32-8.34)	0.548
ALT (U/L)	2.05 (1.39-3.01)	<0.001*	1.43 (0.326.46)	0.639
Hepatitis B		0.821		0.446
Negative	Ref		Ref	
Positive	0.94 (0.55-1.62)		1.85 (0.38-8.98)	
Hepatitis C		0.101		0.685
Negative	Ref		Ref	
Positive	0.47 (0.19-1.16)		1.67 (0.14-19.8)	
Total cholesterol	1.16 (1.02-1.32)	0.026*	0.87 (0.69-1.10)	0.254
LDL- Cholesterol	1.12 (0.94-1.33)	0.205	0.45 (0.21-1.00)	0.050
HDL- Cholesterol	1.54 (1.07-2.23)	0.021*	2.11 (1.29-3.45)	0.003*
Triglyceride	2.70 (1.90-3.82)	<0.001*	3.23 (1.78-5.88)	<0.001*
Fasting Blood Glucose	3.92 (1.53-10.02)	0.004*	10.98 (2.73-44.16)	0.001*
BMI (Kg/m^2)		0.186		<0.001
Underweight (<18.5)	Ref		Ref	
Healthy Weight (18.5-24)	0.75 (0.22-2.55)		1.51 (0.45-0.50)	
Overweight (25-29)	1.48 (0.46-4.78)		10.9 (4.58-36.3)	
Obese (>30)	2.20 (0.68-7.06)		11.2 (4.13-30.6)	
WHR		0.010 *		0.215
Abdominal Obesity Absent	Ref		Ref	
Abdominal Obesity Present	1.66 (1.13-2.43)		1.44 (0.81-2.60)	
Waist Circumference (cm)		<0.001*		0.003*
Abdominal Obesity Absent	Ref		Ref	
Abdominal Obesity Present	2.49 (1.71-3.62)		5.13 (1.76-14.9)	
Blood Pressure		<0.001*		0.029*
Non Hypertensive	Ref		Ref	
Hypertensive	4.10 (2.61-6.45)		2.05 (1.08-3.92)	

***Statistically Significant; **AST**: Aspartate transaminase; **ALT**: Alanine Aminotransferase; **HDL**: High density lipoprotein; **LDL**: Low density lipoprotein; **BMI**: Body Mass Index; **WHR**: Waist-to-hip-ratio

4.3 Objective 4: Cardiovascular disease risk score assessment

Table 15 shows the various CVD risk score assessments which has been classified as low, moderate and high risks. Majority of the participants were at low risk of developing CVD in the next 10 years using the 10-year FRS (65.7%) and the 10-year WHO/ISH prediction risk scores (76.3%). Using the D:A:D 5-year score, 56.2% of the participants were at moderate to high risk of developing CVD in 5 years. Those with MetS had a high risk of developing CVD using all the prediction scores in Table 4.15. There was an insignificant poor agreement between the D:A:D risk score and the FRS (K=0.01, p=0.558) and a significantly fair agreement between the D:A:D and the WHO/ISH risk score (K=0.35, p=0.010) as shown in Table 4.16.

Table 4. 15: Cardiovascular risk of sampled HIV positive patients at the Tema General Hospital

CVD risk Scoring system N=283		**N (%)**	**MetS**		**P-value**
			Present	**Absent**	
FRS	Low	186 (65.7)	59 (30.1)	137 (69.9)	
	Moderate	76 (26.9)	38 (57.6)	28 (42.4)	<0.001*
	High	21 (7.4)	18 (85.7))	3 (14.3)	
WHO/ISH	Low	216 (76.3)	74 (34.3)	142 (65.7)	
	Moderate	47 (16.6)	25 (53.2)	22 (46.8)	<0.001*
	High	20 (7.1)	16 (80.0)	4 (20.0)	
D:A:D	Low	124 (43.8)	30 (24.2)	94 (75.8)	
	Moderate	141 (49.8)	74 (52.5)	67 (47.5)	<0.001*
	High	18 (6.4)	11 (61.1)	7 (38.9)	

*Statistically Significant; **MetS**: Metabolic Syndrome; **CVD**: Cardiovascular disease; **FRS**: Framingham risk score; **D:A:D**: Data Collection on Adverse Events of Anti-HIV drugs; **WHO/ISH**: World Health Organization/International Society of Hypertension

Table 4. 16: Level of Agreement between the CVD risk Scoring systems

CVD risk Scoring system	**Comparison with FRS Score**		**Comparison with D.A.D Score**	
	Kappa	**P-value**	**Kappa**	**P-value**
FRS	-	-	0.01	0.558
WHO/ISH	0.02	0.592	0.35	*0.010
D:A:D	0.35	*0.010	-	-

*Statistically Significant; **CVD**: Cardiovascular disease; **FRS**: Framingham risk score; **D:A:D**: Data Collection on Adverse Events of Anti-HIV drugs; **WHO/ISH**: World Health Organization/International Society of Hypertension

4.4 Objective 5: To assess the level of adherence and challenges to the baseline assessments before ART initiation

4.4.1 Review of Folders

Fifty folders were reviewed in the 10 HIV Clinics (5 in each clinic) to ascertain whether the baseline requirements before ART initiation and the routine checks are carried out. It was observed that:

- The baseline laboratory tests to be done before ART initiation had not been done after 6 months of initiation.
- Most of the physical measurements (height, weight and blood pressure) and observations were not done before ART initiation and also during routine visits.
- Some patients had incomplete information on their medical and family history.

4.4.2 In-depth Interview with Heads and Patients

4.4.2.1 Background Characteristics of Heads of HIV Clinics Interviewed

Ten heads of the HIV Clinics providing comprehensive HIV services were interviewed. Majority of the respondents were females and 8/10 heads were registered nurses, 1 doctor and 1 pharmacist. Sixty percent (60%) of the heads interviewed had worked for more than 5 years in that unit as shown in Table 4.17.

Table 4. 17: Background Characteristics of Heads of HIV Clinics

Variables (N=10)	N (%)
Sex	
Male	8 (30.1)
Female	2 (69.9)
Profession	
Doctor	1 (10.0)
Pharmacist	1 (10.0)
Registered Nurse	8 (80.0)
Years Worked at the HIV Clinic	
<1	1 (10.0)
1-5	3 (30.0)
>5	6 (60.0)

4.4.2.2 Challenges to adhering to the baseline assessments before and routine checks after the ART initiation

The heads of the HIV units were asked about some of the challenges they are facing in adhering to the new HIV guidelines for treatment. About ninety (90%) of the heads complained of inadequate staff in order to do their work effectively.

"We do not have any pharmacist here so the patients would have to go to the main pharmacy which makes some of them uncomfortable" (Female, 6 years).

Another head also stated,

"Hmmm as for the guidelines we would love to follow but we have no physician to attend to the patients thus some of the requirements are ignored" (Female, 9 years).

Others reported that even though the new guidelines are being used, the baseline laboratory tests are not mandatory before ART initiation.

"They said we should test and treat so whether the labs are done or not we administer the drugs to the patients" (Female, 4 years).

Some attributed the absence of patients medical and family history, physical measurements and other observations to be done before ART initiation and also during routine visits to the workload and also absence of instruments.

"*I have to attend to and counsel about 100 people in a day with different issues thus adding all that makes it stressful" (Female, 10 years).*

Another recounted,

"*We are ready to work if they provide us with a working sphygmomanometer and a nurse to support with the physical measurements" (Female, 5 years).*

Some reported that most of the baseline laboratory tests were not done because the patients could not afford them since they have to pay out-of-pocket for some facilities.

"The labs are not free, they are quite expensive so we do not force those who cannot afford to do them" (Female, 2 years).

Some of the facilities complained about inadequate folders and test kits. And also expired test kits giving false results.

"Imagine doing a test for someone who is about to donate blood and the results come as false negative, sometimes we are being forced to do all three tests even if the patient tests negative with the first test" (Female, 8 years).

Unavailability of antiretroviral drugs was also a major challenge which compelled them to sometimes turn the patients away or change the medication back to the old EFV-based regimen.

"With this frequent drug shortage, if the government cannot afford the new drug regimen (dolutegravir-based regimen) they should just tell us so we maintain the patients on the EFV-based regimen" (Female, 5 years).

They also complained about the viral load results not forthcoming thus some Clinics had stopped taking samples to be analysed.

"They claim the old machine is spoilt and are getting a new one but it's taking forever and our patients are running out of patience so we have stopped taking new samples" (Female, 9 months).

When they were asked about their capacity to treat patients with other co-mobidities, all the heads said No, this is due to inadequate staff, patient numbers and insufficient logistics. Thus, they will refer the patients to the main hospital for further treatment.

"For us we are ready to work if the facility or NACP can provide us with all the things we need to improve our work. Even though we know some of the patients we refer to the main hospital do not go, we have no control of it" (Male, 8 years).

They also complained about the inability to follow-up with defaulters due to the increasing numbers and lack of sufficient funds for call credit and motivate staff to follow-up on them.

"If they pay someone to follow-up on the defaulters it will be great since it will motivate the patients to come because of the concern showed" (Female, 3 years).

4.4.2.3 Background Characteristics of Newly Diagnosed HIV Positive Patients Interviewed

Twenty patients were interviewed with two (2) from each of the ten selected facilities providing comprehensive HIV care. Majority of the patients interviewed were between the ages 25 – 42 years (90%) with most of them being females (65%) as indicated in Table 4.18.

Table 4. 18: Background Characteristics of newly diagnosed HIV positive patients

Variables (N=20)	N (%)
Sex	
Male	7 (35.0)
Female	13 (65.0)
Age (Years)	
20-24	2 (10.0)
25-34	25 (25.0)
35-42	13 (65.0)

4.4.2.4 Adherence to the HIV guidelines for ART initiation

All the patients interviewed were initiated on the ART after being diagnosed and counselled. They all had their weight checked but only 65% had their blood pressure measured. They were all informed about the baseline tests but only 20% (4/20) were able to afford to do the test. Two of the patients had it done for them for free at one facility and the rest said it was too expensive.

"*They asked me to do some test but it all cost about GHS300 which I couldn't afford but they gave me the drugs anyway" (Female, 25 years)*.

One of those who did the baseline test said,

"Even though is expensive, I had to do it because I want to get better and go back to work" (Male, 32 years).

The patients were all treated with respect and without judgement at all the facilities which made them feel belonged. They were also informed about the possible side effects of the drugs and to report if they notice anything unusual after consuming the drugs.

"Madam, when I was told I had HIV, I thought it was the end of my life but the way they received me at the clinic and explained everything to me made me feel better" (Female, 40 years).

CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

The current study assessed the effect of dolutegravir-based regimen on the incidence of MetS and its components, risk factors associated with MetS and estimated the risk of Cardiovascular disease among the study participants. It also assessed challenges and the level of adherence to the baseline requirements before ART initiation. Thus, this chapter discusses the key findings of the study.

5.2 Socio-demographic Characteristics of Study Participants

Results of the current study shows a study population with the majority (81%) of them aged ≥30 years. This age structure is similar to most reported findings in studies that has been conducted in SSA including Ghana (Dimodi et al., 2014; Hamooya et al., 2021; Mashinya et al., 2015; Nguyen et al., 2017a; Obirikorang et al., 2016; Osoti et al., 2018; Todowede et al., 2019; van Wyk et al., 2021). This shows an ageing population of PLHIV in Ghana and SSA. Thus, there is the need to focus on age-related morbidities including MetS and its associated factors in order to sustain the gains made in the ART roll out.

More than two-thirds were females (69.9%) which is also comparable to similar observational studies conducted in SSA (Dimodi *et al.*, 2014; Mashinya *et al.*, 2015; Nguyen *et al.*, 2017; Osoti *et al.*, 2018; Todowede, Mianda and Sartorius, 2019; Hamooya *et al.*, 2021). A cross-sectional study conducted in Ghana reported 58.7% of the 433 participants to be females (Obirikorang et al., 2016). This high proportion of females found among PLHIV in studies from SSA could be

attributed to the health seeking behaviour of the SSA population and the policy of HIV screening of all pregnant women to prevent mother-to-child HIV transmission. Also, the main route of transmission of HIV in SSA is heterosexual which makes women more vulnerable to HIV infection than men unlike most European and North American countries. A study in Thai found 96% of the study participants being males (Goh et al., 2019).

Over the follow-up period, the mean levels of the ALT, AST and creatinine increased. This could be attributed to the use of DTG which has been found to cause an increase in the level of liver enzymes and the level of enzymes produced in the muscles (creatine phosphokinase) (NAM AIDSMAP, 2022). Also, about 22% of the participants had some drug related side effects (diarrhoea, dizziness, nausea, headache, itching, frequent thirst and lack of sleep). This rate of DTG-related adverse effect is comparable to those reported in previous studies (13%-22%) (Goh et al., 2019; Llibre et al., 2015; Walmsley et al., 2013).

5.3 Prevalence of MetS and its subcomponents among screened participants

The current study found the prevalence of MetS to be 46.7% using the NCEP-ATPIII diagnosis and 23.8% when the IDF diagnosis was also used. Even though MetS prevalence found in this study was lower than what was reported in a study conducted in Ghana in 2016 by Obirikorang, Osei-Yeboah, Asare, Quaye & Odame (48.3% - NCEP ATPIII and 42.3%-IDF) it falls within the estimated MetS prevalence in SSA (6.23% to 58%) by Todowede et al (2019). Evidence from several studies indicates that MetS could be associated with different ART use thus might have accounted for the differences in the MetS prevalence of the present study and that of Obirikorang where majority of the participants were on zidovudine, efavirenz and indinavir. In the current

study, we observed a higher prevalence of MetS than previously reported in Nigeria (12.7%) (Ayodele et al., 2012), Cameroon (13.9%) (Husain, Noor, Elmadhoun, Almobarak, Awadalla, Woodward, Mital, Ahmed, et al., 2017), Kenya (16.9%) (Osoti et al., 2018), Lesotho (16.7%) (Labhardt et al., 2017), Ethiopia (18.1%) (Tesfaye et al., 2014) and Zambia (26.3%) (Hamooya et al., 2021) using NCEP-ATPIII criteria. This study's result was also higher than the estimated global MetS prevalence of 16.7% to 31.3% reported by Nguyen et al in 2016 using the NCEP-ATPIII criteria. This difference could be attributed to the small amount of research from Africa (9/65) which was used to estimate the global prevalence as majority of the studies were from Europe and America where they have a well-functioning health system. And also, most of the components of MetS are monitored frequently at their health facilities. These differences in MetS prevalence across the globe could be partly explained by differences in socio- demographics and ART regimens. It has also been shown that different definitions of MetS, duration of exposure on ART and the different sampled population size used (Worm et al., 2010) can lead to varied results as shown in this current study and other studies.

Those on ART had a relatively high MetS prevalence (56.5%) as compared to the ART naïve (31.1%). This finding is similar to most studies conducted in SSA (Carr *et al.*, 2006; Ayodele *et al.*, 2012; Dimodi *et al.*, 2014; Nguyen *et al.*, 2016; Obirikorang *et al.*, 2016; Todowede and Sartorius, 2017; Gooneratne et al., 2018; Todowede, Mianda and Sartorius, 2019; Hamooya *et al.*, 2021) even though a study conducted in Western Kenya found no difference in the prevalence between the ART exposed and ART naïve (Osoti et al., 2018). However, reports are inconsistent with some published research studies in the United States (Jeric´o et al., 2005; Mondy et al., 2007). Despite these disparities, this study found a high prevalence of MetS among patients on ART compared to their ART-naïve counterparts. It is important to note that a previous study conducted

in Ghana to determine the prevalence of MetS among PLHIV indicated a prevalence of 61.6% among those on ART and 20.1% among the ART naïve (Obirikorang et al., 2016). This differential observation could be differences in geographical locations, study settings and clinical characteristics of study participants. Both ARVs and HIV infection have been postulated to have direct and indirect effect on MetS development (Mbunkah et al., 2014; Sani et al., 2014; W. et al., 2013; De Socio et al., 2014; Krauskopf et al., 2013; Manner et al., 2013). ART has been shown to induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis leading to endothelial dysfunction and vascular damage and hence MetS (Fiala et al., 2004). Thus, the difference in MetS prevalence among the two groups. The present study also found a significantly higher prevalence of metabolic syndrome in women (53.8%) than men (30.5%) and this finding is consistent with report by Samaras *et al.*, (2007), Ayodele *et al.*, (2012) and Todowede, Mianda and Sartorius, (2019). However, other studies did not show significant gender difference in the prevalence of metabolic syndrome (Jeric´o et al., 2005; Mashinya et al., 2015; Mondy et al., 2007; Worm et al., 2010). Although the prevalence of metabolic syndrome increased with increasing age from other studies (Ayodele et al., 2012; Dimodi et al., 2014; Todowede et al., 2019), this was different for the current study. The prevalence rates of metabolic syndrome in patients aged > 50 years were lower compared to those <50 years. This could be attributed to the routine screening for other co-morbidities among those over 50 years and also because they know their risk of metabolic abnormalities are high at this age, they take extra care of themselves.

The most prevalent components of MetS were elevated blood pressure and fasting blood glucose. These components are measured easily and with low cost. Prior studies have similarly shown that elevated blood pressure is the most prevalent feature of the MetS among PLHIV (Hamooya et al., 2021; Jeric´o et al., 2005; Mbunkah et al., 2014b; Obirikorang et al., 2016; Osoti et al., 2018;

Todowede et al., 2019). Hypertension is perhaps the most important CVD risk factor among ART patients and it is very treatable thus it should be measured routinely at the HIV clinics (Martin-Iguacel et al., 2016; Pangmekeh et al., 2019; Todowede et al., 2019). Some of the factors that have been implicated in hypertension are aging, metabolic abnormalities, endothelial dysfunction, inflammation and antiretroviral drugs (Pangmekeh et al., 2019; Todowede et al., 2019). These factors might have been the major drivers of elevated blood pressure in our study. Also, the lack of routine blood pressure checks at the HIV clinics could have accounted for the high prevalence.

5.4 Incidence of Metabolic Syndrome and its subcomponents

The incidence rate of MetS per 100 person-years after 12 months on dolutegravir based-regimen using the NCEP-ATPIII diagnosis was 41.68 with an incidence of 115. Other few studies that have looked at the incidence of MetS after dolutegravir-based regimen initiation found a lower incidence compared to this current study. A prospective cohort study conducted in Ivory Coast among PLHIV found the incidence of metabolic syndrome to be 5.5per 100 person-years of follow-up (Tchounga et al., 2016) and MetS incidence of 9.13 per 100 person-years in South Africa (Sobieszczyk et al., 2016). Other prevalence studies have also found high prevalence after a year on dolutegravir-based regimen (Eholié et al., 2015; Fourie et al., 2010; Krishnan et al., 2012; Samaras et al., 2007; Zannou et al., 2009). At the end of 6 months, the incidence of MetS was 28 and 87 between 6-12 months. This high incidence could be attributed to the elevated levels of the individual MetS subcomponents, especially the blood pressure at baseline of the present study. Also, the MetS diagnosis that was used (NCEP-ATPIII- any three of the metabolic disorders), the socio-demographics (for instance, in the study by Sobieszczyk et al., 2016, the mean age of the participants was 24 years whiles that of the current study is 40 years), geographical locations, study

settings and clinical characteristics of the study participants could have accounted for the differences in incidence among the various studies. The current study also found that the waist circumference also increased over time with more people having abdominal obesity. Thus, this might have influenced the high incidence of MetS as abdominal obesity has been shown to be a risk factor for MetS (Bourgi et al., 2020; Calza et al., 2019; Galdamez et al., 2019). Studies have shown that the incidence of MetS can begin as early as 6 weeks of initiation of ART (Macdonald, 2008) whiles others have shown to be more than 6 months (Bonfanti et al., 2007) and a year of ART initiation (Berhane et al., 2012; Estrada et al., 2006). This is similar to this study where the incidence of MetS started at 6 months (28) and increased between 6-12 months (87).

Among the metabolic subcomponents, waist circumference recorded the highest incidence (100) with an incidence rate of 3.31 per 100 person-months with blood pressure having the lowest incidence (73) with an incidence rate of 3.54 per 100 person-months. This could be attributed to the intake of the dolutegravir-based regimen as various studies have found a significant weight increase after 12 months (Calza et al., 2019; Goh et al., 2019; Krishnan et al., 2015; Sobieszczyk et al., 2016; Trottier et al., 2017). A study conducted in Spain to access the incidence of weight gain among HIV positive patients on various drug regimen found those on dolutegravir-based regimen having a significantly higher weight compared to those on other regimen (Galdamez et al., 2019). A number of observational studies have also reported an increasing prevalence of overweight and clinical obesity in HIV-infected patients starting DTG (Eckard & McComsey, 2020; Kuo et al., 2020; Phillips et al., 2020; Ruderman et al., 2019; van Wyk et al., 2021; Venter et al., 2019b). This raise a concern for obesity-related complications, particularly cardiovascular events.

5.5 Effect of dolutegravir-based regimen on MetS among sampled participants

The probability of MetS development was significantly higher among those who had switched from efavirenz-based regimen (92%; incidence 78) than those who initiated on dolutegravir-based regimen after being diagnosed of HIV (89%; incidence 37). Also, the hazard of developing MetS was 2.76 times higher among the Switch cohort compared to the New cohort which was statistically significant ($p<0.001$).This difference among the cohorts could be attributed to the mean age of the participants (the mean age in the New cohort was 37 years whiles that of Switched cohort was 43 years), family history of hypertension (majority of the Switched cohort had family history of hypertension) and the duration on ART (all those in the switched cohort had been exposed to ART for more than 1 year). Studies have shown that age, family history of hypertension and ART duration are significant risk factors for MetS development (Bosho et al., 2018; Dimodi et al., 2014; Hamooya et al., 2021; Obirikorang et al., 2016; Todowede et al., 2019; van Wyk et al., 2021). A sensitivity analysis showed that those who had been on the efavirenz-based regimen for more than 1 year among the switched cohort were twice as likely to develop MetS compared to those below 1 year. Other prevalence studies have also found INST (DTG) to be a risk factor for MetS (Jeric´o et al., 2005; Obirikorang et al., 2016; Todowede et al., 2019). The expansion of body fat associated with DTG use could have influenced the high incidence of MetS among both cohorts (Bourgi et al., 2020; Goh et al., 2019; Sax et al., 2019). This was evident in the high proportion (100, 33%) of the participants developing abdominal obesity at the end of the 12 months on dolutegravir-based regimen. Also, 74 of the 100 people with abdominal obesity developed MetS based on the IDF diagnosis as abdominal obesity is the main causative factor plus any two of the metabolic abnormalities. Numerous studies have shown an increasing incidence and prevalence of overweight/obesity in PLHIV and this has been attributed to dolutegravir use (Bourgi et al., 2020;

Cahn et al., 2019; Calza et al., 2019; Eckard & McComsey, 2020; Hamooya et al., 2021; Hill et al., 2019; Khan et al., 2019; Norwood et al., 2017; Sax et al., 2019; Vizcarra et al., 2020); the tendency of PLHIV to be overweight to remove suspicion and its accompanying stigmatisation of HIV infection (Aboud et al., 2010; Edwards-Jackson et al., 2011; Muronya et al., 2011) and age-related increase in body weight (Denue et al., 2012). Although weight gain during ART has been shown to be beneficial among underweight individuals, it may be detrimental for those who are overweight/obese. This calls for concerns for obesity-related complications, particularly cardiovascular events.

The use of DTG have been shown to affect lipid profiles which may alter triglyceride levels, LDL cholesterol levels and HDL levels and may also influence insulin secretion increasing the risk of insulin resistance or type 2 diabetes (Akl et al., 2017; De Socio et al., 2014; Kaur, 2014; Mondy et al., 2007; van Wyk et al., 2021). In addition, weight gain from INSTI (DTG) has been associated with insulin resistance (Cahn et al., 2019; Katlama et al., 2019), diabetes (Fong et al., 2017) and hyperglycemia in PLHIV in Uganda (Lamorde et al., 2020). Thus, the use of dolutegravir-based regimen is a significant risk factor for MetS development as it indirectly affect the incidence of the various MetS subcomponents.

5.6 Risk factors associated with MetS among sampled participants

Cox proportional hazards model was used to calculate unadjusted (HR) and adjusted (aHR) hazard ratios and 95% CI. This found ART Status, age, sex, employment status, marital status, number of adults in household, WHO Stage, family history of hypertension, platelets count, creatinine levels, High density lipoprotein-Cholesterol, triglyceride levels, fasting blood glucose, body mass index,

waist circumference and blood pressure to be significantly associated with MetS after adjusting for all covariates.

5.6.1 Socio-demographic factors

Among the socio-demographic factors, increasing age is a well-known risk factor for most metabolic abnormalities (especially hypertension) in the general population, with PLHIV being at higher odds (Todowede et al., 2019). The contribution of ageing to the pathogenesis hypertension is attributed to arterial stiffness that is reduced elasticity of the large arteries which is attributed to smooth-muscle hypertrophy and thinning, collagen deposition and fragmenting, and fracture of the elastin fibres in the arteries (Chobanian et al., 2003). Increasing age has been shown to be a significant risk factor for MetS among PLHIV and this is particularly evidenced in people over 40 years which was evident in this study even though those between 30 to 39 years also had a high risk of developing MetS compared to those below 30 years. A study reported by Nguyen et al., (2016) indicated that PLHIV above the age of 40 years have a higher risk of developing MetS as compared with those <40 years. Those above 60 years in the present study had a lower risk of MetS compared to those between 30-60 years. This could be attributed to the frequent screening of some metabolic abnormalities among the age group during routine visits at the HIV clinics thus those with abnormal results are treated reducing their risk of MetS. Also, in the present study, the hazard of MetS increased by 1% for every additional one-year increase in age. This result is comparable and consistent with several prevalence studies conducted in PLHIV in both developed and developing countries (Achhra et al., 2016; Akl et al., 2017; De Socio et al., 2014; Dimala et al., 2016; Friis-Moller et al., 2003; Guira et al., 2016; Hamooya et al., 2021; Hirigo & Tesfaye,

2016; Jeric´o et al., 2005; Mbunkah et al., 2014a; Obirikorang et al., 2016; Van Wyk et al., 2021; Zannou DM et al., 2009).

Females had a 68% hazard of developing MetS compared to males from the present study which is evident in many studies which reported women being at a greater risk of MetS than men even though men have been shown to have a higher blood pressure (Akl et al., 2017; Ayodele et al., 2012; Guira et al., 2016; Hirigo & Tesfaye, 2016; Mashinya et al., 2015; Nguyen et al., 2016; Obirikorang et al., 2016; Zannou et al., 2009). Although most study results are in this direction, Pan & Pratt (2008) reported in a cross sectional study that males were at a higher risk of developing MetS than females which is also similar to findings from the cross sectional section of the current study. Thus, more research is required to understand the differences in MetS incidence by gender which is usually driven by higher rates of obesity (Nguyen et al., 2016). Among those with incident abdominal obesity (100), more women (68%) had abdominal obesity thus might have accounted for their high risk of MetS in this study. Also, the higher disposition of women to develop MetS could be due to biologic, psychological, and environmental factors (Dimodi et al., 2014).

A Study which determined the association between marital status and MetS reported married individuals having elevated blood pressure and higher risk of MetS than single, widowed or divorced (Akl et al., 2017) which was similar to the current study where married/ cohabiting participants had 8.31 hazard of developing MetS than single participants in the adjusted model. A study by Berhane et al., (2012) also found no association. This could be attributed to the fact that married individuals are under constant pressure as to whether they can have HIV negative children and also whether their partners will continue to be with them. This might increase their blood pressure which is a significant risk factor for MetS.

The present study found no association between educational level attained and MetS in PLHIV which was similar to other studies (Mondy et al., 2007; Obirikorang et al., 2016; Zannou et al., 2009). Other studies have also reported an association between education and MetS in PLHIV where they found formal education to be an independent predictor of MetS (Bosho et al., 2018; Hirigo & Tesfaye, 2016; Kaduka et al., 2012).

In terms of employment, an association was found between employment status and MetS with those who were employed and unemployed having a higher hazard of MetS compared to the students. This could be attributed to the age of the participants where the mean age of the students was 23 years and that of the employed and unemployed was 42 years. This results is also consistent with findings from other studies (Akl et al., 2017; Bosho et al., 2018; Hamooya et al., 2021; Jeric´o et al., 2005).

There was also an association between MetS and the number of adults in the households. Those living with others had thrice the hazard of developing MetS than those living alone. A sensitivity analysis found that those living with others had elevated blood pressure compared to those living alone. This might have accounted for the high risk among them. The fear of being found to be HIV positive by others in the household could have also been attributed to their elevated blood pressure. This was inconsistent with a study by Yang, Boen and Mullan Harris, (2015) where they reported that those who had lived alone had an elevated blood pressure.

Even though a study by Bosho et al. (2018) found an association between higher income level and MetS, this study found no association between them which is similar to a study which was conducted in South West Ethiopia (Berhane et al. 2012).

Cardiovascular disease which is a significant risk factor for MetS have been known to run in families and individuals with family history of hypertension are classified as high risk targets for

hypertensive preventive measures (Wang et al., 2008). In the current study, those with family history of hypertension were associated with MetS. This finding is consistent with prevalence studies that have associated family history of hypertension with increased odds of MetS (Achhra et al., 2016; Hamooya et al., 2021; Mondy et al., 2007; Sobieszczyk et al., 2016). This present study also found no association between family history of diabetes and MetS even though other studies found otherwise (Achhra et al., 2016; Hamooya et al., 2021; Mondy et al., 2007; Sobieszczyk et al., 2016). This could be attributed to the study design and socio-demographics of the study participants as only few of the participants reported having a family history of diabetes.

5.6.2 Lifestyle factors

Even though smoking of tobacco products is considered a major risk factor for MetS in the general population especially among PLHIV (Alberti, Zimmet, & Shaw, 2005; Alvarez et al., 2010; Hirigo & Tesfaye, 2016; Husain et al., 2017), results from this study indicated lack of association between smoking and MetS which is similar to reports from other countries in SSA (Bosho et al., 2018; Tesfaye et al., 2014). This could be attributed to the low prevalence of smoking generally in SSA compared with the developed countries. For instance, the current study found a prevalence of 0.7%. Also, PLHIV are counselled to stop smoking thus might have accounted for the low risk of MetS.

The present study found no association between alcohol consumption, physical activity, fruit and vegetable intake even though other studies have found them to be associated with the prevalence of MetS (Alberti, Zimmet, & Shaw, 2005; Alvarez et al., 2010; Hirigo & Tesfaye, 2016; Husain et al., 2017; Kingery et al., 2016; Pan & Pratt, 2008; Todowede & Sartorius, 2017 Samaras et al., 2007). Results from other studies also reported no association between these factors (Bosho et al.,

2018; Tesfaye et al., 2014). This could be attributed to the prevalence of alcohol consumption (19% in the current study) and also the counselling of PLHIV to reduce their alcohol consumption.

5.6.3 Anthropometric, haematological and biochemical/metabolic factors

As a measure of abdominal obesity, body mass index and waist circumference were found to be associated with MetS. Several prevalence and epidemiological studies have also established overweight/obesity as a risk factor for the prevalence and incidence of MetS among PLHIV (Bosho et al., 2018; Hamooya et al., 2021; Hirigo & Tesfaye, 2016; Idiculla et al., 2018; Maseko & Masuku, 2017; Mondy et al., 2007; Ruderman et al., 2019; van Wyk et al., 2021).

The hazard of developing MetS was about 11 times among the overweight and obese participants than those with normal weight. Studies among PLHIV in SSA have also reported an increased risk of MetS in overweight/obese individuals (Dimodi et al., 2014; Jacobson et al., 2006; Krishnan et al., 2012, 2015; Shankalala et al., 2017; Todowede et al., 2019). The accumulation of visceral fat/ abdominal obesity has been attributed to development of metabolic risk factors including hypertension, Type 2 diabetes, insulin resistance and dyslipidaemia (GBD 2015 Obesity Collaborators et al., 2017) in both HIV-negative (Matsuzawa et al., 2011; Nomura et al., 2010) and PLHIV (Darbandi et al., 2014; Lake, 2017; Sax et al., 2019). A study has found that, obesity causes the serum concentrations of leptin and resistin to increase, whereas adiponectin decreases. The increased production of leptin and resistin and the decreased secretion of adiponectin increase the risk of developing the MetS components (Bakhshayeshkaram et al., 2020).

It has been estimated that approximately 58% of type 2 diabetes is attributable to overweight and obesity globally, and also 90% of type 2 diabetes in western countries is attributed to weight gain

(Kumar et al., 2013). The use of DTG has also been shown to cause a significant weight gain among PLHIV by various studies which is also consistent with the present study (Calza et al., 2019; Eckard & McComsey, 2020; Hill et al., 2019; Khan et al., 2019; Norwood et al., 2017; Sax et al., 2019; Vizcarra et al., 2020). A study by Nduka et al (2016) also emphasized the strong impact of central fat distribution in mediating the causal pathway between ART and increased blood pressure. These findings also support that preventive lifestyle interventions should be targeted at lowering both BMI and central obesity in Ghana.

Elevated blood pressure was found to be a significant risk factor for MetS. The current study showed that, those who were hypertensive based on the NCEP-ATPIII criteria had twice the hazard of developing MetS as compared to the non-hypertensives. Prior studies have similarly shown that hypertension is one of the most significant risk factors in MetS development especially among ART-experienced patients (Akl et al., 2017; Ayodele et al., 2012; Hamooya et al., 2021; Mondy et al., 2007; Obirikorang et al., 2016; Todowede et al., 2019; van Wyk et al., 2021). Studies in Brazzaville, Cameroon and Ghana also have observed high cardiometabolic risk in PLHIV, with high blood pressure as the most prevalent risk factor (Agyemang, 2006; Fezeu et al., 2007; Gombet et al., 2010).

Among all the haematological factors measured, platelet count and creatinine level were the significant risk factors for metabolic syndrome which is similar to a study conducted in Zambia (Hamooya et al., 2021). Most of the studies that had looked at MetS did not access the haematological aspect thus there is limited information on MetS and hematological parameters in sub-Saharan Africa and globally as a whole.

Findings from the current study suggests that the incidence of MetS is positively correlated with adverse alterations in HDL-C, triglyceride and fasting blood glucose levels. Most studies have

suggested that low HDL-C levels have a more significant effect on patients who develop MetS (Akl et al., 2017; Bakhshayeshkaram et al., 2020; Hamooya et al., 2021; Palaniappan et al., 2004; van Wyk et al., 2021). Some molecules of INSTI including DTG affect lipid, and glucose thus increasing their risk of MetS (Hamooya et al., 2021). After adjusting for other covariates, the hazard of developing MetS was highest (10.98, CI: 2.73-44.16) when one has elevated fasting blood glucose compared to the other components of MetS in the present study. This is similar to studies conducted in Zambia (van Wyk et al., 2021) and Uganda (Buchacz et al., 2008).

5.6.4 HIV/ART factors

Several studies have been conducted in determining the relationship between HIV/ART and MetS. In studies that have included HIV-negative individuals as controls, the association between HIV status and MetS has been conflicting. Some studies found a significant association between HIV status and MetS where HIV-positive patients were found to have a higher odds/risk of MetS compared with HIV-negative patients (Moreira et al., 2014; Okafor, 2012; Paula et al., 2013; Todowede et al., 2019). Although most of the studies conducted in SSA were among HIV-positive individuals, the few that were conducted among HIV-positive and HIV-negative people reported significantly higher MetS risk among the HIV-positives than the HIV-negatives (Mbunkah et al., 2014a; Sani et al., 2014; W. et al., 2013). Despite these conflicting results, studies that have associated HIV positive status with MetS have suggested various mechanisms to account for the higher incidence of MetS. These include endothelial activation and dysfunction as well as direct infection of the virus on arterial vascular smooth cells (Kline & Sutliff, 2008) and endovascular changes (Kaplan, 2008; Martin-Iguacel et al., 2016). HIV infection is also associated with high levels of triglycerides (results of impaired lipase activity) and decreased levels of HDL-C and

correlated high concentration of cytokines which may have lead to the development of MetS (Pan & Pratt, 2008). The present study however did not include HIV-negative controls in the design hence, the relationship between HIV status and incident of MetS was not investigated.

With the exception of disease stage at ART initiation, none of the HIV-related characteristics such as the duration of infection and viral suppression were associated with the risk of MetS in this study which is similar to a study conducted in Brazil (Akl et al., 2017) and US (Mondy et al., 2007) which reported no association between HIV- infection duration and the risk of MetS among PLHIV. Fourie, Van Rooyen, Kruger & Schutte (2010) also found no significant association between HIV status and MetS. A study which assessed the relationship between viral load and MetS also reported no association between them (Sobieszczyk et al., 2016) even though viral load is used as a marker of immune suppression in PLHIV. On the other hand, other researchers have reported an increased risk of MetS in PLHIV as the duration of the HIV-infection increases (De Socio et al., 2014; Krauskopf et al., 2013; Manner et al., 2013). This disparity can be attributed to differences in population structure between the studies and the prevalence and incidence of MetS in the general population.

Although literature abounds in studies on the association between ART exposure and the risk of MetS, the results have been inconclusive. The present study found no association between exposure to ART and MetS even though those on ART had 1.23 odds of developing MetS, it was not statistically significant. And also, there was no association between duration of ART and Mets in the prevalence study. This is similar to a systematic review conducted in SSA which found a two-fold higher risk of MetS among PLHIV than HIV-negative people (Todowede et al., 2019). Even though this ratio was not statistically significant as a result of limited studies, the findings suggests that HIV infection and ART appear to contribute to a significant excess burden of MetS.

The findings of this review are also similar to ones reported in other studies which also found no association between ART exposure and duration of ART use (Moreira et al., 2014; Okafor, 2012; Paula et al., 2013). Several studies have also reported the association between ART and MetS in PLHIV. PLHIV and are on the ART have been shown to have a higher risk of MetS than their ART naïve counterparts (Alvarez et al., 2010; Hansen et al., 2009; Obirikorang et al., 2016; Samaras et al., 2007; Tesfaye et al., 2014; Todowede et al., 2019). Although it remains debatable due to conflicting results and the prevalence nature of the studies conducted, our incidence study could not determine the risk of MetS among ART naïve patients due to the current "Test and Treat" policy.

Even though efavirenz have been shown to induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis leading to endothelial dysfunction and vascular damage and hence MetS (Fiala et al., 2004), our prevalence study found otherwise. This is as a result of differences in the study population and the duration of efavirenz intake by the participants.

5.7 Cardiovascular Risk Score Assessment

The introduction of ART for the management of HIV has improved the lives of PLHIV. However, since the onset of the ART era more than two decades ago, there is mounting evidence that both HIV infection and the various ART regimen are risk factors for the development of cardiovascular diseases (Reinsch et al., 2012). The results of the Data Collection on Adverse Events of Anti-HIV Drugs study showed that ART is associated with a 26% relative risk increase in the rate of CVD per year of ART exposure (Mashinya et al., 2015).

In addition, the ongoing demographic and epidemiological transition in terms of disease burden from infectious diseases to non-communicable diseases in most countries in SSA has drawn attention to the burden of CVD among PLHIV. Cardiovascular disease is a leading cause of death in the general population and has been recognized as an important cause of morbidity and mortality among PLHIV (Reinsch et al., 2012).

The risk of CVD has been estimated in the general population using various cardiovascular risk scoring systems of which some exist as online calculators. This gives an estimate of the probability that an individual will develop CVD within a specified length of time. Thus, this current study estimated the risk of CVD using the 10-year FRS, the 5-year D:A:D risk score and the 10-year WHO/ISH risk score in 283 HIV-positive patients without any previous history of CVD attending the Tema General Hospital HIV clinic. It estimated a 10-year moderate to high risk of CVD to be 23.7% using the WHO/ISH risk score, 34.3% using FRS and 56.2% using the D:A:D risk score. These results indicate that using the FRS and the WHO/ISH cardiovascular scoring systems classifies majority of the study participants as having a low risk of CVD (65.7% and 76.3% respectively). This is similar to other studies conducted among Nigerians where 88.3% had a low risk (Edward et al., 2013), 93.3% among South Africans (Mashinya et al., 2015), 72.3% among Slovenians (Pirs et al., 2014) and 60.3% among Germans (Reinsch et al., 2012) when the FRS was used. However, the use of the D:A:D cardiovascular scoring system classified more than 50% of the study participants to be moderate to high risk of CVD. This is likely to be a true reflection among the study participants as majority had abnormal metabolic components which are risk factors for CVD. Also, the D:A:D 5-year risk score was developed purposely to be used among PLHIV which addresses the effect of HIV and the ART (D'Agostino, 2012).

Even though the Framingham 10-year risk score was previously used to estimate the risk of CVD among PLHIV, there are arguments on its appropriateness in evaluating the risk of CVD among PLHIV. Studies from the European countries have suggested that the FRS overestimates the risk of CVD in the general population (D'Agostino, 2012; Hadigan et al., 2002; Hense et al., 2003) and also among PLHIV (Edwards-Jackson et al., 2011; Krikke et al., 2016; Nery et al., 2013). However, the present study points to an underestimation of the risk of CVD using the FRS compared with the D:A:D risk score. This is similar to a study conducted by Mashinya *et al.* (2015) which noted that despite the level of agreement between the FRS and the D:A:D score in HIV-infected South Africans, the FRS still underestimate the risk of CVD among PLHIV. Also, another study in South Africa among HIV negative participants using the FRS underestimated the risk of CVD as well (Klug et al., 2015). This underestimation might lead to the exclusion of individuals who otherwise will benefit from CVD risk prevention and management if not addressed. Thus, this shows the inappropriateness of using the FRS in sub-Saharan Africa populations and in particular among PLHIV.

This current study reported that 76.3% of the study population were at low risk of CVD using the WHO/ISH prediction chart which is consistent with a study conducted in Nigeria where 87.2% were at low risk of CVD (Edward et al., 2013). The WHO/ISH score may also have underestimated the risk of CVD among PLHIV in SSA since it is mostly used in the general population but there is limited literature to support this statement.

Although all the three cardiovascular scoring systems relatively had similar scores for study participants with high risk of CVD in this study, there are differences in their scoring of participants with either low or moderate risk of CVD. The D:A:D scoring system classified more participants into the moderate CVD risk than the FRS and the WHO/ISH risk prediction chart

which is similar to a study in Brazil (Nery et al., 2013). The most important aspect of those in the moderate risk category is their relatively shorter progression time to the high-risk category if not appropriately managed because of the HIV-infection and ART. This makes the D:A:D risk scoring system more appropriate to be used in HIV-infected population and especially those on ART. A thorough review of literature has been undertaken by D'Agostino (2012) to establish the accuracy of using the D:A:D risk score in identifying HIV-positive individuals with high risk of CVD.

The present study showed that irrespective of the CVD risk scoring system used, majority of those with MetS were classified as high risk of CVD whiles majority of those without MetS were at low risk of CVD. This is similar to a study conducted in Uganda (Muyanja et al., 2016). These findings could be attributed to the fact that all the CVD risk scoring systems captures most of the risk factors of CVD in participants with MetS. This means majority of PLHIV with MetS will have CVD within 10 years putting more pressure on our limited health facilities. There is therefore the need to screen PLHIV frequently for this MetS components for early treatment thus, reducing the risk of CVD among them.

5.8 Level of adherence and challenges to the baseline assessments before ART initiation and routine checks after initiation

5.8.1 Level of adherence

Findings from the current study showed that all the HIV clinics were adhering to the ART guidelines before ART initiation which includes counselling and advising the clients on the effect of the ART and likely side effects. This will help the clients to make informed decisions on the drug intake and also improve their adherence in consuming the drugs. Even though the weight and blood pressure of the patients were checked at initiation, only the weight is checked routinely. This

explains why majority of the study participants had elevated BP results without their knowledge. Thus, there is a missed opportunity of preventing and managing newly diagnosed patients with elevated blood pressure. This if not curbed early, will cause a drastic increase in cardiometabolic events. In addition, the initial laboratory tests that needs to be carried out were not done due to the "Test and Treat" policy. So patients who cannot afford to do the laboratory tests are given the medication without convincing them on the need for them to do the tests. These investigations help determine the type of drug combination to be given to the patients as some drugs cause liver-related conditions. There is therefore the need for routine checks to monitor weight and blood pressure as DTG is now being used in the whole of Ghana. Also, waist circumference (easy to measure) as a marker of abdominal obesity should be regularly measured in patients attending the HIV clinics to help prevent the incidence of the metabolic components.

5.8.2 Challenges to adhering to the HIV treatment guidelines

Some of the challenges encountered by the health professionals in adhering to the guidelines included inadequate staff (doctors, nurses, nutritionist, pharmacists) and logistics (sphygmomanometer). This inhibits their output as it increases the workload thus, they ignore some necessary information and routine checks in order to attend to everyone. They are also unable to do some physical measurements which are essential to monitor the progress of the patients as they take the antiretrovirals. These prevent the early diagnosis of some co-infections and morbidities which might influence the well-being of the patients. In some facilities, the HIV clinics do not have a pharmacist to dispense the drugs so the patients have to go to the main hospital pharmacy for their drugs which some complained it compromise their privacy. This will discourage the patients from routinely going to the facility for their drugs. Others complained of

inadequate folders, test kits and the new dolutegravir-based regimen which is to be given as a first line medication. This makes it impossible for the staff to do their work effectively. In addition, changing and rechanging medication for the patients makes them lose trust in the drugs. It can also make it difficult to document adverse events of the new medication. The absence of folders and test kits may let them loose people who might be HIV-positive back to the general population thus might increase the incidence of HIV-positive patients through unprotected sex or they might get worse with HIV-related conditions.

5.8.3 Capacity of the HIV Clinics to treat other Co-morbidities

The heads of the various facilities were asked whether they will be capable of treating PLHIV with other co-morbidities in this current study and none of them said yes which is of great concern. Studies have shown that PLHIV have a higher risk of developing other NCDs (Akl et al., 2017; Hamooya et al., 2021; Muyanja et al., 2016; Kim Anh Nguyen et al., 2017b; Obirikorang et al., 2016; Todowede et al., 2019; van Wyk et al., 2021) which is also evident in this study. Clinicians need to be aware that, while weight gain is traditionally thought to be a good prognostic factor in PLHIV, excess weight gain post ART initiation could be detrimental to future cardiometabolic health. Metabolic syndrome which was found in this study to be high compared to other studies is an important risk factor for some of the most common and deadly conditions, including cardiovascular disease and diabetes. We therefore need to figure out how to prevent and treat it in the various HIV clinics as they go for refill of their medications, particularly because it appears to be on the rise. A good starting point is to pay more attention to risk factors such as excess weight, lack of exercise, and an unhealthy diet. In addition, there has to be routine checks on the metabolic components (blood sugar, lipid levels and blood pressure).

5.9 Contribution to knowledge/ Strength of the study

The current study have several strengths. It is the first study to determine the incidence of MetS among PLHIV on dolutegravir-based regimen and the first to look at the causal relationship between ART (DTG) and MetS (using a cohort study) in Ghana and part of few studies that has been conducted in Africa and globally as a whole. It is also the second study to the best of my knowledge to determine the prevalence of MetS among HIV-infected patients in Ghana. In addition, the study examined adults without known diagnosis of CVD-related diseases, thus showing the true risk of MetS before onset of CVD. Another strength of the study is that, it is one of the few studies conducted in Ghana to assess the general risk of cardiovascular events among PLHIV using recognized cardiovascular risk score assessment tools. We also had complete data for all parameters required to make diagnosis of MetS. Thus, our study results can be generalizable in similar settings.

5.10 Limitation of the study

This current study examined the role of current self-reported behaviours (i.e., smoking, alcohol consumption, physical exercise, fruit and vegetable consumption, etc.), which may not entirely reflect past behaviours that may have influenced the development of MetS. We were not able to assess the association of current CD4+ cell count and baseline viral load with MetS in our cohort because those data were not measured. The exclusion of patients with preexisting CVD-related diseases, including the known hypertensives, a component for MetS, may have resulted in underestimation of the true prevalence of MetS in the screened population. Likewise, inclusion of HIV-positive adults not on any medication in the cohort study would have made it possible to

compare biochemical changes due to the dolutegravir-based regimen in the absence of treatment. I believe that findings from this study can be extrapolated to HIV clinics in many parts of Ghana and sub-Saharan Africa, where patients are mostly on the same standardized ART regimens and have comparable gender and age distributions.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

The outcome of this study shows a high incidence and prevalence of MetS in patients attending the HIV clinic at the Tema General Hospital. The current findings acknowledges DTG-associated increase in MetS and results from the Kaplan Meier curves and cox proportional hazard indicate a relationship between ART and MetS. Cox proportional hazard to determine the factors associated with MetS development indicated that the risk factors for MetS were ARV intake, age, sex, employment status, marital status, number of adults in household, WHO Stage, family history of hypertension, abnormal platelets count, abnormal creatinine levels, low High density lipoprotein-Cholesterol, elevated triglyceride levels, elevated fasting blood glucose, abdominal obesity and elevated blood pressure to be associated with the incidence of MetS. In addition, using the D:A:D risk assessment tool found that more than 50% of the study participants were having a moderate to high risk of CVD. This highlights the need to perform cardiovascular risk assessment before ART initiation and periodic assessment to ensure early detection and management of these risk factors to prevent the occurrence of cardiovascular events. Even though the NACP guidelines recognises the adverse events monitoring for metabolic abnormalities, the routine screening, prevention and management of these metabolic disorders among PLHIV are not enforced in the HIV clinics. The results of this study will help shape policy considering the fact that incidence of MetS and its subcomponents are on the ascendency and also the magnitude of those at risk of CVD among PLHIV in Ghana is also high. As PLHIV are growing older and cardiovascular events are yet to reach an alarming proportion among them, this study presents a great opportunity to

understand and decrease cardiovascular risk among PLHIV. Finally, the study found that if the challenges being encountered at the HIV clinics especially the inadequate staff and logistics are met, it will go a long way to reduce the current burden of missed diagnosis and management of the metabolic disorders.

6.2 Recommendations

6.2.1 Policy-related recommendations

With the current shift of HIV being the main cause of mortality among PLHIV to non-communicable diseases, policy makers (NACP and Ghana AIDS commission) can take the opportunity to integrate services for NCDs especially hypertension and diabetes mellitus into the well-established HIV care infrastructure. The diagnostic tools for both conditions are inexpensive and readily available in the local setting thus can easily be implemented. Integrating HIV, hypertension and diabetes care will prevent patients making multiple visits to different clinics which often generates high costs and may affect adherence, which is crucial for the treatment of all three conditions. This will also encourage PLHIV to access care without the uncomfortable disclosure of their HIV status to care givers as stigma is still on the increase.

Our study shows that screening of HIV patients in care can address a large unmet need, as majority of cases of hypertension and diabetes were not diagnosed previously. It is therefore critical that national guidelines and ART programs include efficient and cost-effective methods to detect and institute appropriate interventions for individuals with abdominal obesity, diabetes mellitus and hypertension.

Policy framework on CVD risk assessment, prevention and management in PLHIV attending HIV clinics should be formulated. This is crucial for Ghana as HIV prevalence is on the increase and ART coverage is also anticipated to increase. Trends in cardiovascular disease risk factors are also increasing exponentially among PLHIV. Thus, the D:A:D risk tool can be used to assess their risk. In addition, for accurate estimation of the burden of MetS and appropriate policy development, there is need for pragmatic data on country-specific cutoff points for metabolic characteristics.

6.2.2 Practice-related recommendations

Laboratory investigations before ART initiation will help with the drug dispensation to reduce liver related conditions and other conditions. Thus, the National Health Insurance Scheme (NHIS) can help subsidize the cost of the baseline tests to help patients afford it. Routine checks to monitor weight and blood pressure should be more of purposeful for all PLHIV as DTG is now being used in the whole of Ghana and it has been shown to cause a weight gain with time.

Patients should be encouraged to check their blood pressure frequently at home and not wait till is time to come to the health facility and also waist circumference (easy to measure) as a marker of abdominal obesity should be regularly measured in patients attending the HIV clinics. Finally, Health facilities should make the HIV clinics a priority to deploy more staff to help them.

6.2.3 Further research-related recommendations

- Cohort studies and randomized trials have shown increasing body weight in the short term after DTG initiation in HIV-infected people, but risk factors for weight gain, role of specific

antiretroviral drugs, type of weight gain and its long-term complications are still unknown. Thus, there is a need for more research in this area.

- More research on CVD risk in PLHIV is urgently needed to generate evidence that is based on clinical endpoints. The benefits of integrating care for hypertension and diabetes at HIV clinics also needs further study as well as the optimal model of care.
- There is need for more research to establish the true burden and causes of MetS and diabetes across the country. The inclusion of NCDs in national surveys such as the Ghana Demographic Health Surveys would serve as a start.

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7.0 APPENDICES

7.1 Informed Consent Form for Cohort Study

Title of study: Effect of dolutegravir-based regimen on metabolic syndrome among people living with HIV in the Greater Accra Region.

Introduction

I am a PhD student at the School of Public Health, University of Ghana, legon. As part of the programme, we carry out research work. My work is on the health effects of dolutegravir-based regimen (Tenofovir + Lamivudine/Emtricitabine+Dolutegravir) on metabolic syndrome. We say you have metabolic syndrome when you have three or more of some non-communicable diseases (high blood pressure, abnormal cholesterol level, high blood sugar, central obesity and insulin resistance). It is hoped that the findings of this study will help identify the effect of this new drug regimen on the development of other co-mobilities and also some of the causes of these conditions so that the required interventions can be put in place to prevent you from getting other conditions from the drugs.

Purpose of the study

The study aims to determine the incidence of metabolic syndrome and its components and to evaluate the relationship between dolutegravir use and other risk factors with MetS development among PLHIV in the Greater Accra Region.

Eligibility criteria

PLHIV aged 18 years and above, non-pregnant (for females) who are about to switch or have switched to DTG-based regimen for 2 weeks or less and HIV positive patients about to start ART treatment or have started in less than 2 weeks on the first-line dolutegravir-based regimen who attend the clinic for both clinical assessment and dispensing of ARVs. Persons who are not willing or able to understand or comply with study procedures will not be allowed to be part of the study.

Study Procedure

If you agree to take part in the study, we will take blood samples from a vein in the arm (maximum 3 teaspoons) that will be collected by a healthcare professional and analysed at the laboratory. We will also measure your blood pressure, weight, height and body circumference. A short interview will be conducted to obtain the contact information, age, sex, highest educational level, ethnicity, family history, smoking habits, nutritional habits, alcohol use and HIV and ART history prior to the sample collection using a brief questionnaire that takes about 20 minutes.

_____ If you agree to provide a blood sample as described above, please initial here to have this sample taken.

In addition to testing you now and asking you to complete the survey questionnaire, we would like to follow-up with you during the months ahead, with follow-ups at 6 and 12 months to see how you are feeling and also depending on how you are doing and the results of your initial tests we may take the anthropometric measurements and blood samples again during those periods. We may test samples from about 292 people.

Risks and Benefits

It will cost you nothing to take part in this study but there is a potential benefit to you if we do this study, as it will let us know whether or not you are developing other conditions as a result of the drugs. Knowing this will help us make sure that you are getting appropriate medical attention and will help in making plans to minimize the possibility of developing further complications. A better understanding of these relationships may provide information to put in place measures to prevent these conditions among people living with HIV and are on the antiretrovirals. Furthermore, this research may provide evidence to support the need for infrastructure in Ghana to address metabolic syndrome.

Possible risks/ complications of blood collection include bruising or swelling at the puncture site, accidental blood spillage, damage to underlying tissue and infection at the puncture site. The risks of any serious complication occurring is very low. These risks will be avoided by ensuring strict hygienic practices by cleaning skin with alcohol swabs before blood is taken; using single-use disposable needles; using experienced persons for taking blood samples; removing tourniquet

immediately after entering the vein; using clean dressing/plaster to cover the puncture site when needle is removed from vein; ensuring puncture site is away from vital/ important tissue; and also ensuring great care to prevent accidental spillage.

Freedom to participate/ Voluntary withdrawal

Participant opinions and experiences are important to us, so we want you to be honest and truthful in answering our questions. Your participation is completely voluntary and you may refuse to participate at any time. You may ask me to stop the interview, anthropometric measurements or blood sample collection at any point or you may also decline to answer any question if it makes you uncomfortable.

Privacy and Confidentiality

To ensure confidentiality and privacy we will not mark any of the samples with study participant's names: rather we will code numbers to the samples and keep an encrypted file that coordinates numbers to names on a secure laptop.

Protection of subjects' privacy

Participants do not have to answer any questions that they feel are an invasion of their privacy. Also, subjects do not have to participate in any particular aspects of the study that they find invasive. Results from their biochemical tests will be communicated directly to them through the contact details they will provide. Additionally, client with abnormal test results will be assisted with a referral letter to the appropriate facility.

Provision to prematurely end a particular subject's participation in the study

Participants can opt to be interviewed in a location of their choice to increase privacy at the health facilities. In the case of an adverse event or situation of distress, a subject's participation in the study will be concluded.

Compensation for participants

Compensation will be given at the time of data/specimen collection. Compensation is not payment for participating in this study but serves as a token of appreciation for participants' time. A milo drink will be provided for all participants who agree to participate in the study. Additionally, a

payment of GH¢25 will be given to study participants who will travel to the facility during each follow-up period to support their transportation cost.

Funding information

This study is supported by the National Institute of Health, Fogarty D43 grant but data from this study will not be shared with anyone.

Data storage and protection

All research records, data and blood (specimens) will be protected against inappropriate use or disclosure, or malicious or accidental loss or destruction. Data will be locked with restricted access on a secure laptop. There will be safe disposition/destruction of data or devices, as appropriate (e.g., shredding paper documents, secure erasure of electronic media) at the conclusion of the study.

The data and/or any specimens will be destroyed at the conclusion of this study.

Specimens of blood will be stored for a maximum of 2 weeks during the analysis period to enable us to confirm inconsistent or abnormal results after which they will be destroyed as well as the identifiers on their storage containers. Study survey forms (hard copy) will be destroyed at the conclusion of the study.

Provision of Information and Consent for participants

A copy of the Information sheet and Consent form will be given to you after it has been signed or thumb-printed to keep.

Declaration of conflict of interest

I Marian Offei (Principal Investigator), declare that, to the best of my knowledge, there is no actual, perceived or potential conflict of interest that will or may arise as a result of my involvement with this study.

Who to contact

In cases of any questions regarding the research, you can contact:

- School of Public health, University of Ghana, Legon.
- Marian Offei

Mobile number: 0246945940

Email: marianoffei@yahoo.com

Or for Ethical issues only, you can contact:

- **GHS/ Ethics Review Committee administrator, Nana Abena Apatu (mobile: 0503539896)**

Before taking Consent

Do you have any questions you wish to ask about the study? Yes ☐ No ☐

(If yes, please, indicate the questions below) ……

……

7.2 Informed Consent Form for Interview

Title of study: Effect of dolutegravir-based regimen on metabolic syndrome among people living with HIV in the Greater Accra Region.

Introduction

I am a PhD student at the School of Public Health, University of Ghana, legon. As part of the programme, we carry out research work. My work is on the health effects of dolutegravir-based regimen (Tenofovir + Lamivudine/Emtricitabine+Dolutegravir) on metabolic syndrome. We say you have metabolic syndrome when you have three or more of some non-communicable diseases (high blood pressure, abnormal cholesterol level, high blood sugar, central obesity and insulin resistance). As part of this research, I would want to know some of the challenges that hinders the adherence to the new HIV guidelines before antiretroviral therapy (ART) initiation. It is hoped that the findings of this study will help identify the bottlenecks and help put in appropriate measures to ensure the clinics adhere to them.

Purpose of the study

The study aims to assess the level of adherence and challenges to the baseline assessments before the ART initiation among health facilities providing comprehensive HIV care to HIV-positive patients in Greater Accra Region.

Eligibility criteria

HIV-positive patients who are 18 years and above attending the clinic on the day of the study to start the ART and heads of HIV clinics.

Study Procedure

If you agree to take part in the study, we will ask questions on the service and information provided or you provide to patients before they start the ART. This will take about 20 minutes. We may interview 20 HIV-positive patients and 10 heads of HIV clinics. This interview will be audio recorded.

_____ If you agree for us to record this interview as described above, please initial here to have us record.

Risks and Benefits

It will cost you nothing to take part in this study but there is a potential benefit to you if we do this study, as it will let us know some of the challenges in adhering to the guidelines. A better understanding of these relationships may provide information to put in place measures to increase adherence. There is no possible risks/ complications in participating in this study.

Freedom to participate/ Voluntary withdrawal

Participant opinions and experiences are important to us, so we want you to be honest and truthful in answering our questions. Your participation is completely voluntary and you may refuse to participate at any time. You may ask me to stop the interview at any point or you may also decline to answer any question if it makes you uncomfortable.

Privacy and Confidentiality

To ensure confidentiality and privacy we will not use participants names. Codes will be used instead.

Protection of subjects' privacy

Participants do not have to answer any questions that they feel are an invasion of their privacy.

Provision to prematurely end a particular subject's participation in the study

Participants can opt to be interviewed in a location of their choice to increase privacy at the health facilities. In the case of an adverse event or situation of distress, a subject's participation in the study will be concluded.

Compensation for participants

There will be no compensation. Participants will be thanked for their time.

Funding information

This study is supported by the National Institute of Health, Fogarty D43 grant but data from this study will not be shared with anyone.

Data storage and protection

All research records and recordings will be protected against inappropriate use or disclosure, or malicious or accidental loss or destruction. Data will be locked with restricted access on a secure laptop. There will be safe disposition/destruction of data or devices, as appropriate (e.g., shredding paper documents, secure erasure of electronic media) at the conclusion of the study.

Provision of Information and Consent for participants

A copy of the Information sheet and Consent form will be given to you after it has been signed or thumb-printed to keep.

Declaration of conflict of interest

I Marian Offei (Principal Investigator), declare that, to the best of my knowledge, there is no actual, perceived or potential conflict of interest that will or may arise as a result of my involvement with this study.

Who to contact

In cases of any questions regarding the research, you can contact:

- School of Public health, University of Ghana, Legon.
- Marian Offei
  Mobile number: 0246945940
  Email: marianoffei@yahoo.com

Or for Ethical issues only, you can contact:

- **GHS/ Ethics Review Committee administrator, Nana Abena Apatu (mobile: 0503539896)**

Before taking Consent

Do you have any questions you wish to ask about the study? Yes ☐ No ☐

(If yes, please, indicate the questions below)……

……

STATEMENT OF CONSENT

- **Participants' Statement**

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and all questions satisfactorily explained to me in a language I understand (Twi/Ga/Ewe). I fully understand the contents and any potential implications as well as my right to change my mind (i.e. withdraw from the research) even after I have signed this form.
I voluntarily agree to be part of this research.

Name of Participant…….. Date:…….

Participants' Signature ……...OR Thumb Print……

- **Interpreters' Statement**

I interpreted the purpose and contents of the Participants' Information Sheet to the afore named participant to the best of my ability in the (Twi/Ga/Ewe) language to his proper understanding. All questions, appropriate clarifications sort by the participant and answers were also duly interpreted to his/her satisfaction.

Name of Interpreter…… Date:…….

Signature of Interpreter…….. OR Thumb Print …….....

- **Statement of Witness**

I was present when the purpose and contents of the Participant Information Sheet was read and explained satisfactorily to the participant in the language he/she understood (Twi/Ga/Ewe). I confirm that he/she was given the opportunity to ask questions/seek clarifications and same were duly answered to his/her satisfaction before voluntarily agreeing to be part of the research.

Name:…… Date:……

Signature…….... OR Thumb Print …….....

INVESTIGATOR STATEMENT AND SIGNATURE

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.)

Researcher's name…….

Signature …….

Date…….

7.3 Medical Referral Form

MEDICAL REFERRAL FORM

Date:

RE: (Patient Name)
Patient Date of Birth

Dear Dr. .....,

The above named client was recently involved in a research project where samples of his/her blood were taken for analysis of certain parameters. The following abnormalities were noted in his laboratory results;

Parameter and abnormalities identified

We are therefore referring him/her to your facility for appropriate medical care. We are most grateful for your assistance.

Sincerely,

Marian Offei
Principal investigator
School of Public Health
University of Ghana

7.4 Ethical Clearance

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App 21/522
Your Ref. No.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Digital Address: GA-050-3303
Mob: +233-50-3539896
Tel: +233-302-681109
Fax + 233-302-685424
Email: ethics.research@ghsmail.org
21st January, 2021

Marian Offei
P. O. Box CT1842
Cantonments, Accra

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC 005/11/20**
Study Title	Effect of Dolutegravir-Based Regimen on Metabolic Syndrome among People Living with HIV in the Greater Accra Region
Approval Date	21st January, 2021
Expiry Date	20th January, 2022
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of six monthly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

You are kindly advised to adhere to the national guidelines or protocols on the prevention of COVID -19

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....Bannerman.....
Dr. Cynthia Bannerman
(GHS ERC Chairperson)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

My Ref:ghs/rdd/erc-admin/ren/app/22
Your Ref. No.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra.
Digital Address: GA-050-3303

Tel: +233-0302-960628
Mob + 233-050-3539896
Email:
ethics.research@ghsmail.org
23rd March 2022

Marian Offei
University of Ghana
School of Public Health
P. O. Box LG 13 Legon, Accra

RE: REQUEST FOR RENEWAL OF ETHICAL APPROVAL

Reference is made to your letter dated 21st March 2022 on the above subject matter.

Please be informed that the Ghana Health Service Ethics Review Committee has reviewed the request and has given approval for renewal of the ERC letter.

GHS-ERC Number	**GHS-ERC: 005/11/20**
Study Title	Effect of Dolutegravir-Based Regimen on Metabolic Syndrome among People Living with HIV in the Greater Accra Region
Effective Date of Renewal	23rd March, 2022
Expiry Date	22nd March, 2023
GHS-ERC Decision	**Renewal Approved**

The following applies:

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC).
- Renewal of ethical approval if the study lasts for more than 12 months.
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report **after completion** of the study.
- Informing the ERC if study is discontinued and reasons why.
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

7.5 Study Questionnaire

QUESTIONAIRE: COHORT STUDY

Survey Information

Location and Date		Response	Code
1	Interviewer ID *Record interviewer's identification*	⌊_⌊_⌊_⌊_	I1
2	Date of completion of the instrument *Record date when instrument actually completed*	⌊_⌊_ ⌊_⌊_ ⌊_⌊_⌊_⌊_ dd mm year	I2
3	Consent has been read and obtained	Yes 1 No 2	I3

Demographic Information

	Question	Response	Code
4	Sex	Male 1 Female 2	C1
5	What is your date of birth? *Don't Know 99* *Record date of birth of participant.*	⌊_⌊_ ⌊_⌊_ ⌊_⌊_⌊_⌊_ dd mm year	C2
6	How old are you?	Years ⌊_⌊_	C3
7	What is the **highest level of education** you have completed?	No formal education 1 Primary education 2 Junior high school 3 Senior high school 4 Tertiary 5 Don't know 99	C4
8	What is your *ethnicity?*	Akan 1 Ewe 2 Ga/ Adangbe 3 Dagomba/ Hausa 4 Other ……	C5
9	What is your **marital status**?	Never married 1 Married/ Cohabitating 2 Separated/ Divorced/ Widowed 3 Refused 88	C6
10	Which of the following best describes your **main work**	Unemployed 1 Student 2 Self-employed 3 Employed (Government) 4 Retired 5 Refused 88	C7
11	How many people older than 18 years, including yourself, live in your household?	Number of people ⌊_⌊_	C8
12	What is your monthly income?	Amount (GHS)…… Not applicable 77	C9

Circle what applies

Behavioural Measurements

Now I am going to ask you some questions about various health behaviours. This includes things like smoking, drinking alcohol, eating fruits and vegetables and physical activity. Let's start with tobacco.

Tobacco Use

13	Do you currently smoke any **tobacco products**, such as cigarettes, cigars or pipes?	Yes 1 No 2 *If No, go to B6*	T1
14	Do you currently smoke tobacco products?	Yes 1 No 2 ***If No, go to A1***	T2
15	How often do you smoke?	Daily 1 Occasionally 2 Never 3 ***If 2 or 3, go to A1***	T3
16	How old were you when you **first started** smoking daily? *If known, go to T5*	Age (years)…… Don't know 99	T4
17	Do you remember how long ago it was? *(RECORD ONLY 1, NOT ALL 3)*	In Years/ Months/ Weeks ⌊_⌊_ *If known, go to T5*	T5

	Question	Response	Code
	Don't know 99		
18	On average, **how many** of the any **tobacco products**, such as cigarettes, cigars or pipes do you smoke each day?	Number ⌊_⌋⌊_⌋ Other ⌊_⌋⌊_⌋ If other, go to T9	T6
19	In the past, did you **ever** smoke **daily**?	Yes 1 No 2 *If No, go to T9*	T7
20	How old were you when you **stopped** smoking **daily**? *Ask the participant to think of the time when he/she stopped smoking tobacco products on a daily basis.*	Age (years) ⌊_⌋⌊_⌋ Don't Know 99 *If Known, go to T9*	T8
21	Do you remember how long ago it was? *Don't know 77*	In Years/ Months/ Weeks ⌊_⌋⌊_⌋ *If Known, go to T9*	T9
22	Do you **currently use** any **smokeless tobacco** such as [*snuff, chewing tobacco, betel*]?	Yes 1 No 2	T10
23	Do you **currently use** any **smokeless tobacco** products **daily?**	Yes 1 No 2	T11
24	On average, how many **times a day** do you use any **smokeless tobacco** such as [*snuff, chewing tobacco, betel*]? *Don't Know 77*	Number ⌊_⌋⌊_⌋ Other ⌊_⌋⌊_⌋ If other, go to T13	T12
25	In the past, did you **ever** smoke or use smokeless tobacco **daily**?	Yes 1 No 2	T13
26	During the past 7 days, on how many days did someone **in your home** smoke when you were present?	Number of days ⌊_⌋⌊_⌋ Don't know 77	T14
27	During the past 7 days, on how many days did someone smoke in closed areas **in your workplace** (in the building, in a work area or a specific office) when you were present?	Number of days ⌊_⌋⌊_⌋ Don't know or don't work in a closed area 99	T15
	Alcohol Consumption		
	The next questions ask about the consumption of alcohol.		
28	Have you **ever** consumed an alcoholic drink such as beer, wine, spirits, fermented cider or *[add other local examples]*)?	Yes 1 No 2 *If No, go to D1*	A1a
29	Have you consumed an alcoholic drink within the **past 12 months**? *Think of any drinks that contain alcohol.*	Yes 1 No 2 *If No, go to D1*	A1b
30	During the past 12 months, **how frequently** have you had at least one alcoholic drink? *Think of the past year only.*	Daily 1 5-6 days per week 2 1-4 days per week 3 1-3 days per month 4 Less than once a month 5	A2
31	Have you consumed an alcoholic drink within the **past 30 days**?	Yes 1 No 2 *If No, go to D1*	A3
32	During the past 30 days, on how many **occasions** did you have at least one alcoholic drink?	Number ⌊_⌋⌊_⌋ Don't know 77	A4
33	During the past 30 days, when you drank alcohol, **on average**, how many **standard alcoholic drinks** did you have during one drinking occasion?	Number Don't know 77 ⌊_⌋⌊_⌋	A5
34	During the past 30 days, what was the **largest number** of standard alcoholic drinks you had on a single occasion, counting all types of alcoholic drinks together?	Largest number Don't Know 77 ⌊_⌋⌊_⌋	A6
35	During the past 30 days, how many times did you have for **men**: **five or more** for **women**: **four or more** standard alcoholic drinks in a single drinking occasion?	Number of times ⌊_⌋⌊_⌋ Don't Know 77	A7

	Question	Response	Code
36	During the past 30 days, when you consumed an alcoholic drink, how often was it with meals? Please do not count snacks. *Think of the past 30 days only.*	Usually with meals 1 Sometimes with meals 2 Rarely with meals 3 Never with meals 4	A8

Diet

The next questions ask about the fruits and vegetables that you usually eat. I have a nutrition card here that shows you some examples of local fruits and vegetables. Each picture represents the size of a serving. As you answer these questions please think of a typical week in the last year.

37	In a typical/ normal week, on how many days do you **eat fruit**?	Number of days ⌊_⌋⌊_⌋ *If Zero days, go to D3* Don't Know 77	D1
38	In a typical week, on how many days do you **eat vegetables**?	Number of days ⌊_⌋⌊_⌋ *If Zero days, go to D5* Don't Know 77	D2
39	What type of **oil or fat is most often** used for meal preparation in your household? *Circle the appropriate response.*	Vegetable oil 1 Lard or suet 2 Butter or ghee 3 Margarine 4 Other 5 *If Other, go to D5other* None in particular 6 None used 7 Don't know 77	D3
		Other ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	D3other
40	On average, how many meals per week do you eat that were not prepared at a home? By meal, I mean breakfast, lunch and dinner.	Number ⌊_⌋⌊_⌋ Don't know 77	D4

Physical Activity

Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person. Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

Question		Response	Code
41	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like *[carrying or lifting heavy loads, digging or construction work]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 4*	P1
42	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days ⌊_⌋	P2
43	How much time do you spend doing vigorous-intensity activities at work on a typical day? vigorous-intensity activities as part of your work? *"activities undertaken continuously for 10 minutes or more"*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P3
44	Does your work involve moderate-intensity activity, that causes small increases in breathing or heart rate such as brisk walking *[or carrying light loads]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 4*	P4
45	In a typical week, on how many days do you do moderate-intensity activities as part of your work? *Valid responses range from 1-7*	Number of days ⌊_⌋	P5

	Question	Response	Code
46	How much time do you spend doing moderate-intensity activities at work on a typical day? *Think of one day you can recall easily. Consider only those activities undertaken continuously for 10 minutes or more.*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P6
Travel to and from places			
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship. [insert other examples if needed]			
47	Do you walk or use a bicycle (*pedal cycle*) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to P 10*	P7
48	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places? *Valid responses range from 1-7*	Number of days ⌊_⌋	P8
49	How much time do you spend walking or bicycling for travel on a typical day? *Total amount of time walking or bicycling for trips of 10 minutes or more*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P9
Recreational activities			
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure),[insert relevant terms]. *Activities reported should be done regularly and not just occasionally. It is important to focus on only recreational activities*			
50	Do you do any vigorous-intensity sports, fitness or recreational (*leisure*) activities that cause large increases in breathing or heart rate like [*running or football,*] for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 13*	P10
51	In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (*leisure*) activities? *Valid responses range from 1-7.*	Number of days ⌊_⌋	P11
52	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day? *Consider the total amount of time doing vigorous recreational activities for periods of 10 minutes or more.*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P12
53	Do you do any moderate-intensity sports, fitness or recreational *(leisure*) activities that causes a small increase in breathing or heart rate such as brisk walking, (*cycling, swimming, volleyball*) for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P16*	P13
54	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊_⌋	P14
55	How much time do you spend doing moderate-intensity sports, fitness or recreational (*leisure*) activities on a typical day? *Periods of 10 minutes or more.*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P15
Sedentary behavior			
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent sitting at a desk, sitting with friends, traveling in car, bus, train, reading, playing cards or watching television, but do not include time spent sleeping.			
56	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs min s	P16

History of Raised Blood Pressure

Question		Response	Code
57	Have you ever had your blood pressure measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to H6*	H1

Question		Response	Code
58	Have you ever been told by a doctor or other health worker that you have raised blood pressure or hypertension?	Yes 1 No 2 *If No, go to H6*	H2
59	Have you been told in the past 12 months?	Yes 1 No 2	H2
59b	Does any member of your family have high blood pressure?	Yes 1 No 2	H2b
60	Are you currently receiving any of the following treatments/advice for high blood pressure prescribed by a doctor or other health worker?		
	Drugs (medication) that you have taken in the past two weeks	Yes 1 No 2	H3a
	Advice to reduce salt intake	Yes 1 No 2	H3b
	Advice or treatment to lose weight	Yes 1 No 2	H3c
	Advice or treatment to stop smoking	Yes 1 No 2	H3d
	Advice to start or do more exercise	Yes 1 No 2	H3e
61	Have you ever seen a traditional healer for raised blood pressure or hypertension?	Yes 1 No 2	H4
62	Are you currently taking any herbal or traditional remedy for your raised blood pressure?	Yes 1 No 2	H5

History of Diabetes

Question		Response	Code
63	Have you ever had your blood sugar measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to M1*	H6
64	Have you ever been told by a doctor or other health worker that you have raised blood sugar or diabetes?	Yes 1 No 2 *If No, go to M1*	H7a
65	Have you been told in the past 12 months?	Yes 1 No 2	H7b
65b	Does any member of your family have Diabetes?	Yes 1 No 2	H7c
66	Are you currently receiving any of the following treatments/advice for diabetes prescribed by a doctor or other health worker?		
	Insulin	Yes 1 No 2	H8a
	Drugs (medication) that you have taken in the past two weeks	Yes 1 No 2	H8b
	Special prescribed diet	Yes 1 No 2	H8c
	Advice or treatment to lose weight	Yes 1 No 2	H8d
	Advice or treatment to stop smoking	Yes 1 No 2	H8e
	Advice to start or do more exercise	Yes 1 No 2	H8f
67	Have you ever seen a traditional healer for diabetes or raised blood sugar?	Yes 1 No 2	H9
68	Are you currently taking any herbal or traditional remedy for your diabetes?	Yes 1 No 2	H10

HIV, ART & CO-MORBID/OPPORTUNISTIC INFECTIONS MEASUREMENTS

HIV

Question		Response	Code
69	Time since HIV infection	⌊_⌊_⌊ Months	V1
70	CD4 cell count	⌊_⌊_⌊	V2

71	Viral load	⌊_____⌋	V3
72	WHO Stage	Stage 1 Stage 2 Stage 3 Stage 4	V4
	Co-morbid Conditions/ Opportunistic Infection		
73	Presence of co-morbid conditions/ infections *Co-morbid conditions like diabetes, hypertension, TB, hepatitis B or C, chronic kidney disease, within the last 6 months as documented in clinical folder*	Yes 1 No 2	O1
74	If Yes, specify	…… …… ……	O2
	ART		
75	Have you switched to the new ART regimen?	Yes 1 *If Yes, go to A4* No 2	R1
76	ART duration	⌊_⌋⌊_⌋ Months	R2
77	Type of ART regimen	TDF/3TC/EFV 1 TDF/FTC/EFV 2	R3
78	ART duration before switching	⌊_⌋⌊_⌋ Months	R4
79	Type of ART regimen before switching	TDF/3TC/EFV 1 TDF/FTC/EFV 2	R5
80	ART duration after switching	⌊_⌋⌊_⌋ Months	R6
81	Type of ART regimen after switching	TDF/3TC/DTG 1 TDF/FTC/DTG 2	R7

Physical Measurements

Height and Weight

	Question	Response	Code
82	Device IDs for height and weight *Record device IDs.*	Height ⌊_⌋⌊_⌋ Weight ⌊_⌋⌊_⌋	M1 M2
83	Height *Record participant's height in cm.*	in Centimetres (cm) ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋	M3
84	Weight *If too large for scale, code 666.6* *Record participant's weight in kg.*	in Kilograms (kg) ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋	M4
	Waist		
85	Device ID for waist *Record device ID.*	⌊_⌋⌊_⌋	M5
86	Waist circumference *Record participant's waist circumference in centimetres.*	in Centimetres (cm) ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋	M6
	Blood Pressure		
87	Device ID for blood pressure *Record device ID.*	⌊_⌋⌊_⌋	M7
88	Cuff size used *Circle size used*	Small 1 Medium 2 Large 3	M8
89	Reading 1 *Record first measurement after the participant has rested for 15 minutes. Wait 3 minutes intervals before taking second and third measurements*	Systolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋ Diastolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M9a M9b
90	Reading 2 *Record second measurement.*	Systolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋ Diastolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M10a M10b

91	Reading 3 *Record third measurement.*	Systolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M11a
		Diastolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M11b
	Question	**Response Code**	**Question**
92	During the past two weeks, have you been treated for raised blood pressure with drugs (medication) prescribed by a doctor or other health worker? *Circle appropriate response.*	Yes 1 No 2	M12
	Hip Circumference and Heart Rate		
93	Hip circumference *Record participant's hip circumference in cm.*	in Centimeters (cm) ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋	M13
94	Heart Rate *Record the three heart rate readings.*		
	Reading 1	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14a
	Reading 2	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14b
	Reading 3	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14c

Biochemical Measurements

Blood Glucose			
Question		**Response**	**Code**
95	During the past 12 hours have you had anything to eat or drink, other than water? *participant has fasted.*	Yes 1 No 2	B1
96	Technician ID	⌊_⌋⌊_⌋⌊_⌋⌊_⌋	B2
97	Device ID	⌊_⌋⌊_⌋⌊_⌋	B3
98	Time of day blood specimen taken (24 hour clock)	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	B4
99	Fasting blood glucose *Double check that the participant has fasted.*	mmol/l ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋	B5
100	Today, have you taken insulin or other drugs (medication) that have been prescribed by a doctor or other health worker for raised blood glucose?	Yes 1 No 2	B6
	Blood Lipids		
101	Device ID	⌊_⌋⌊_⌋⌊_⌋	B7
102	Total cholesterol	mmol/l ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋	B8
103	During the past two weeks, have you been treated for raised cholesterol with drugs (medication) prescribed by a doctor or other health worker?	Yes 1 No 2	B9
	Triglycerides, LDL and HDL Cholesterol		
104	Triglycerides	mmol/l ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋	B10
105	HDL Cholesterol	mmol/l ⌊_⌋ . ⌊_⌋⌊_⌋	B11
106	LDL Cholesterol	mmol/l ⌊_⌋ . ⌊_⌋⌊_⌋	B12
	Full blood Count		
107	Haemoglobin level	g/dL ⌊_⌋ . ⌊_⌋⌊_⌋	B13

108	Platelets count	10^9/L ⌊__⌋⌊__⌋.⌊__⌋	B14
109	White blood Cells	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B15
	Question	**Response**	**Code**
110	Red blood Cells	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B16
111	Monocytes	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B17
112	Lymphocytes	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B18
113	Neutrophils	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B19
114	Eosinophils	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B20
115	Basophils	10^9/L ⌊__⌋.⌊__⌋⌊__⌋	B21
115	Creatinine	µmol/L ⌊__⌋.⌊__⌋⌊__⌋	B22
116	High-sensitivity C-reactive protein	mg/L ⌊__⌋.⌊__⌋⌊__⌋	B23

DATA EXTRACTION TOOL FROM FOLDERS: OBJECTIVE 1

CLINICAL EVALUATION		
Medical History	**Yes (1)**	**No (2)**
Date of initial HIV diagnosis and		
Type of HIV infection		
Current symptoms and concerns including a symptom screen for tuberculosis		
Past Medical History including diagnosis of tuberculosis		
Drug history including treatment for TB and Hepatitis B		
Previous ARV exposure		
Sexual history and past symptoms of STI		
Obstetrics and Gynaecological history including family planning		
Social history including family support systems and income		
History of drug use		
Physical Examination		
Client's height		
Client's weight		
Skin- looking out for the following: Herpes Zoster (old scars and new lesions), Herpes simplex, Molluscum contagiosum, Kaposi's sarcoma, Pruritic Papular Dermatitis or Eruptions or Prurigo and Plane warts.		
Mouth- Oropharyngeal mucosa, Candidiasis, Oral hairy Leukoplakia, Gingivitis, Mouth ulcers and Kaposi sarcoma.		
Lymphadenitis/lymphadenopathy		
Respiratory (sinusitis, Otitis, pneumonia, TB) and Cardiovascular system (Cardiomyopathy)		
Genito-urinary system		
Gastrointestinal system (Oesophagitis, Diarrhoea etc.)		
Anorectal area for discharge, ulcers, enlarged glands and growths.		
Nervous and musculo-skeletal systems including mental status, motor and sensory deficits		
Fundoscopy whenever possible for retinitis or papilloedema and Cytomegalovirus (CMV) retinitis.		
Detailed examination of Genital Tract for discharge, ulcers, enlarged glands and growths.		
Laboratory Evaluation		
Confirmation of HIV infection and type (HIV1, HIV2, HIV1 and 2)		
Whether female clients are pregnant.		
The presence of opportunistic infections.		
The presence of co-morbid diseases		
Baseline Laboratory Investigations		
Haematological test		
Full blood count		
Biochemical test		
Blood Urea		
Electrolytes and Creatinine		

Liver Function tests		
Fasting Blood Sugar		
Cholesterol and lipid profile		
Routine examinations	**Yes (1)**	**No (2)**
Urinalysis (Urine R/E)		
Stool R/E		
Respiratory examinations		
TB screening		
Gene Xpert		
Chest X-ray		
Serological test		
Hepatitis B Surface antigen		
Immunological test		
CD4		
Other test dependent on signs and symptoms		
Histology on skin and lymph node Biopsy		
Screening for STIs		
Histology on skin and lymph node Biopsy		
Pap smear, HPV DNA		
Abdominal Ultrasound		

INTERVIEW GUIDE

Participants ID:

Date of Interview:

Name of HIV Clinic:

Occupation:

Position/ Duration of work at Clinic:

Interviewer:

Gender:

Age:

Questions for Heads of HIV Clinics

1. What is your staff strength?

2. Do you think you have all the required staff needed to ensure the guidelines are adhered to?

3. If No, which cadre of workers do you need?

4. Have you started using the new updated HIV guidelines for ART initiation?

5. What information do you gather from new registrants before you start them on the ART?

6. What laboratory tests or physical measurements do you carry out before you start new registrants on the ART?

7. Do you have challenges with adhering to the requirements based on the guidelines?

8. What do you think can be done to help you do your work better?

9. Do you have any questions or more information for me?

Thank you for your time.

Questions for HIV-Positive patients about to start ART

1. Is it your first time here?

2. What information did they take from you before they introduced the drugs to you?

3. What information were you given before they gave you the drugs (antiretrovirals)?

4. What laboratory tests or physical measurements did you do before they gave you the drugs?

5. Did you pay for the laboratory tests yourself?

6. If Yes, in your opinion was it expensive?

7. Were you satisfied with the services you received today?

8. What do you think can be done to make you feel comfortable and satisfied any time you visit the clinic?

9. Do you have any questions or more information for me?

Thank you for your time.

QUESTIONAIRE: FOLLOW-UP

Survey Information

Location and Date		Response	Code
1	Interviewer ID *Record interviewer's identification*	⌊_⌊_⌊_⌊_	I1
2	Date of completion of the instrument *Record date when instrument actually completed*	⌊_⌊_ ⌊_⌊_ ⌊_⌊_⌊_⌊_ dd mm year	I2
3	Consent has been read and obtained	Yes 1 No 2	I3

Circle what applies

Behavioural Measurements

Now I am going to ask you some questions about various health behaviours. This includes things like smoking, drinking alcohol, eating fruits and vegetables and physical activity. Let's start with tobacco.

Tobacco Use

4	Do you currently smoke any **tobacco products**, such as cigarettes, cigars or pipes?	Yes 1 No 2 *If No, go to B6*	T1
5	Do you currently smoke tobacco products?	Yes 1 No 2 ***If No, go to A1***	T2
6	How often do you smoke?	Daily 1 Occasionally 2 Never 3 ***If 2 or 3, go to A1***	T3
7	How old were you when you **first started** smoking daily? *If known, go to T5*	Age (years)..... Don't know 99	T4
8	Do you remember how long ago it was? *(RECORD ONLY 1, NOT ALL 3)* *Don't know 99*	In Years/ Months/ Weeks ⌊_⌊_ *If known, go to T5*	T5
9	On average, **how many** of the any **tobacco products**, such as cigarettes, cigars or pipes do you smoke each day?	Number ⌊_⌊_ Other ⌊_⌊_ If other, go to T9	T6
10	In the past, did you **ever** smoke **daily**?	Yes 1 No 2 *If No, go to T9*	T7
11	How old were you when you **stopped** smoking **daily**? *Ask the participant to think of the time when he/she stopped smoking tobacco products on a daily basis.*	Age (years) Don't Know 99 ⌊_⌊_ *If Known, go to T9*	T8
12	Do you remember how long ago it was? *Don't know 77*	In Years/ Months/ Weeks ⌊_⌊_ *If Known, go to T9*	T9
13	Do you **currently use** any **smokeless tobacco** such as [*snuff, chewing tobacco, betel*]?	Yes 1 No 2	T10
14	Do you **currently use** any **smokeless tobacco** products **daily?**	Yes 1 No 2	T11
15	On average, how many **times a day** do you use any **smokeless tobacco** such as [*snuff, chewing tobacco, betel*]? *Don't Know 77*	Number ⌊_⌊_ Other ⌊_⌊_ If other, go to T13	T12
16	In the past, did you **ever** smoke or use smokeless tobacco **daily**?	Yes 1 No 2	T13
17	During the past 7 days, on how many days did someone **in your home** smoke when you were present?	Number of days ⌊_⌊_ Don't know 77	T14
18	During the past 7 days, on how many days did someone smoke in closed areas **in your workplace** (in the building, in a work area or a specific office) when you were present?	Number of days ⌊_⌊_ Don't know or don't work in a closed area 99	T15

Alcohol Consumption

The next questions ask about the consumption of alcohol.

19	Have you **ever** consumed an alcoholic drink such as beer, wine, spirits, fermented cider or *[add other local examples]*)?	Yes 1 No 2 *If No, go to D1*	A1a
20	Have you consumed an alcoholic drink within the **past 12 months**? *Think of any drinks that contain alcohol.*	Yes 1 No 2 *If No, go to D1*	A1b
21	During the past 12 months, **how frequently** have you had at least one alcoholic drink? *Think of the past year only.*	Daily 1 5-6 days per week 2 1-4 days per week 3 1-3 days per month 4 Less than once a month 5	A2
22	Have you consumed an alcoholic drink within the **past 30 days**?	Yes 1 No 2 *If No, go to D1*	A3
23	During the past 30 days, on how many **occasions** did you have at least one alcoholic drink?	Number ⌊_⌋⌊_⌋ Don't know 77	A4
24	During the past 30 days, when you drank alcohol, **on average**, how many **standard alcoholic drinks** did you have during one drinking occasion?	Number Don't know 77 ⌊_⌋⌊_⌋	A5
25	During the past 30 days, what was the **largest number** of standard alcoholic drinks you had on a single occasion, counting all types of alcoholic drinks together?	Largest number Don't Know 77 ⌊_⌋⌊_⌋	A6
26	During the past 30 days, how many times did you have for **men**: **five or more** for **women**: **four or more** standard alcoholic drinks in a single drinking occasion?	Number of times ⌊_⌋⌊_⌋ Don't Know 77	A7
27	During the past 30 days, when you consumed an alcoholic drink, how often was it with meals? Please do not count snacks. *Think of the past 30 days only.*	Usually with meals 1 Sometimes with meals 2 Rarely with meals 3 Never with meals 4	A8

Diet

The next questions ask about the fruits and vegetables that you usually eat. I have a nutrition card here that shows you some examples of local fruits and vegetables. Each picture represents the size of a serving. As you answer these questions please think of a typical week in the last year.

28	In a typical/ normal week, on how many days do you **eat fruit**?	Number of days Don't Know 77 ⌊_⌋⌊_⌋ *If Zero days, go to D3*	D1
29	In a typical week, on how many days do you **eat vegetables**?	Number of days ⌊_⌋⌊_⌋ Don't Know 77 *If Zero days, go to D5*	D2
30	What type of **oil or fat is most often** used for meal preparation in your household? *Circle the appropriate response.*	Vegetable oil 1 Lard or suet 2 Butter or ghee 3 Margarine 4 Other 5 *If Other, go to D5other* None in particular 6 None used 7 Don't know 77	D3
		Other ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	D3other
31	On average, how many meals per week do you eat that were not prepared at a home? By meal, I mean breakfast, lunch and dinner.	Number ⌊_⌋⌊_⌋ Don't know 77	D4

Physical Activity

Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person. Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

	Question	Response	Code
32	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like *[carrying or lifting heavy loads, digging or construction work]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 4*	P1
33	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days ⌊__⌋	P2
34	How much time do you spend doing vigorous-intensity activities at work on a typical day? vigorous-intensity activities as part of your work? *"activities undertaken continuously for 10 minutes or more"*	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P3
35	Does your work involve moderate-intensity activity, that causes small increases in breathing or heart rate such as brisk walking *[or carrying light loads]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 4*	P4
36	In a typical week, on how many days do you do moderate-intensity activities as part of your work? *Valid responses range from 1-7*	Number of days ⌊__⌋	P5
37	How much time do you spend doing moderate-intensity activities at work on a typical day? *Think of one day you can recall easily. Consider only those activities undertaken continuously for 10 minutes or more.*	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P6
	Travel to and from places		
	The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship. [insert other examples if needed]		
38	Do you walk or use a bicycle (*pedal cycle*) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to P 10*	P7
39	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places? *Valid responses range from 1-7*	Number of days ⌊__⌋	P8
40	How much time do you spend walking or bicycling for travel on a typical day? *Total amount of time walking or bicycling for trips of 10 minutes or more*	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P9
	Recreational activities		
	The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure),[insert relevant terms]. *Activities reported should be done regularly and not just occasionally. It is important to focus on only recreational activities*		
41	Do you do any vigorous-intensity sports, fitness or recreational (*leisure*) activities that cause large increases in breathing or heart rate like [*running or football,*] for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 13*	P10
42	In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (*leisure*) activities? *Valid responses range from 1-7.*	Number of days ⌊__⌋	P11
43	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day? *Consider the total amount of time doing vigorous recreational activities for periods of 10 minutes or more.*	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P12

44	Do you do any moderate-intensity sports, fitness or recreational *(leisure)* activities that causes a small increase in breathing or heart rate such as brisk walking, (*cycling, swimming, volleyball*) for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P16*	P13
45	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊_⌋	P14
46	How much time do you spend doing moderate-intensity sports, fitness or recreational (*leisure*) activities on a typical day? *Periods of 10 minutes or more.*	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P15

Sedentary behavior

The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent sitting at a desk, sitting with friends, traveling in car, bus, train, reading, playing cards or watching television, but do not include time spent sleeping.

47	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs min s	P16

History of Raised Blood Pressure

Question		Response	Code
48	Have you ever had your blood pressure measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to H6*	H1
49	Have you ever been told by a doctor or other health worker that you have raised blood pressure or hypertension?	Yes 1 No 2 *If No, go to H6*	H2
50	Have you been told in the past 6/12 months?	Yes 1 No 2	H2
51	Are you currently receiving any of the following treatments/advice for high blood pressure prescribed by a doctor or other health worker?		
	Drugs (medication) that you have taken in the past two weeks	Yes 1 No 2	H3a
	Advice to reduce salt intake	Yes 1 No 2	H3b
	Advice or treatment to lose weight	Yes 1 No 2	H3c
	Advice or treatment to stop smoking	Yes 1 No 2	H3d
	Advice to start or do more exercise	Yes 1 No 2	H3e
52	Have you ever seen a traditional healer for raised blood pressure or hypertension?	Yes 1 No 2	H4
53	Are you currently taking any herbal or traditional remedy for your raised blood pressure?	Yes 1 No 2	H5

History of Diabetes

Question		Response	Code
54	Have you ever had your blood sugar measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to M1*	H6
55	Have you ever been told by a doctor or other health worker that you have raised blood sugar or diabetes?	Yes 1 No 2 *If No, go to M1*	H7a
56	Have you been told in the past 6/12 months?	Yes 1 No 2	H7b
57	Are you currently receiving any of the following treatments/advice for diabetes prescribed by a doctor or other health worker?		
	Insulin	Yes 1 No 2	H8a
	Drugs (medication) that you have taken in the past two weeks	Yes 1 No 2	H8b
	Special prescribed diet	Yes 1 No 2	H8c
	Advice or treatment to lose weight	Yes 1 No 2	H8d

	Advice or treatment to stop smoking	Yes 1 No 2	H8e
	Advice to start or do more exercise	Yes 1 No 2	H8f
58	Have you ever seen a traditional healer for diabetes or raised blood sugar?	Yes 1 No 2	H9
59	Are you currently taking any herbal or traditional remedy for your diabetes?	Yes 1 No 2	H10

HIV & CO-MORBID/OPPORTUNISTIC INFECTIONS MEASUREMENTS

HIV

Question		Response	Code
60	CD4 cell count	⌊_⌊_⌋	V2
61	Viral load	⌊_⌊_⌊_⌋	V3

Co-morbid Conditions/ Opportunistic Infection

62	Presence of co-morbid conditions/ infections *Co-morbid conditions like diabetes, hypertension, TB, hepatitis B or C, chronic kidney disease, within the last 6 months as documented in clinical folder*	Yes 1 No 2	O1
63	If Yes, specify	…… …… ……	O2

Physical Measurements

Height and Weight

Question		Response	Code
64	Device IDs for height and weight *Record device IDs.*	Height ⌊_⌊_⌋ Weight ⌊_⌊_⌋	M1 M2
65	Height *Record participant's height in cm.*	in Centimetres (cm) ⌊_⌊_⌊_⌋.⌊_⌋	M3
66	Weight *If too large for scale, code 666.6* *Record participant's weight in kg.*	in Kilograms (kg) ⌊_⌊_⌊_⌋.⌊_⌋	M4

Waist

67	Device ID for waist *Record device ID.*	⌊_⌊_⌋	M5
68	Waist circumference *Record participant's waist circumference in centimetres.*	in Centimetres (cm) ⌊_⌊_⌊_⌋.⌊_⌋	M6

Blood Pressure

69	Device ID for blood pressure *Record device ID.*	⌊_⌊_⌋	M7
70	Cuff size used *Circle size used*	Small 1 Medium 2 Large 3	M8
71	Reading 1 *Record first measurement after the participant has rested for 15 minutes. Wait 3 minutes intervals before taking second and third measurements*	Systolic (mmHg) ⌊_⌊_⌊_⌋ Diastolic (mmHg) ⌊_⌊_⌊_⌋	M9a M9b
	Reading 2	Systolic (mmHg) ⌊_⌊_⌊_⌋	M10a

72	*Record second measurement.*	Diastolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M10b
73	Reading 3 *Record third measurement.*	Systolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M11a
		Diastolic (mmHg) ⌊_⌋⌊_⌋⌊_⌋	M11b
	Question	**Response Code**	**Question**
74	During the past two weeks, have you been treated for raised blood pressure with drugs (medication) prescribed by a doctor or other health worker? *Circle appropriate response.*	Yes 1 No 2	M12
	Hip Circumference and Heart Rate		
75	Hip circumference *Record participant's hip circumference in cm.*	in Centimeters (cm) ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋	M13
76	Heart Rate *Record the three heart rate readings.*		
	Reading 1	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14a
	Reading 2	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14b
	Reading 3	Beats per minute ⌊_⌋⌊_⌋⌊_⌋	M14c

Biochemical Measurements

Blood Glucose

Question		Response	Code
77	During the past 12 hours have you had anything to eat or drink, other than water? *participant has fasted.*	Yes 1 No 2	B1
78	Technician ID	⌊_⌋⌊_⌋⌊_⌋⌊_⌋	B2
79	Device ID	⌊_⌋⌊_⌋⌊_⌋	B3
80	Time of day blood specimen taken (24 hour clock)	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	B4
81	Fasting blood glucose *Double check that the participant has fasted.*	mmol/l ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋	B5
82	Today, have you taken insulin or other drugs (medication) that have been prescribed by a doctor or other health worker for raised blood glucose?	Yes 1 No 2	B6
	Blood Lipids		
83	Device ID	⌊_⌋⌊_⌋⌊_⌋	B7
84	Total cholesterol	mmol/l ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋	B8
85	During the past two weeks, have you been treated for raised cholesterol with drugs (medication) prescribed by a doctor or other health worker?	Yes 1 No 2	B9
	Triglycerides, LDL and HDL Cholesterol		
86	Triglycerides	mmol/l ⌊_⌋⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋	B10
87	HDL Cholesterol	mmol/l ⌊_⌋.⌊_⌋⌊_⌋⌊_⌋	B11
88	LDL Cholesterol	mmol/l ⌊_⌋.⌊_⌋⌊_⌋⌊_⌋	B12
	Full blood Count		

89	Haemoglobin level	g/dL ⌊__⌋.⌊__⌋	B13
90	Platelets count	10^9/L ⌊___⌋	B14
91	White blood Cells	10^9/L ⌊__⌋.⌊__⌋	B15
	Question	**Response**	**Code**
92	Red blood Cells	10^9/L ⌊__⌋.⌊__⌋	B16
93	Monocytes	10^9/L ⌊__⌋.⌊__⌋	B17
94	Lymphocytes	10^9/L ⌊__⌋.⌊__⌋	B18
95	Neutrophils	10^9/L ⌊__⌋.⌊__⌋	B19
96	Eosinophils	10^9/L ⌊__⌋.⌊__⌋	B20
97	Basophils	10^9/L ⌊__⌋.⌊__⌋	B21
98	Creatinine	µmol/L ⌊__⌋.⌊__⌋	B22
99	High-sensitivity C-reactive protein	mg/L ⌊__⌋.⌊__⌋	B23

7.6 Supplementary Table

Table 1: Summary of Variables Measured

Variable	Definition	Type of variable	Scale of measurement
1. **Socio-demographic variables**			
Age	Current age (years) of study participant	Explanatory	2. Continuous 3. Categorical • 18-30 • 31-40 • 41-50 • 51-60 • >60
Sex	Sex of study participant	Explanatory	Binary • Male • Female
Highest Education	Highest educational level attained by study participant	Explanatory	Categorical • No Formal Education • Primary • Middle/ JHS • Secondary/ SHS • Tertiary
Ethnicity	Ethnic group of study participant	Explanatory	Categorical • Akan • Ga Adangbe • Ewe • Northern
Marital Status	Marital status of study participant	Explanatory	• Categorical • Single • Married/Co-Habiting • Separated/Divorced/Widowed

Variable	Definition	Type of variable	Scale of measurement
Employment Status	Employment status of study participant Categorical	Explanatory	Categorical • Student • Employed • Unemployed
Monthly Income Level	Income received/ gotten at the end of the month of study participant	Explanatory	Categorical • <=500 • 501-1000 • >1000
Residence	Place of residence of study participant in and around Tema Metropolis	Explanatory	Binary • Yes • No
Number of adults in household	Adults (18 years and above) living with study participant	Explanatory	Binary • Living alone • Live with others
Lifestyle and family history of diabetes and hypertension			
Smoking Status	Smoking of any form of tobacco or e-cigarette	Explanatory	Binary • Yes • No
Alcohol Intake	Drinking of Alcohol regularly	Explanatory	Binary • Yes • No
Fruit Intake	Number of days study participant consumes fruit in a week	Explanatory	Binary • 0-2 • 3-7
Vegetable Intake	Number of days study participant consumes vegetables in a week	Explanatory	Binary • 0-2 • 3-7
Physical Activity	How frequent study participant engages in physical activities	Explanatory	Binary • Yes

Variable	Definition	Type of variable	Scale of measurement
			• No
Family History of Hypertension	Family history of hypertension in study participants parents or siblings	Explanatory	Binary • Yes • No
Family History of Diabetes	Family history of diabetes in study participants parents or siblings	Explanatory	Binary • Yes • No
ART and HIV			
WHO Stage	WHO clinical stage at which study participant was diagnosed with HIV	Explanatory	Stage I Stage II Stage III Stage IV
ART Duration	Number of months study participant has been on Efavirenz-based regimen	Explanatory	<12 12-60 >60
Viral Load	Measure of viral load in the study participant after 12 months on Dolutegravir-based regimen	Explanatory	<1000 ≥1000
Anthropometric, Haematological and Biochemical			
Height	Height (in meters) of study participant	Explanatory	Continuous
Weight	Weight (in kg) of study participant	Explanatory	Continuous
Hip Circumference	Hip circumference (in meters) of study participant	Explanatory	Continuous
Waist-Hip Ratio (WHR)	Waist circumference (in meters) of study participant	Explanatory	Continuous
Waist Circumference	Abdominal obesity of study participant was measured based on NCEP-ATPIII criteria (waist circumference ≥88 cm for females and ≥102 cm for males)	Secondary Outcome	Binary • Abdominal Obesity Present • Abdominal Obesity Absent
Body Mass Index (BMI)	BMI was measured as: Underweight (<18.5) Healthy Weight (18.5-24) Overweight (25-29)	Explanatory	Categorical • Underweight • Healthy Weight • Overweight

Variable	Definition	Type of variable	Scale of measurement
	Obese (>30)		• Obese
Blood Pressure	Blood pressure was measured and categorized based on the NCEP-ATPIII criteria • Hypertensive - nSystolic >= 130 & Diastolic >= 85 • Non hypertensive - nSystolic < 130 & Diastolic < 85	Secondary Outcome	Binary • Hypertensive • Non hypertensive
Haemoglobin level	Haemoglobin level was measured and categorized • Normal - =>12 • Abnormal - >12	Explanatory	Binary • Normal • Abnormal
Platelets	Platelet level was measured and categorized • Normal - <150 • Abnormal - =<150	Explanatory	Binary • Normal • Abnormal
White blood Cells (WBC)	WBC level was measured and categorized • Normal – 4 to 9 • Abnormal - <4 or <9	Explanatory	Binary • Normal • Abnormal
Red Blood Cells (RBC)	RBC level was measured and categorized • Normal - =<3.76 • Abnormal - <3.76	Explanatory	Binary • Normal • Abnormal
Lymphocytes	Lymphocytes level was measured and categorized • Normal – 17 to 57 • Abnormal - <17 or >57	Explanatory	Binary • Normal • Abnormal
Monocytes	Monocytes level was measured and categorized • Normal - <10 • Abnormal - =<10	Explanatory	Binary • Normal • Abnormal
Creatinine level	Creatinine level was measured and categorized • Normal – 53.04 to 123.8 • Abnormal - <53.04 or >123.8	Explanatory	Binary • Normal • Abnormal
AST	AST level was measured and categorized • Normal - 5 to 34 • Elevated - <5 or >34	Explanatory	Binary • Normal • Elevated
ALT	ALT level was measured and categorized	Explanatory	Binary

Variable	Definition	Type of variable	Scale of measurement
	• Normal - 10 to 36 • Elevated - <10 or >36		• Normal • Elevated
Hepatitis B	Current Hepatitis B level was measured	Explanatory	Binary • Negative • Positive
Hepatitis C	Current Hepatitis C level was measured	Explanatory	Binary • Negative • Positive
Total Cholesterol (TC)	TC was measured and categorized based on the NCEP-ATPIII criteria • Normal - <5.17 • Hypercholesterolemia - =>5.17	Explanatory	Binary • Normal • Hypercholesterolemia
HDL-Cholesterol	HDL-Cholesterol was measured and categorized based on the NCEP-ATPIII criteria (abnormal was low HDL-C concentration (≤1.3 for females and ≤1.1 for males))	Secondary Outcome	Binary • Normal • Abnormal
LDL-Cholesterol	LDL-Cholesterol was measured and categorized based on the NCEP-ATPIII criteria • Normal - <3.6 • Abnormal - =>3.6	Explanatory	Binary • Normal • Abnormal
Triglyceride (TG)	TG was measured and categorized based on the NCEP-ATPIII criteria (elevated TG concentration (≥1.7 mmol/l)	Secondary Outcome	Binary • Normal • Elevated
Fasting Blood Glucose	Fasting Blood Glucose was measured and categorized based on the NCEP-ATPIII criteria (elevated fasting plasma glucose concentration (>6.1 mmol/l)	Secondary Outcome	Binary • Normal • Elevated
Metabolic Syndrome (MetS)	MetS presence was measured based on the NCEP-ATPIII criteria (presence of any three of the following: abdominal obesity (waist circumference ≥88 cm for females and ≥102 cm for males), high TG concentration (≥1.7 mmol/l), low HDL-C concentration (≤1.3 for	Primary Outcome	Binary • Present • Absent

Variable	Definition	Type of variable	Scale of measurement
	females and ≤1.1 for males), high Blood pressure (systolic blood pressure (SBP) ≥130mmHg and/or a diastolic blood pressure (DBP) ≥85mmHg) and elevated fasting plasma glucose concentration (>6.1 mmol/l))		