MAKERERE  **UNIVERSITY**

PREVALENCE AND FACTORS ASSOCIATED WITH HYPERGLYCEMIA AMONG HIV INFECTED INDIVIDUALS ON DOLUTEGRAVIR HIV ANTI-RETROVIRAL THERAPY AT KIRUDDU NATIONAL REFERRAL HOSPITAL

BY

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DECLARATION

I declare that the work submitted in this dissertation has been done by me and has not been submitted for any other degree award in any university.

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DEDICATION

I dedicate this work to;

The Almighty God, The Lord Jesus Christ and The Holy Spirit.

My children Josiah Christian Arinaitwe and Joash Emmanuel Arinaitwe

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ABBREVIATIONS

ADE- Adverse drug reactions

AIDS - Acquired Immune Deficiency Syndrome

ART - Antiretroviral therapy

CD4 - Cluster of differentiation 4

DM - Diabetes Mellitus

DNA - Deoxyribonucleic acid

DTG - Dolutegravir

HAART- Highly Active Antiretroviral Therapy

FBG - Fasting Blood Glucose

HbA1C - Glycated hemoglobin.

HDL- High Density Lipoprotein

HIV- Human Immunodeficiency Virus

IDF: International Diabetic Federation

IFG- Impaired Fasting Glucose

IGT- Impaired Glucose Tolerance

NGT - Normal Glucose Tolerance

NNRTIs- Non- Nucleoside Reverse Transcriptase Inhibitor

NRTIs- Nucleoside Reverse Transcriptase Inhibitor

OGTT - Oral Glucose Tolerance Test

PI- Protease Inhibitor

PLWHA- People Living with HIV/AIDS

RBS – Random Blood Sugar

VLDL- Very Low-Density Lipoprotein

WHO - World Health Organization

OPERATIONAL DEFINITIONS

- Hyperglycemia was defined as HBA1C > 5 .7%

ABSTRACT

Background: Dolutegravir-based (DTG) regimens are rapidly replacing older antiretroviral therapy (ART) in low and middle-income countries as first line ART. DTG is preferred due to its efficacy, tolerability and cost-effectiveness. Some patients switched to dolutegravir are reported to have developed hyperglycemia, which causes endothelial damage resulting in micro and macro-vascular complications of diabetes mellitus. However, evaluation of blood glucose among HIV patients is not routinely done in most public health facilities due to high cost.

Objectives: To determine the prevalence and factors associated with hyperglycemia among HIV positive individuals receiving DTG- based HIV Anti-retroviral therapy at Kiruddu National Referral Hospital

Methods: This was a cross-sectional study conducted at the in-patient wards and the communicable disease outpatient clinic of Kiruddu National Referral Hospital between May 2022 to July 2022 following ethical approval by the School of Medicine at Makerere University and Kiruddu Hospital.

We consecutively recruited 398 eligible participants who gave informed consent. Data collection tools were used to collect information from patients. Data was cleaned, entered into Epi-Info, and exported to STATA 17 for analysis. Cross tabulations were done using Chi-square of Fischer's exact test for categorical variables. Associations were analyzed using logistic regression models after adjusting for the necessary confounding co-variables and presented as crude and adjusted odd ratios with their 95% confidence intervals and corresponding p-values.

Utility: Essentially to understand the magnitude of hyperglycemia in these settings and provide more generalizable scientific based evidence regarding the need for rigorous evaluation of blood glucose control in HIV positive patients after initiating DTG-based therapy in a public health setting and to provide data for future research on prevalence and factors associated with hyperglycemia for patients on DTG-based HIV ART in resource limited settings.

Results: We enrolled 398 participants, 89.2% (n= 355) were outpatients and 10.8 % (n=43) were in-patients. Participants who were 18-40 years were 50% (199/398), 45.2% (180/398) between 41- 60 years, 4.8% (19/398) were over 60 years. median (interquartile range) age

was 40.5 years (32-49) .58.3% (232/398) were female. 9.3% (37/398) were hypertensive. 10.3 % (41/398) had a CD4 count < 200 .16.7 % (64/398) had a BMI ≥30. The prevalence of hyperglycemia in this study was 13%. Factors associated for hyperglycemia included: age > 40 years AOR 2.55 (P= 0.039, 95% CI 1.05 – 6.23), being hypertensive AOR 2.93 (P=0.036, 95% CI 1.07 – 8.02).

Conclusion:

HIV positive patients receiving DTG based ART regimens are at increased risk of development of hyperglycemia. Risk factors for hyperglycemia should be identified and blood glucose monitored in all patients receiving DTG.

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

The quality and prognosis of people living with HIV/AIDS has greatly improved because of the widespread use of lifelong anti-retroviral therapy (ART) in clinical practice with improved tolerability (Hjelm and Atwine 2011). The 95-95-95 UNAIDS strategy to end AIDS by 2030 (HIV/AIDS, 2014) aims to start more people on ART using a "test and treat approach", whereby an individual testing positive for HIV is initiated on ART regardless of the CD4 or World Health Organization (WHO) clinical stage (Organization ,2017) (Medlock, Pandey et al. 2017).

The HIV epidemic in Sub-Saharan Africa contributes to the increasing prevalence of DM (Omech, Sempa et al. 2012). Hyperglycemia in persons living with HIV/AIDS (PLWHA) is associated with ART, herbal medicines, other co-morbid conditions such as hypertension, chronic pancreatitis, a high fat diet, and a sedentary life style (Kalra and Agrawal 2013). Specifically, ART can cause insulin resistance (Acheampong, Roschel et al. 2009), fat redistribution, and increase in plasmatic lipids (Worm and Lundgren 2011). However, data are inadequate on hyperglycemia among HIV/AIDS patients in Africa (Dimala, Atashili et al. 2016). Recently, World Health Organization (WHO) and Uganda ART guidelines have been updated and recommend dolutegravir-based regimens (Walmsley, Antela et al. 2013), (Kanters, Vitoria et al. 2016). However, DTG use has also been associated with an increased risk of developing hyperglycemia (Lamorde, Atwiine et al. 2020)).

Developing countries often do not have adequate resources to provide adequate clinical services in public facilities for Non-Communicable Diseases (NCDs) rendering prevention as the best strategy (DART, 2010). Prevention involves identifying risk factors early, continuous health education/screening of the infected/affected people and appropriate referral for proper management to delay complications. When ART programs in Uganda started, emphasis was put on initial evaluation of patients for risk factors for comorbidities before starting treatment, but as the number requiring ART has substantially increased along with full implementation of the test and treat strategy, this has not always been the case (DART, 2010).

Diabetes Mellitus is a chronic progressive disease that causes micro vascular and macro vascular complications developing over time in relation to glycemic control. It causes morbidity and mortality thereby decreasing life expectancy (Hjelm and Atwine 2011).

Without screening and prompt treatment, patients may present to the hospital with complications of diabetes mellitus such as diabetic ketoacidosis, diabetic foot with greater morbidity and mortality for patients and greater medical care costs for resource constrained health systems (Dimala, Atashili et al. 2016)

1.2 Global prevalence of Hyperglycemia.

The International Diabetes Federation (IDF) report on diabetes mellitus reported global prevalence in 2019 to be estimated at 9.3% (463 million people), to rise to 10.2% (568 million) by 2030 and to 10.9% (700 million) by 2040.1 in 2 people with diabetes are unaware of it. In 2019, Impaired Glucose Tolerance (IGT) was estimated at 7.5% and projected to be 8.0% by 2030 and 8.6% by 2040. (IDF Atlas, 2019 edition).

Worldwide, the prevalence of hyperglycemia among adults between 20-79 years is 8.3% (382 million people) with 14 million men more than females with many between 40-59 years and the number is expected to increase beyond 592 million by 2035 with a 10.1% global prevalence report by IDF. 175 million people with diabetes mellitus are thought to have undiagnosed diabetes.

Countries in Middle East and North Africa have the highest prevalence of hyperglycemia. The western Pacific region has the highest number of adults diagnosed with hyperglycemia. Low- and middle-income countries have 80% of the cases (Kharroubi 2015).

The United States is said to have 17 million people with diabetes mellitus and this number is expected to rise to 29 million by 2050 (Winer and Sowers 2004).

1.3 Hyperglycemia in Africa.

According to the International Diabetes Federation (IDF) Diabetes Atlas 9th Edition, 19.4 million adults aged 20-79 years had diabetes mellitus in the IDF Africa region, making a regional prevalence of 3.9%. 60% are unaware they have diabetes, making Africa the region with highest estimate of undiagnosed patients.

Ojuka *et al*, 2014 found that the prevalence of Type 2 diabetes was noted to be increasing steadily in Sub- Saharan Africa. In 2010, about 12.1 million people were affected with diabetes mellitus with 26.9 million having impaired glucose tolerance and by 2030 this is expected to increase to 23.9 and 47.3 million respectively. (Ojuka and Goyaram 2014).

1.4 Hyperglycemia in Uganda.

Diabetes mellitus prevalence in Uganda is 4.1% and 6.6% is the estimated Impaired Glucose Tolerance (IGT). 469.3 per 1000 are living with undiagnosed diabetes mellitus (Chiwanga, Njelekela et al. 2016)

Nyanzi *et al*, 2014 noted that the diabetic population in Uganda in 2000 was estimated to be 98,000 and in a decade increased 15 times to 1.5 million and the number is likely to increase due to changing lifestyle like high fat diet and a sedentary lifestyle. (Nyanzi, Wamala et al. 2014).

In a recent study by Namulindwa et al looking at adverse side effects of DTG based regimen in HIV positive patients at Mbarara regional referral hospital noted that the prevalence of hyperglycemia was 7.3% and the associated factors included male sex and WHO staging.(Namulindwa, Wasswa et al. 2022)

In a qualitative study by Zakumumpa et al, 2021in which they held in-depth interviews for clinicians in 12 health facilities across Uganda, it was found that patients were reporting hyperglycemia as the most adverse side effect, then insomnia ,weight gain and reduced libido(Zakumumpa, Kitutu et al. 2021).

1.5 Problem statement

WHO recommended DTG-based HAART regimen as first line therapy. Hyperglycemia in persons living with HIV/AIDS (PLWHA) is associated with ART. 19.4 million adults aged 20-79 years had diabetes mellitus in the IDF Africa region, making a regional prevalence of 3.9%. 60% are unaware they have diabetes, making Africa the region with highest estimate of undiagnosed patients.

In March 2018, Uganda rolled out the use of DTG among HIV positive patients with a viral load less than 1000 cells/ml (Doherty, Vitoria et al. 2019). Increased cases of new onset symptomatic hyperglycemic patients were observed at Kiruddu NRH soon after scaling up DTG. Whether this is still the case has not been documented in Kiruddu NRH. Despite this growing problem, assessment for hyperglycemia among HIV-infected individuals is not routinely performed in public hospitals partly due to limited resources for health including trained personnel and diagnostic kits, large patient numbers, and ignorance. This study was conducted to determine the prevalence of hyperglycemia in a public healthcare setting,

which will further inform the current policy on screening patients before starting them on DTG-based regimen.

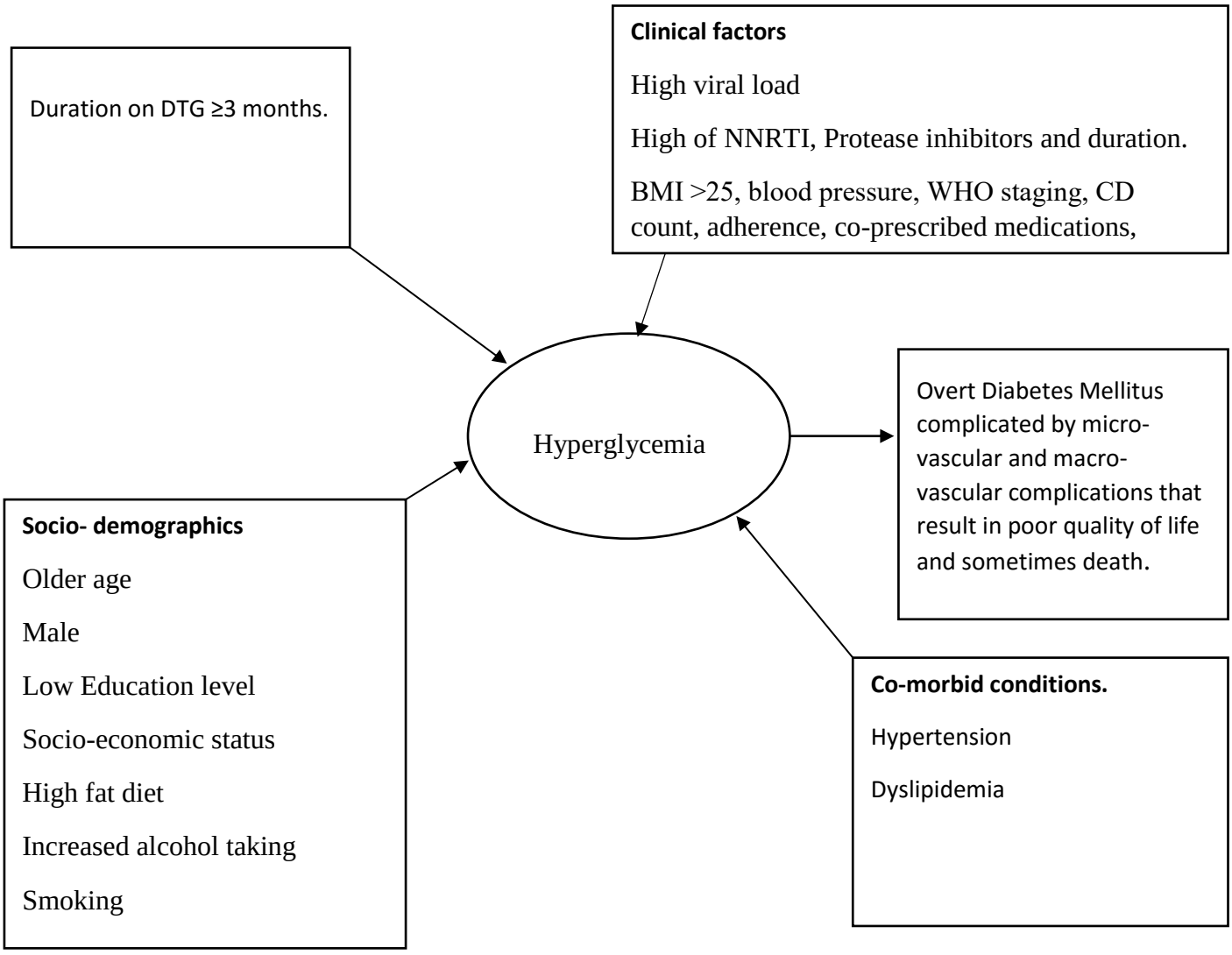
1.6 Justification of the study

The prevalence of hyperglycemia is growing in Uganda and soon overlapping with infectious diseases. In Uganda, according to the Uganda Diabetes Association, the prevalence of diabetes is 1.4%, impaired fasting glucose of 2.1% with 90.5% impaired fasting glucose and 48.9% not aware of their hyperglycemic status.

DTG use has been associated with an increased risk of developing hyperglycemia (Lamorde, Atwiine et al. 2020). Previous studies on hyperglycemia have been conducted in research settings with meticulous follow-up and monitoring of patient appointments and adverse events with better funding compared to larger public hospitals with patient numbers who are sicker, have fewer staff, and minimal tests done due to limited funding.

Understanding the magnitude of hyperglycemia in these settings will inform the current policy on evaluation of blood glucose in HIV positive patients from receiving DTG-based therapy in a public healthcare setting by providing more generalizable scientific based evidence around practice, provide data for future research , identify high risk patients not to be started on DTG, closer monitoring or switching patients back to non- DTG regimens, strengthening evidence for guidelines about DTG use. Developing countries lack resources to provide adequate clinical services in public healthcare facilities for NCDs rendering prevention as the best strategy.

Figure 1. Conceptual framework for hyperglycemia in HIV positive patients on DTG.



Hyperglycemia was the primary outcome among HIV infected patients on DTG.

Factors studied;

1. Duration on DTG must have been ≥3 months to see clear effects of DTG.
2. Social demographics like family history of DM, physical inactivity, older age, male gender, low education level, socio-economic status, high fat diet, increased alcohol consumption, smoking as risk factors predisposing patients to early DM.
3. Cor-morbid conditions like hypertension.
4. Clinical factors; high blood pressure, Opportunistic infections, high viral load, CD4 count, WHO staging, co-prescribed medications, co-morbidity, adherence, history of NNRTI,

history of being on protease inhibitors and duration as it was associated to getting impaired hyperglycemia.

1.7 Research questions

1. What was the prevalence of hyperglycemia among HIV infected individuals on DTG-based ART regimens at Kiruddu National Referral Hospital?
2. What factors were associated with hyperglycemia among HIV infected individuals on DTG-based ART regimens at Kiruddu National Referral Hospital?

1.8 Objectives of the study

1.8.1 General objectives

1. To determine the prevalence and factors associated with hyperglycemia among HIV infected individuals on DTG-based ART regimens at Kiruddu National Referral Hospital.

1.8.2 Specific objectives;

1. To determine the prevalence of hyperglycemia among HIV infected individuals on DTG-based ART regimen at Kiruddu National Referral Hospital.
2. To determine the factors that were associated with hyperglycemia among HIV infected individuals on DTG-based ART regimens at Kiruddu National Referral Hospital.

CHAPTER TWO

2.0 LITERATURE REVIEW

Type 2 diabetic mellitus frequently manifests as hyperglycemia in HIV positive patients. Hyperglycemia can adequately be managed if identified, however, many patients develop complications of diabetes mellitus, which has become an important co-morbidity among HIV infected persons (Dimala, Atashili et al. 2016) since the introduction of ART, the number of deaths due to opportunistic infections has significantly declined, a greater proportion of patients are living longer and developing chronic conditions not traditionally related to HIV, such as diabetes mellitus, liver and kidney diseases (Kalra & Agrawal, 2013). As the prevalence of HIV infection increases, diabetes mellitus is projected to increase (Kalra & Agrawal, 2013).

HIV positive patients can now achieve a near-normal lifespan with ART, which decreases the HIV viral load that is responsible for their immunodeficiency therefore making them susceptible to diseases that result in death, however, long term use of ART can also lead to metabolic complications such as insulin resistance, hyperglycemia, type 2 diabetes and dyslipidemia with abnormal fat distribution with greater visceral adiposity compared to ART naïve HIV patients (Manuthu, Joshi *et al*. 2008). These metabolic complications are of concern to scientists, patients, and clinicians. Shen Y *et al* have reported the prevalence of diabetes mellitus to vary from 2% to 14% in HIV positive patients in China with variable characteristics including; a low CD4 count, increasing age on long term-ART, minority ethnicity, lifestyle and demographic characteristics. Spollet *et al*, 2006 showed that the risk of getting diabetes mellitus in men who were seropositive and on ART was four times greater than those that were HIV seronegative (Spollett 2006). Omech *et al*, 2012 showed that among 442 HIV positive patients on stavudine and zidovudine at the Infectious Diseases Institute, borderline and overt diabetes was similar (Omech, Sempa et al. 2012). In a recent study by Lamorde *et al*, 16 of the 3,417 (0.5%) patients on a DTG-based regimen developed new-onset hyperglycemia to 1 of 3,230 (0.03%) patients who were not on a DTG-based regimen. (Lamorde, Atwiine et al. 2020)

2.1 Dolutegravir and hyperglycemia.

Dolutegravir is a second-generation integrase strand transfer inhibitor for treatment of wild type HIV-1 in adolescents and adults. It achieves therapeutic concentrations without the need for pharmacokinetic boosting. It has a high barrier to resistance and it is active against viral strains resistant to first generation integrase inhibitors such as elvitegravir, efavirenz, ritonivar boosted based regimens in suppressing plasma HIV-1 RNA to < 50 copies/mL. Integrase

resistant mutations for dolutegravir are lower compared to raltegavir and elvitegravir. It is well tolerated with few adverse effects (McCormack 2014). DTG inhibits strand transfer of retroviral DNA into the cell host genome. Within the host nucleus, it binds to magnesium in the integrase enzyme like it binds to other HIV integrase inhibitors to interrupt the final step of strand transfer. It chelates magnesium which affects the glucose transport via Glucose transporter (GLUT) 4 receptor and gluconeogenesis causing insulin resistance. Dolutegravir undergoes hepatic metabolism primarily by uridine diphosphate glucuronosyltransferase (Rathbun, Lockhart et al. 2014).

There is limited resistance to DTG in HIV antiretroviral experienced patients. (Fokam, Takou et al. 2020) It is widely used and is now the most prescribed antiretroviral drug in a number of countries. It is taken once a day and this promotes adherence to medication while reducing the pill burden when used in a fixed dose combination. DTG was therefore recommended as part of first- or second line regimens by WHO (WHO, July 2019) to all HIV positive patients. This was implemented by the Ugandan government in March 2018 starting as a cohort in few specialized clinics such as Infectious Diseases Institute for naïve and eligible treatment experienced HIV positive patients (Lamorde, Atwiine et al. 2020). A study on rapid and sustained antiviral response occurred at all DTG doses, tolerability was better than efavirenz and there was no protocol defined virological failure. The DTG regimen was associated with a higher rise in CD4 count compared to EFV regimen. Discontinuation in DTG was 2% compared to 10% in the Efavirenz arm (Taha, Das et al. 2015).

2.2 The prevalence of hyperglycemia in HIV positive patients.

HIV positive patients on HAART have an increased prevalence of metabolic disorders that include glucose dysregulation, dyslipidemia and cardio-metabolic syndrome (Gutierrez and Balasubramanyam 2012). The mechanism by which hyperglycemia occurs in patients with HIV is still unclear but several studies suggest HIV itself, cytokine dysregulation, and thymidine nucleoside-induced mitochondrial toxicity that contribute to these abnormalities. The prevalence of diabetes mellitus in patients on Stavudine and Zidovudine was similar with 3% and 5 % respectively. Those with borderline diabetes were 63.8% while 36.2% had overt diabetes mellitus. Fasting diabetes was observed in 14.4% of the patients for both drugs (Omech, Sempa et al. 2012). The natural history of HIV infection, co-morbidities, and treatment link HIV infection and diabetes mellitus and impaired glucose tolerance. The increasing prevalence of HIV infection could mask the rising epidemic of obesity in Africa

due to HIV related weight loss and wasting (Kengne, Echouffo-Tcheugui et al. 2013). In another study, HIV positive patients were found to have a higher risk of developing non communicable diseases resulting from HIV infection, antiretroviral therapy, HIV related immunosuppression, increasing age of PLHIV, HIV related inflammation compared to the traditional NCD risk factors that include tobacco smoking, alcohol use, physical inactivity, unhealthy diets, demographic and epidemiologic transitions (Kansiime, Mwesigire et al. 2019).

A prospective study by Tien *et al*, 2007 found that 2088 HIV positive and HIV negative women were followed for incidence of diabetes mellitus, 116 developed diabetes mellitus in the HIV positive group and 36 in the HIV negative over 6802 person years. The HAART naïve positive women had a lower incidence of 1.53/100 person years, those on protease inhibitor had incidence of 2.50/100 person years compared to 2.89/100 person years for those not on Protease Inhibitors (PI) however, cumulative exposure to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) was associated with increased risk of DM incidence than non-nucleoside Reverse Transcriptase Inhibitors (non - NRTIs) exposure (Tien, Schneider et al. 2007). Glucose intolerance in some patients is associated with older age and ethnicity (Gutierrez & Balasubramanyam, 2012).

Being overweight and obese were the most prevalent patho-genetic factors. The link between obesity and insulin resistance is not clear and the contribution of insulin resistance and B-cell dysfunction in early disease stages is still unclear in Africa. Patho-genetic processes in type 2 diabetes mellitus are triggered by environmental factors namely physical inactivity and dietary changes and the genetic basis has not been fully investigated (Kengne, Echouffo-Tcheugui et al. 2013). A North African study by Bos *et al,* 2013 found that increased prevalence of obesity was due to cheap availability of high fat and high energy food in combination with less physical activity. (Bos and Agyemang 2013)

Diabetes is a chronic progressive disease that causes micro vascular and macro vascular complications developing over time in relation to glycemic control. It causes morbidity and mortality thereby decreasing life expectancy (Hjelm & Atwine, 2011). Type 2 diabetes mellitus commonly manifests as hyperglycemia and it is major emerging NCDs in Sub-Saharan Africa.

2.3 Signs and symptoms in hyperglycemia.

Classic symptoms of hyperglycemia are polyuria, polydipsia, and weight loss. Other symptoms include increased thirst and headaches. Mayega et al, 2015 found that 103 new diabetic mellitus

patients, mean age was 49 years and the majority presented to hospital with frequent passing of urine (79%), frequent thirst (79%), general body weakness (51%), moderate symptoms included blurred vision (38%), frequent eating (31%), excessive sweating (27%), joint pains (22%), numbness (21%), and headache (21%). One fifth of patients were obese while one quarter were overweight, 43.1% had a normal BMI and 10.7% were underweight. Some presented with hypertension (Mayega and Rutebemberwa 2018).

Kirk *et al,* 2015 studied older rural adults above 60 years, Classic symptoms included thirst, hunger, frequent urination, increased fatigue in the morning upon awakening, lack of energy, visual blurring, numbness and tingling in the extremities, calf pain on walking, sleepiness, or drowsiness and difficult concentrating and paying attention, depression and cognitive impairment (Kirk, Arcury et al. 2015).

2.4 Factors associated with hyperglycemia in HIV positive patients.

Manuthue *et al,* 2008 and colleagues reported that the morbidity and mortality of HIV positive patients has markedly diminished due to the advent of ART, however, there has been an increase in metabolic complications due to some ART such as PI, NRTIs, NNRTI that lead to insulin resistance, type 2 diabetes mellitus, dyslipidemia, increased levels of plasminogen activator inhibitor type 1, apo-lipoprotein B, abnormal fat distribution, and greater visceral adiposity. In untreated HIV positive patients, lipid abnormalities were common. These included elevated triglycerides, cholesterol, low density lipoprotein, but decreased high density lipoprotein. Insulin resistance in HIV positive patients is seen by subcutaneous lipo-atrophy, buffalo hump, accumulation of fat and central obesity. Increase in visceral fat and decrease in subcutaneous fat may contribute indirectly to insulin resistance. Visceral adiposity increases levels of circulating free fatty acids causing abnormal insulin signaling (Manuthu et al., 2008).

Omech *et al*, 2012 discovered that mechanism is still unclear but studies suggest that HIV itself, cytokine dysregulation, thymidine nucleosides-induced mitochondrial toxicity contribute to these abnormalities (Omech, Sempa et al. 2012). Chia *et al*, 2018 looked at age and diabetes mellitus for cardiovascular disease, the ability to regulate glucose wanes with increasing age. There was worsening glucose tolerance with increasing age in > 770 healthy men and women. This could be explained by influences of body fat and physical fitness but glucose levels higher in men than women but similar in response to Oral Glucose Tolerance Test (OGTT) (Chia, Egan et al. 2018).

Zhang et al ,2017 looked at lifestyle factors related to developing diabetes including diet, physical activity, sleep duration and quality, psychosocial factors, related knowledge and attitude early life factors, economic and social factors. Diet consistent with whole grains, fruits and vegetables, calcium, magnesium was low risk for diabetes while that with red meat, high fat dairy products, sugar sweetened beverages, fried food would risk getting diabetes. Smoking, alcohol, and physical inactivity increased risk of diabetes. Sleep duration ≤ 6 hours and ≥ 9 hours and poor sleep quality increase risk to developing diabetes. For psychosocial factors, emotional stress, anger, anxiety, hostility increased risk to diabetes. It was also noted that the more educated higher income earners had lower stress levels than the least educated and poorest putting the latter at higher risk for diabetes. Knowledge and self-care management in patients with diabetes correlated with education level. Early life factors like gestational diabetes, smoking, junk food diet and smoking, stress catch-up growth increase risk to get diabetes in the offspring later in life. Improved economic and social factors have increased life expectancy and people have adopted urban high fat diet and sedentary lifestyles all that increase the risk of diabetes (Zhang, Du et al. 2017). Long *et al*, 2011 noted that 75% of patients with diabetes are said to have hypertension, and those with hypertension alone have insulin resistance (Long and DagogoJack 2011).

2.5 Laboratory characteristics of hyperglycemia.

Glucose tolerance is classified into 3 broad categories: normal glucose homeostasis, impaired glucose homeostasis, or diabetes mellitus. Assessment for these can be done using the fasting plasma glucose, oral glucose tolerance test, or the hemoglobin A1C. A Fasting Plasma Glucose (FPG) < 5.6 mmol /l (100mg/d L), a plasma glucose < 7.9mmol/L (140mg/d L) following an oral glucose challenge, and HbA1c<5.7% are the normal glucose levels. Abnormal glucose homeostasis is impaired fasting glucose values 5.6 - 6 .9 mmol/l (100-125mg/dL) but 6.1- 6.9 mmol/l (110 – 125mg/dL) according to the World Health Organization, impaired glucose tolerance test is between 7.8 and 11mmol/l (140 - 199 mg/dL) and HbA1c of 5.7 – 6.4%. Patients with Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) are at risk of developing diabetes and cardiovascular disease. To diagnose diabetes mellitus; A FPG ≥7.0 mmol/L (126 mg/dL), a glucose ≥11.1 mmol/L (200 mg/dL) 2 hours after an oral glucose challenge, random blood glucose of ≥11.1 mmol/L (200 mg/dL) or an HbA1c ≥6.5%. Current criteria to diagnose diabetes mellitus emphasizes HbA1c or the FPG. For screening, FPG and HbA1c are used. The American Diabetes Association recommends screening individuals > 45 years every 3 years, or overweight BMI > 25kg/m^2 (Kasper, Fauci et al. 2015).

CHAPTER THREE: METHODOLOGY

3.1 Study design:

This was a cross-sectional study among HIV positive individuals on DTG-based ART regimens at Kiruddu National Referral Hospital, Kampala (Kiruddu NRH), Uganda.

3.2 Study period

This was from May 2022 to July 2022

3.3 Study approach

It was a quantitative analysis

3.4 Study setting;

The study was conducted at Kiruddu National Referral Hospital in-patient (wards) and out-patient (Kiruddu Communicable Diseases Clinic - KCDC) in Kampala, Uganda. Kiruddu NRH has a 200-bed capacity with several medical outpatient clinics. The communicable disease clinic is supported by Makerere University Joints AIDS Program (MJAP) and mainly caters to managing HIV positive patients. It was started in 2007 and operates as an outpatient clinic weekly every Tuesday, Thursday and Friday between 8am to 5pm. Approximately 180 HIV patients per clinic day, which now has close to 2,249 active patients enrolled into care. About 2,249 patients are all on ART, of whom 918 are on a DTG-based regimen.

3.5 Population

3.5.1 Target population

All HIV positive patients receiving a DTG-based ART regimen in Uganda.

3.5.2 Accessible population

All HIV positive patients who had received DTG - based ART regimen at Kiruddu Hospital.

3.5.3 Study population – All HIV positive patients on DTG based regimen ART at Kiruddu hospital during the study period, who meet the eligibility criteria and are enrolled.

3.6 Selection/eligibility criteria

3.6 .1 Inclusion criteria

- All HIV positive patients 18 years or older at Kiruddu hospital.
- Currently on a DTG- based ART regimen ≥ 3 months
- Provided written informed consent.

3.6.2 Exclusion criteria

1. Documented evidence of DM before HAART initiation even when they are on DTG.

3.7 Sampling method

Consecutive sampling was used to recruit participants into the study until desired sample size was achieved. OPD recruitment was limited to Tuesday, Thursday and Friday.

3.7.1 Sample size estimation

For objective 1; The sample size was estimated using the Kish Leslie Formula (1965) for descriptive studies (Leslie, 1965).

$N=\frac{Z^2pq}{d^2}$

Where

N= sample size required

Z= standard normal value corresponding to 95% confidence interval=1.96

P= Prevalence of hyperglycemia in HIV positive patients receiving HAART at Jugal Hospital, Harar, Ethiopia was 7.1 % (Ataro, Ashenafi et al. 2018)

q=1-p

d= acceptable error limit =5%

So, the estimated prevalence of Hyperglycemia among HIV positive patients on DTG-based HAART regimen among patients attending Kiruddu National Referral Hospital was 0.05

Hence sample size needed was

$N=\frac{1.96 \times 1.96 \times 0.071 \times 0.929}{0.05 \times 0.05} = 102$

Adjusting for non-response of 10% -

N = n / 0.9 = 102 /0.9

= 114

Therefore, the sample size estimation was 114.

For 2nd objective

The sample size needed to study the factors associated with hyperglycemia among patients on DTG attending Kiruddu NRH was calculated using the formula for sample size for two proportions where by $n = (Z_{\alpha/2} + Z_{\beta})^2 * (p_1 (1-p_1) + p_2 (1-p_2))$

$$(p_1 - p_2)^2$$

Whereby the number of participants per group

$Z_{\alpha/2} = 1.96$ is the standard normal value of z corresponding to 5% level of confidence

$Z_{\beta} = 0.84$ is the standard normal value of z corresponding to the power of the study of 80%

P_1 and p_2 correspond to proportions with and without the factor of interest but with hyperglycemia

Using age as one of the associated factors from literature,

$P_{1=}$ 11.1% is the proportion of participants greater or equal to 40 years of age who were on

HAART and had diabetes mellitus (Ataro, Ashenafi et al. 2018)

P_2= 3.5% is the proportion of participants less than 40 years of age who were on HAART and had diabetes mellitus (Ataro, Ashenafi et al. 2018) n = 179 participants per group

Therefore, for two proportions, the participants will be twice n, that was 358 participants

Adjusting for non-response of 10%, N=358/ (1-non-response) = **398 participants**

Therefore, the participants for the study were **398 participants**.

A higher sample size of 398 participants was considered based on the sample size calculation of 2 proportions.

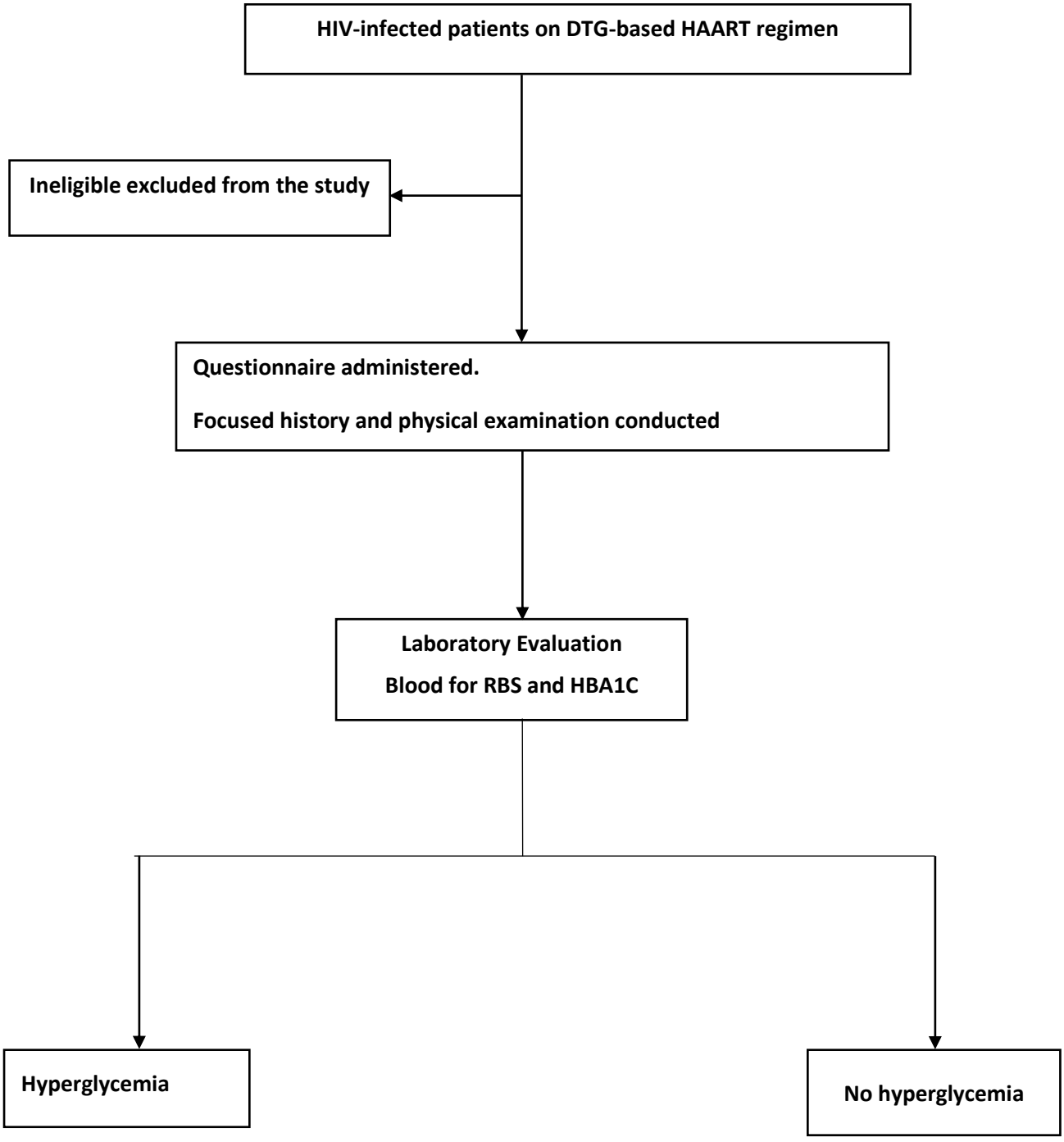
3.8 Study Protocol

3.8.1 Screening and recruitment of participants

The principal investigator and the research assistants screened patients at the Kiruddu Communicable Disease Clinic that run on Tuesday, Thursday and Fridays between 9.00am to 3.00pm and screened patients admitted daily in in-patient wards from 9.00am to 3.00pm. Participants on DTG based regimen were conveniently selected and notified about the study objectives, and risks/benefits. All aspects of the study were explained and questions were encouraged prior to obtaining consent. Pre-tested semi-structured questionnaires were administered to capture information, a focused history was elicited and a physical examination performed. At the bedside or bench, blood was drawn into a purple top vacutainer and labeled with the corresponding patient identification before it is transported to the lab by the research assistant.

The CD4 cell count and viral load results were obtained from patient's records (Ministry of Health HIV ART blue card and electronic data base –OPEN-MRS). The most recent value for CD4 or Viral load were abstracted from the charts and noted in the study files (when available). The clinic implemented guidelines for viral load monitoring using a dried blood spot (DBS) so it was not surprising that some patients only had viral loads in their files as opposed to CD4 counts which combination were done in Kiruddu NRH at no cost to the patient.

Figure 1. Study flow diagram showing participant recruitment:



3.8.2 Study instruments used for data collection

All laboratory request forms were identified using the study numbers. Results of the laboratory were entered in the patient's medical care records.

3.8.4 Laboratory examination procedures

Procedure for blood draw and processing

Blood was drawn as per standard operating procedure in an aseptic condition. A venipuncture site was identified; swabs of 1% tincture of iodine or alcohol were used to swab the site in a circular fashion to avoid contamination and left dry for about 3 seconds before drawing blood. A total of 3 mls of blood was drawn and put into the vacutainer to measure HbA1C for all participants. The procedure was done at the bench at the clinic or the bedside for patients in the in-patient wards. The purple vacutainers with blood were taken to the Kiruddu hospital lab and HBA1C measured and reported in percentages using the equipment called Architect Ci4100, manufacturer is Abbot, USA.

3.9 Study variables

The primary outcome was hyperglycemia defined as HBA1C > 5.7 % among HIV positive individuals on DTG at Kiruddu Communicable Disease Clinic or Kiruddu in-patient wards. Based on these measurements, blood glucose levels were defined as;

The predictor variables were factors associated with hyperglycemia. These were determined by assessing the following variables;

3.9.1 Clinical variables.

1. History

- Symptoms of hyperglycemia - polyuria, polydipsia, polyphagia, fatigue, difficulty in Breathing etc.
- Past medical history; chronic illnesses like hypertension, DTG drug adherence, co-prescribed medications, baseline blood sugar, evidence of blood sugar monitoring, opportunistic infections.
- Co-morbid conditions e. g. obesity and hyperlipidemia.
- Recent drug history – ART especially protease inhibitors, NNRTIs, herbal medication use.
- Family history of diabetes mellitus.

- Social history – marital status, occupation, education level, alcohol/cigarette smoking / use of recreational drugs e.g. cocaine. Marijuana, physical activity, high fat diet,

2. Physical examination;

Body mass index which was calculated from the formula

Equation 4. BMI = Weight (kg)/Height (m) ^{2}

- Blood pressure (BP)
- WHO HIV stage

3.9.2 Laboratory variables

- CD4 cell count and viral load were recorded from patient file or data base (OPEN-MRS), Viral load.
- Blood sugar; RBS, HBA1c was taken.

3.10 Data management

Data was collected using a standardized questionnaire through a face-to-face interview. Individual patient records and forms were kept in files after data collection. Raw data was stored in a secure place and locked at the discretion of the principal investigator to ensure safety and confidentiality. Data collected was entered into the computer using EPI-DATA (version 3.2) software. Data cleaning and validation (for completeness and quality) was performed before analysis and then exported to STATA 17.0 for cleaning and analysis. Data was then backed up and archived in both soft and hard copy to avoid losses.

3.10.1 Data analysis

Statistical analysis was performed using STATA 17.0 software package. Numerical variables were summarized as means and standard deviation for normally distributed data. Categorical variables were summarized as frequencies, percentages and also in tables and figures.

3.10.2 Analysis of specific objectives

Objective 1; The prevalence of hyperglycemia was calculated as a percentage of the number of patients with hyperglycemia on DTG-based ART regimen divided by the total number of study participants on a DTG-based ART regimen.

Objective 2; To determine the factors associated with hyperglycemia, bivariate analysis was performed. Cross tabulations were done using Chi-square of Fisher's exact test for categorical variables. The associations were presented with crude odd ratios, their 95% confidence intervals and the p-values. At multivariate analysis, all factors which had a p-value less than 0.2 at bivariate analysis were considered for the model then using the backward method to reduce them depending on their p-values and the magnitude of the log likelihood. The results for the model were presented with adjusted odds ratios with their 95% confidence intervals – value and factors with a p-value less than 0.05 were considered significant at 95% level of confidence.

3.11 Quality control;

The Principal Investigator worked with one research assistant, who were trained to ensure accurate data is collected. Orientation of personnel on study protocols, ethics and use of all data collection tools like the questionnaire, blood specimen collection and sample transportation to the laboratory prior to initiation of the study was done. The data forms were pre-tested on patients for clarity and standardization to ensure internal validity. The PI cross checked all data to ensure completeness. Laboratory investigations were performed by experienced technologists using standard operating procedures in a credible and certified laboratory.

3.12. Ethical considerations;

Ethical approval to conduct the study was obtained from the Department of Medicine of Makerere University, College of Health Sciences, and School of Medicine Research and Ethics committee number Mak-SOMREC-2022-298, UNCST and the Kiruddu Hospital Ethics committee and Non- Communicable Clinic.

All benefits and potential risks of the study were clearly explained to the participants before obtaining the recruitment consent. Written/thumb print informed consents were obtained from all participants before participation in the study. Participants were allowed to withdraw from the study at any time without impacting their care. All information given was kept confidential by use of patient's identification numbers and not names. For purposes of clarification of raw data by the Principal Investigator, only the patient's clinic file number was recorded to assist in retrieving some laboratory results (CD4 and viral load). Access to data or patient information was limited to those directly involved in the study and the attending physician. For patients who had diabetes mellitus, a note and a copy of results was availed to the primary care giver

so that dolutegravir is replaced with another drug and then the patient was started on ant-diabetics while monitoring him/her.

3.13 Benefits of the study to the participants

- Blood glucose levels were assessed for all study participants.
- Laboratory tests were done at no cost to the patient.
- Results of all laboratory tests were availed to the clinician in charge of the patient as soon as they were available.

3.14 Risks from study

The procedures like blood draw carried a minimal risk to the patients which was minimal pain from the blood drawing.

3.15 Dissemination of results

Our findings will be circulated to the Directorate of Research and Graduate training, Makerere University, Makerere University College of Health Sciences, Kiruddu NRH, and Makerere University Joint AIDS Program, Sir Albert COOK College of health science library and Uganda Health Institute and clinicians taking care of the study patients. We will submit these findings for publication in a peer reviewed international journal. It can also be applied in policy to have all HIV patients going to be started on DTG-based regimen to be screened for risk factors for getting hyperglycemia.

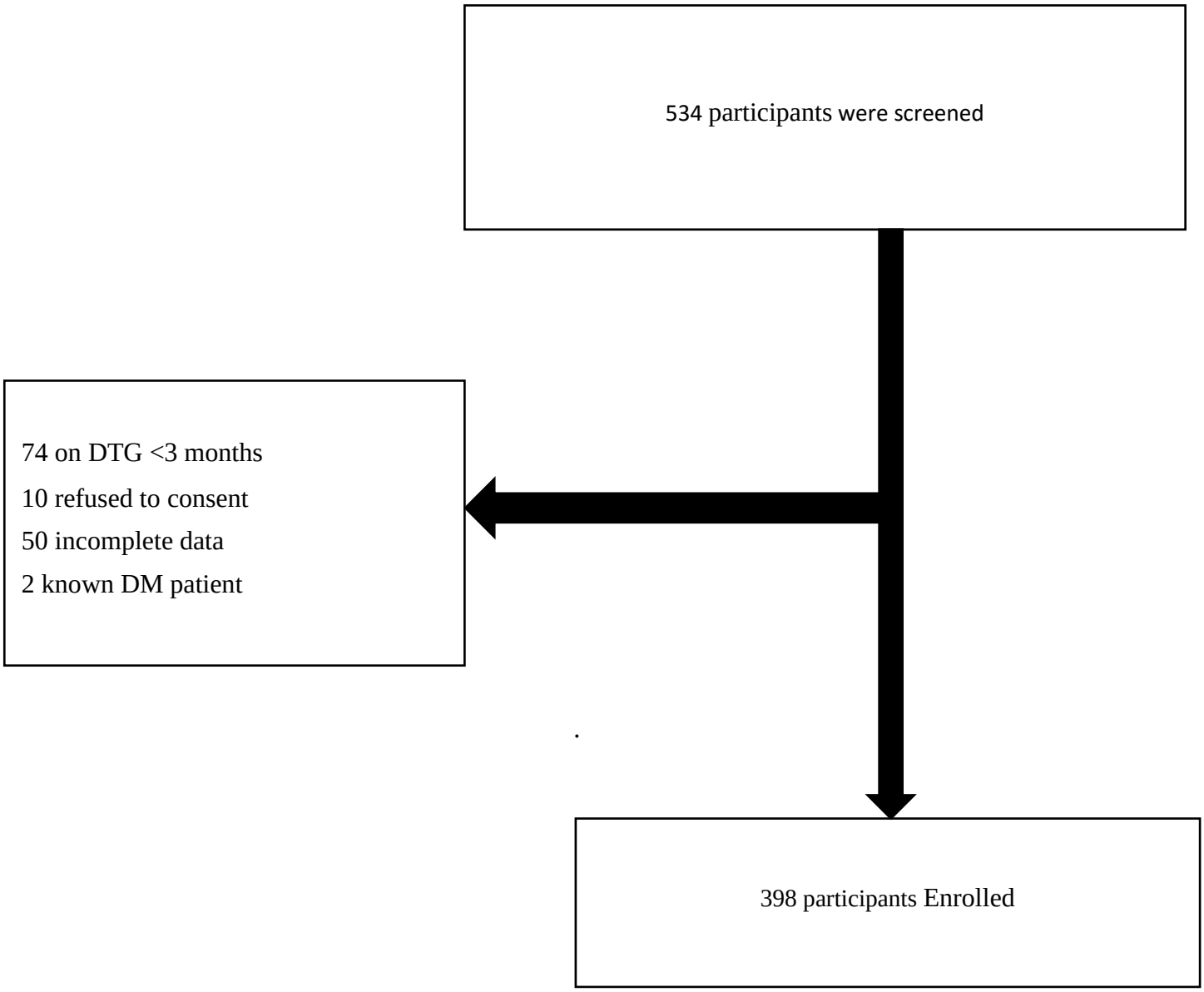
CHAPTER FOUR

4.0 RESULTS

From May 2022 to July 2022, 534 HIV- infected patients on DTG based regimen in Kiruddu National Referral Hospital were screened for eligibility to join the study enrolment.

Reasons for excluding participants were; duration on DTG <3 months (74), 10 refused to consent for the study, 2 known patients with diabetes mellitus ,50 incomplete data. 398 participants met the eligibility criteria and were enrolled. Descriptive, inferential, and logistic analysis was used to determine the prevalence and factors associated with hyperglycemia among participants on DTG. Of the 398 participants, 10.8% (43/398) were in-patient's participants and 89.2% (355/398) were out-patient's participants.

Figure 2. Study recruitment diagram for the study participants receiving DTG > 3 months at Kiruddu National Referral Hospital.



4.1 Social demographic characteristics of study participants receiving DTG for at-least 3 months at Kiruddu National Referral Hospital.

Of the participants enrolled, 89.2% (355/398) were out-patients and 10.8% (43/398) were in-patients. Participants 18-40 years were 50% (199/398), 45.2% (180/398) were between 41-60 years and 4.8% (19/398) were over 60 years with a median (interquartile range (IQR)) age of 40.5 years (32-49)

Females constituted more than half at 58.3% (232/398) of the study population. Participants who were married were 49.8% (198/398). Majority had a primary education 43.2% (172/398). About 16% of the participants admitted a family history of diabetes (61/398). Many were physically active 66.9% (265/398), and those with a high fat diet were (11.9%, 47/398).

The rest of the social demographic findings are shown in Table 1 below.

Table 1.Social and Demographic characteristics.

Variable (N=398)	Frequency	Percentage
Age (Years)		
18 – 40	199	50
41 – 60	180	45.2
>60	19	4.8
Department		
OPD	355	89.2
IPD	43	10.8
Sex		
Female	232	58.3
Male	166	41.7
Marital Status		
Married	198	49.8
Separated	56	14.1
Single	119	29.9
Widowed	25	6.3
Education level		
Informal	44	11.1
Primary	172	43.2
Secondary	147	36.9
Tertiary	35	9
Employment status		
Employed	287	70.6
Formal	10	2.5
Informal	10	2.5
Unemployed	97	24.4
Family history of diabetes or hyperglycemia	67	16.8
Alcohol use	54	13.57
Smoking	4	1.01
Level of physical activity		
Active	265	66.9
Moderate	52	13.1
Minimal	32	8.1
None	47	11.9
High fat diet	274	69.7
Co-prescribed drugs- corticosteroids, thiazides, or beta-blockers.	18	4.5
Herbal medicine use	55	13.8

IPD- In-patient, OPD-Out-patient.

4.2. Description of the clinical characteristics.

Participants with a high Blood Pressure levels were 43.62% (46/398). More than half, 51% (196/398) had a normal BMI between 18.5-24.5kg/m^2. Patients found with co-morbidities were mostly hypertensive at 9.3% (37/398). About 10.3% (41/398) had a CD4 count <200. The majority 54.8% (218/398) had suppressed viral loads <1000(copies/ml)

The majority of participants had WHO staging 1 disease at 81.9% (326/398) while 4.5% (14/398) had stage 4 HIV disease. Tuberculosis was the most frequent opportunistic infection at 4.5% (18/25).

Other clinical characteristics are described in Table 2 below.

Table 2 .Clinical characteristics

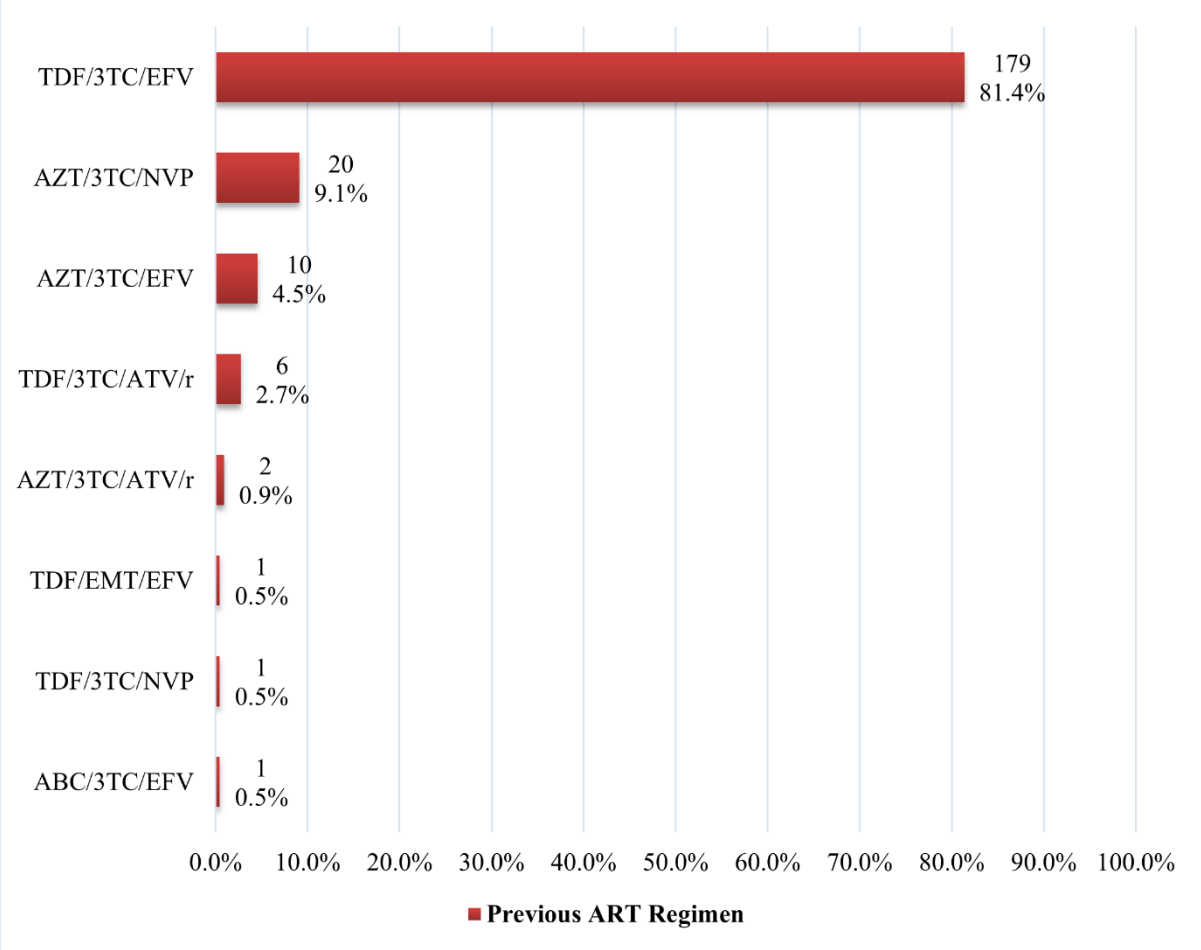
Variable	Frequency	Percentage
Blood Pressure (mm Hg)		
Normotensive (100-129/60-89)	175	44.6
Hypertensive ≥ 130/90	46	11.73
Low Blood Pressure <100/60	171	43.62
BMI (Kg/m^2)		
<18.5	38	9.9
18.5-24.5	196	51
25.0 – 29.9	86	22.4
≥ 30.0	64	16.7
Co-morbidities		
Hypertension	37	9.3
Heart failure	2	0.5
Malignancy	1	0.3
CD4 Count (cells/mm^3)		
CD4 >200	68	17.1
CD4 < 200	41	10.3
No CD4 count	289	72.6
Viral load (copies/ml)		
Viral load >1000	8	2
Viral load <1000	218	54.8
No viral load done	172	43.2
Patient education and counseling DTG ADE	128	32.16%
Duration on DTG (years)		
<1 year	146	36.68
1-2 years	120	30.15
>2 years	132	33.17
Adherence on HAART		
Good>95%	10	2.51
Average 50-95%	380	95.48
Poor < 50%	8	2.01
WHO stage		
1	326	81.9
2	35	8.8
3	19	4.8
4	18	4.5
Concurrent opportunistic infections		
No	373	93.7
Yes	25	6.3

ADE-Adverse Drug Effects.

4.3. Participants Previous HAART regimen before being switched to DTG

About 81.4%(n=179/398) had previously been on a combination of TDF/3TC/EFV. 3.6%(n=8/398) who had been on second line were switched to a DTG based regimen.

Figure 3. Participants previous HAART regimen before being switched to DTG

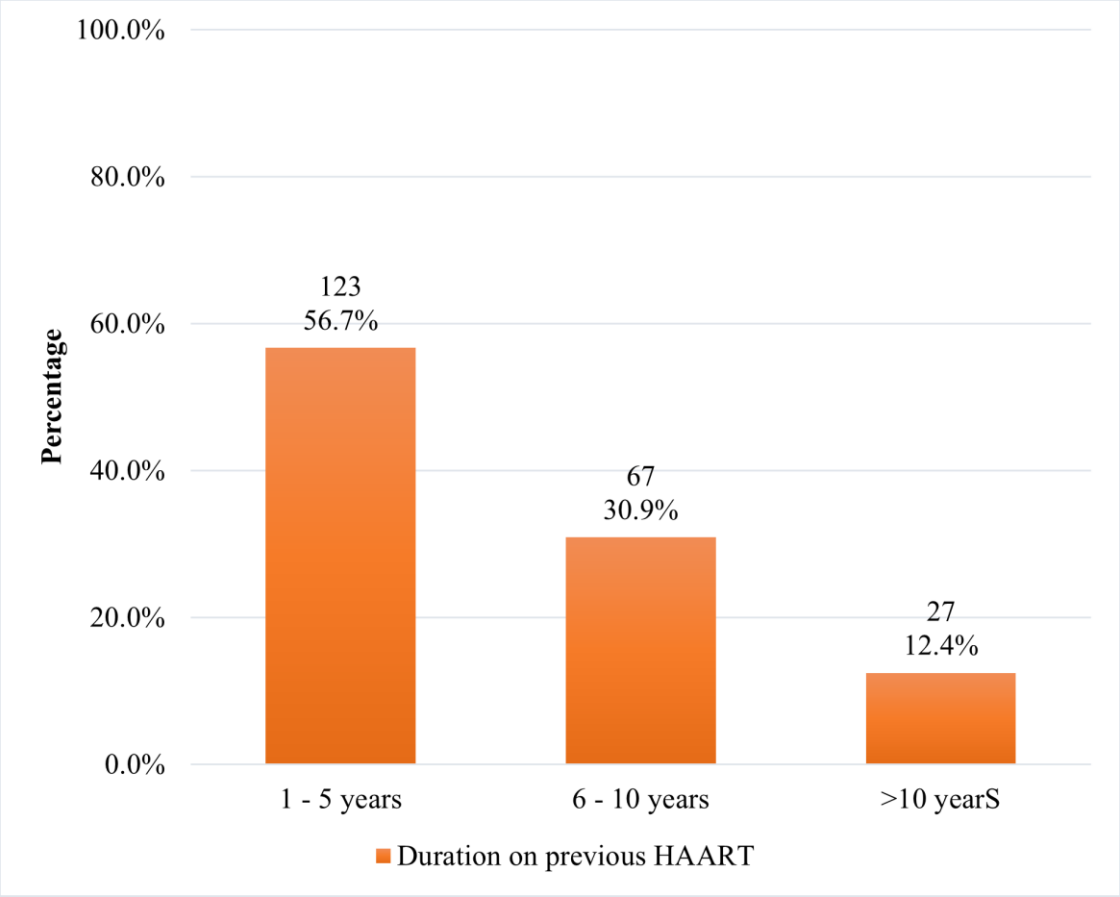


4.4. Duration on previous HAART

Most participant 56.7% (123/398) has been on previous non-DTG HAART between 1 – 5 years.

The rest of the information is shown in the figure below

Figure 4. Duration on previous HAART

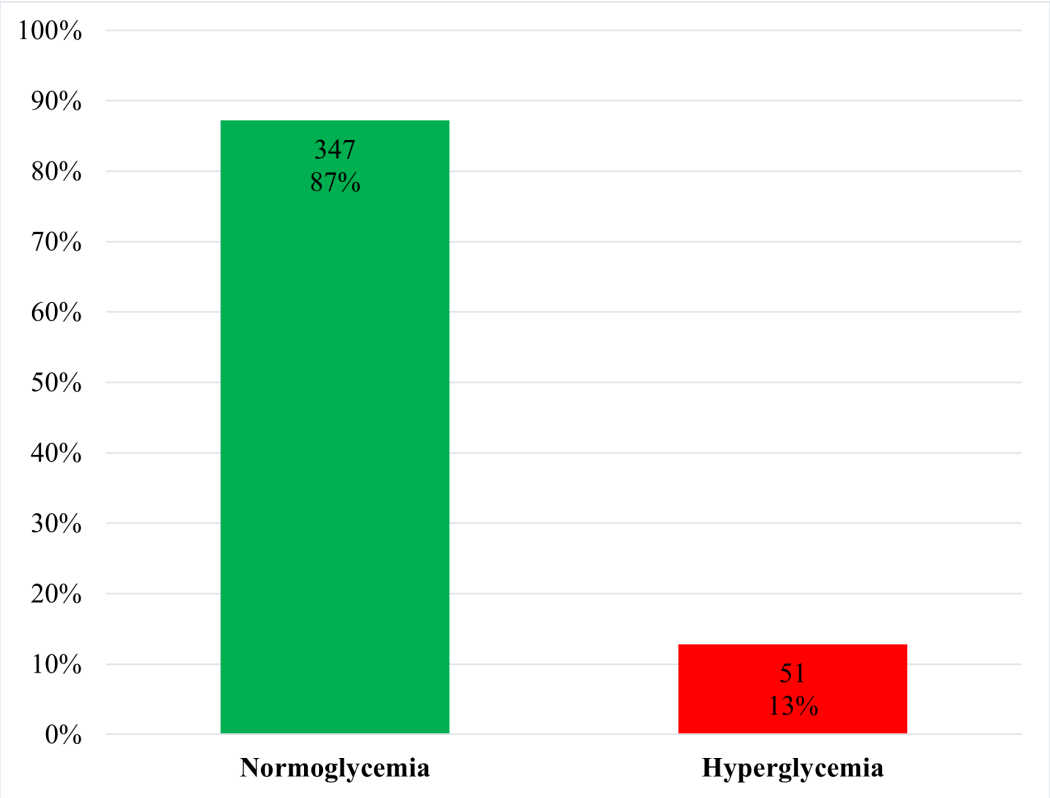


4.5. Participant glycemic status by HBA1C

Of the 398 participants, 51 had HBA1C > 5.7% and were defined as hyperglycemia. Giving the prevalence of 13 % (Figure 6). Of the hyperglycemic participants, 10(3%) were diabetic, 41(10%) were pre-diabetic

Figure 6 shows more detail.

Figure 6. Participant blood glucose levels by HBA1C



4.6. Bivariate analysis showing the distribution and socio-demographic factors associated with hyperglycemia among HIV – infected individuals on dolutegravir-based regimen.

Factors that were significant with a p value < 0.2 included; age 41-60 at OR 4.29 (P 0.000, 95% CI 2.29 – 10.57), Age >60 at OR 15.35 (P = 0.000, 95% CI 4.96 – 47.52) herbal medicine use at OR 2.82 (P 0.003, 95%CI 1.41- 5.66)

More is represented in the table 3 below.

Table 3. Bivariate analysis showing the distribution and socio-demographic factors associated with hyperglycemia among HIV- infected individuals on dolutegravir-based regimen.

Variable (N=398)	Normal: frequency (%)	Hyperglycaemia: frequency (%)	p	Odds ratio (95% CI)	P value
Age (Years)					
18 – 40	190 (54.8)	9 (17.6)	0.000	1.00	
41 – 60	146 (42.1)	34 (66.7)		4.92 (2.29 - 10.57)	**0.000**
>60	11 (3.2)	8 (15.7)		15.35 (4.96 - 47.52)	**0.000**
Department					
IPD	35 (10.1)	8 (15.7)	0.229	1.00	
OPD	312 (89.9)	43 (84.3)		0.6 (0.26 - 1.39)	0.233
Sex					
Female	199 (57.3)	33 (64.7)	0.320	1.00	
Male	148 (42.7)	18 (35.3)		0.73 (0.4 - 1.35)	0.321
Marital Status					
Married	174 (50.1)	24 (47.1)	0.000	1.00	
Separated	47 (13.5)	9 (17.6)		1.39 (0.6 - 3.19)	0.439
Single	112 (32.3)	7 (13.7)		0.45 (0.19 - 1.09)	0.076
Widowed	14 (4)	11 (21.6)		5.7 (2.32 - 13.98)	0.000
Education					
Informal	35 (10.1)	9 (17.6)	0.018	1.00	
Primary	145 (41.8)	27 (52.9)		0.72 (0.31 - 1.68)	0.451
Secondary	138 (39.8)	9 (17.6)		0.25 (0.09 - 0.69)	0.007
Tertiary	29 (8.4)	6 (11.8)		0.8 (0.26 - 2.53)	0.710
Employment status					
Employed	246 (70.9)	35 (68.6)	0.517	1.00	
Formal	8 (2.3)	2 (3.9)		1.76 (0.36 - 8.61)	0.487
Informal	10 (2.9)	0 (0)		-	
Unemployed	83 (23.9)	14 (27.5)		1.19 (0.61 - 2.31)	0.617
Family history of diabetes or hyperglycaemia	56 (16.1)	11 (21.6)	0.333	1.43 (0.69 - 2.95)	0.335
Alcohol use	48 (13.8)	6 (11.8)	0.687	0.83 (0.34 - 2.05)	0.688
Smoking	3 (0.9)	1 (2)	0.424	2.29 (0.23 - 22.41)	0.478
Level of physical activity					
None	41 (11.9)	6 (11.8)	0.142	1.00	
Minimal	42 (12.2)	10 (19.6)		0.81 (0.31 - 2.07)	0.656
Moderate	25 (7.2)	7 (13.7)		1.63 (0.54 - 4.89)	0.386
Active	237 (68.7)	28 (54.9)		1.91 (0.58 - 6.34)	0.289
High fat diet	243 (70)	31 (60.8)	0.203	0.67 (0.36 - 1.24)	0.206
Prescribed corticosteroids, thiazides or beta-blockers.	14 (4)	4 (7.8)	0.267	2.02 (0.64 - 6.41)	0.230
Herbal medicine use	41 (11.8)	14 (27.5)	0.003	2.82 (1.41 - 5.66)	**0.003**

4.7. Bivariate analysis showing the distribution and clinical factors associated with hyperglycemia among HIV- infected individuals on dolutegravir-based regimen.

Factors that were statistically significant included; BMI ≥ 30 OR 3.89 (P 0.042, 95% CI 1.05 - 14.38), being hypertensive OR 3.38 (P 0.002, 95% CI 1.55 – 7.37), CD4 count <200 OR 2.11(P 0.182, 95% CI 0.7-6.34)

More is represented in table 4 below.

Table 4. Bivariate analysis showing the distribution and clinical factors associated with hyperglycemia among HIV positive individuals on dolutegravir-based regimen.

Variable (N=398)	Normal: frequency (%)	Hyperglycaemia: frequency (%)	p	Odds ratio (95% CI)	P Value
BMI(Kg/m2)					
<18.5	35 (10.5)	3 (5.9)	0.010	1.00	
18.5-24.5	178 (53.5)	18 (35.3)		1.18 (0.33 - 4.22)	0.799
25.0 – 29.9	72 (21.6)	14 (27.5)		2.27 (0.61 - 8.41)	0.221
≥ 30.0	48 (14.4)	16 (31.4)		3.89 (1.05 - 14.38)	**0.042**
Blood pressure					
Normal	161 (47.2)	14 (27.5)	0.030	1.00	
Low blood pressure	38 (11.1)	8 (15.7)		2.42 (0.95 - 6.18)	0.065
High blood pressure	142 (41.6)	29 (56.9)		2.35 (1.19 - 4.62)	0.013
Cor-morbidities					
Hypertension	26 (7.5)	11 (21.6)	0.001	3.38 (1.55 - 7.37)	**0.002**
CD4 Count					
CD4 >200 cells /mm2	61 (17.6)	7 (13.7)	0.356	1.00	
CD4 < 200 cells /mm2	33 (9.5)	8 (15.7)		2.11 (0.7 - 6.34)	**0.182**
No CD4 count done	253 (72.9)	36 (70.6)		1.24 (0.53 - 2.92)	0.623
Viral load					
Viral load >1000	8 (2.3)	0 (0)	0.741	1.00	
Viral load <1000	190 (54.8)	28 (54.9)		0.95 (0.53 - 1.73)	0.878
No viral load done	149 (42.9)	23 (45.1)			
Duration on DTG (months)					
<1 year	127 (36.6)	19 (37.3)	0.992	1.00	
1-2 years	105 (30.3)	15 (29.4)		0.95 (0.46 - 1.97)	0.901
>2 years	115 (33.1)	17 (33.3)		0.99 (0.49 - 1.99)	0.973
WHO stage					
1	285 (82.1)	41 (80.4)	0.527	1.00	
2	32 (9.2)	3 (5.9)		0.65 (0.19 - 2.22)	0.494
3	15 (4.3)	4 (7.8)		1.85 (0.59 - 5.86)	0.293
4	15 (4.3)	3 (5.9)		1.39 (0.39 - 5.01)	0.614
Plasma glucose monitoring					
No	340 (98)	50 (98)	1.000	1.00	
Yes	7 (2)	1 (2)		0.97 (0.12 - 8.06)	0.979
Duration from diagnosis with HIV					
1	156 (45)	14 (28.6)	0.020	1.00	
2	105 (30.3)	14 (28.6)		1.49 (0.68 - 3.24)	0.320
3	46 (13.3)	14 (28.6)		3.39 (1.51 - 7.63)	0.003
4	37 (10.7)	7 (14.3)		2.11 (0.79 - 5.59)	0.134

4.8. Multivariate logistic regression showing factors associated with hyperglycemia among patients with HIV on dolutegravir-based regimen at Kiruddu National Referral Hospital

At multivariate level, only age above 40 years was significant at AOR 2.55 (95% CI: 1.05-6.23, P=0.039), being hypertensive at AOR 2.93 (95% CI 1.07-8.02, P =0.036) were significantly associated with high risk of getting hyperglycemia.

More is represented in table 5 below.

Table 5. Multivariate logistic regression showing factors associated with hyperglycemia among patients with HIV on dolutegravir-based regimen at Kiruddu National Referral Hospital

Hyperglycemia (N=398)	Adjusted Odds ratio	95% CI	P value
Age in years			
<40	1.00		
40+	2.55	1.05 - 6.23	**0.039**
Gender			
Female	1.00		
Male	0.90	0.41 - 1.97	0.790
Unit			
In-patient department	1.00		
Out-patient department	0.67	0.21 - 2.15	0.502
Marital status			
Married	1.00		
Separated	1.55	0.6 - 3.99	0.366
Single	0.46	0.17 - 1.24	0.125
Widowed	2.78	0.78 - 9.89	0.113
Level of education			
None	1.00		
Primary	0.67	0.24 - 1.88	0.446
Secondary	0.32	0.1 - 1.02	0.055
Tertiary	1.09	0.28 - 4.3	0.903
Physical activity			
None	1.00		
Minimal	2.33	0.65 - 8.27	0.192
Moderate	2.12	0.47 - 9.48	0.326
Active	0.97	0.32 - 2.9	0.954
Prescribed corticosteroids, thiazides or beta-blockers.	1.01	0.21 - 4.85	0.994
Hypertension	2.93	1.07 - 8.02	**0.036**
Family history of diabetes mellitus or hyperglycaemia	1.61	0.69 - 3.79	0.272
CD4 count			
High >200	1.00		
Low <200	2.70	0.76 - 9.6	0.126
Not done	1.51	0.58 - 3.96	0.401

CHAPTER 5

5.0: DISCUSSION

This was a cross-sectional study that evaluated the prevalence and factors associated with hyperglycemia among HIV infected individuals on DTG-based regimens for ≥3 months at Kiruddu National Referral Hospital.

5.1: Prevalence of hyperglycemia

This study found that 1 in 10 HIV infected individuals on DTG based ART regimen is hyperglycemic.In a recent study at Mbarara Regional Referral Hospital, Namulindwa *et al* found that the prevalence of adverse drug reactions while on a DTG-based regimen was 33.1% with hyperglycemia noted at 7.3% (Namulindwa, Wasswa et al. 2022), which was lower compared to the prevalence of hyperglycemia of 13% in this study. Abebe *et al*, reported in their study that prevalence of hyperglycemia in the HAART group was 7.9% and that in the non-HAART group was 5.6%. (Abebe, Kinde et al. 2014). At the cellular level, DTG is attributed to interference with insulin signaling that causes lipid metabolism defects leading to obesity that causes insulin resistance and therefore increased blood glucose levels. (Namulindwa, Wasswa et al. 2022). DTG chelates magnesium which affects the glucose transport via Glucose transporter (GLUT) 4 receptor and gluconeogenesis causing insulin resistance. (Rathbun, Lockhart et al. 2014).

5.2: Factors associated with hyperglycemia among HIV infected individuals on DTG based regimens.

Factors that were associated with hyperglycemia at multivariate analysis with statistical significance included; age above 40 years, having hypertension as a cor-morbidity.

In this study participants with hypertension had 2.93 odds of getting hyperglycemia and similarly Spieler *et al*, 2019 study reported that HIV infected patients on HAART with hypertension as a comorbidity were at risk of developing hyperglycemia (Spieler, Overton et al. 2019). This was attributed to lipo-accumulation pattern of fat distribution and lipo-dystrophy which increases the risk of insulin resistance and hyperglycemia (Jericó, Knobel et al. 2005) Spieler reported other factors that were associated with hyperglycemia that included low CD4 count, longer duration on HAART > 2 years, co-prescribed medications like thiazides, steroids but this was not statistically significant in our study. (Spieler, Overton et al. 2019).

In this study, persons above 40 years had a 2.55 odds of getting hyperglycemia and this was similar to a study done by Lamorde *et al* at the Infectious Disease Institute ,Uganda where they reported that being older on DTG based regimens was also a risk factor for getting hyperglycemia.(Lamorde, Atwiine et al. 2020) Orlando *et al* reported that altered metabolism of glucose and insulin increased with age resulting in insulin resistance (Orlando, Meraviglia et al. 2006) and also with increase in age, one is more exposed to HAART, which has been implicated in causing insulin resistance (Vance, Fazeli et al. 2014). In this study, duration on DTG which we expected to show statistical significance was not but other studies like the Lamorde study, having been on DTG for 4 months was reported to be statistically significant. (Lamorde, Atwiine et al. 2020). This may be because DTG is a very potent drug and as early as 4 months, an individual will have had enough exposure the hyperglycemic side effect.

Gender did not show statistical signifiacnce like we expected yet in the Lamorde study males were reported to be at more risk. (Lamorde, Atwiine et al. 2020) but in the Namulindwa study, female were reported to be more at risk (Namulindwa, Wasswa et al. 2022). The reason to this is still not so clear. Da Cunho *et al* , reported that prevalence of hyperglycemia was 7.14% in people living with HIV and males were more at risk of developing hyperglycemia(da Cunha, Franco et al. 2020)

In this study, a BMI ≥30 was statisitcally significant at bivariate analysis with 3.89 odds but was not statistically significant at multivariate analysis however BMI ≥30 was reported statistically significant in other studies like McCann*et al* in their study reported that weight gain was associated with being on DTG-based regimens especially TAF/3TC/DTG with an increased risk of developing diabetes. (McCann, Shah et al. 2021). Taramasso *et al* in their SCOLTA cohort study noted that HIV positive patients on DTG had an increase of BMI after 1 year (p=0.004) and compared to the general public, there was a higher BMI gain in HIV positive patients. (Taramasso, Ricci et al. 2017). A study in Cameroon by Noumegni*et al*, obesity was the only factor associated with hyperglycemia in HIV positive patients on HAART (Noumegni, Nansseu et al. 2017). Noubissi *et al* attributed hyperglycemia to drug effects via increased weight and improved wellbeing, metabolic dysfunction like dyslipidemia and insulin resistance reducing insulin secretion by interfering with the GLUT 4 glucose uptake receptors. The drugs also interfere with cellular retinoic acid –binding protein type 1 thereby promoting insulin resistance, release of fatty acids and adipocyte inflammation. (Noubissi, Katte et al. 2018). In the NAMSAL study, Participants on DTG were seen to put on more weight than those on Efavirenz. (Eckard and McComsey 2020). In the ADVANCE study, those on DTG

had a >10% increase in body weight. DTG was implicated in inhibiting the action of radio-labeled α melanocyte stimulating hormone action on the human recombinant melanocortin 4 receptor which is involved in regulating energy homeostasis and food intake (Eckard and McComsey 2020). Obesity alters glucose homeostasis through faulty signal transduction via insulin signaling proteins resulting into decreased muscle reduction in insulin uptake, lipogenesis is altered and glucose output by the liver is increased (Martyn, Kaneki et al. 2008).

In this study, being physically active was not statistically significant yet we expected it to be. La Monte *et al* reported that women who were physically active were 88% protected from getting diabetes and this was attributed to the hypothesis that activity prevents glucose homeostasis dysregulation and delays progression from impaired glycemic control to overt diabetes (LaMonte, Blair et al. 2005).

In this study, participants with a low CD4 < 200 was statistically significant at bivariate analysis with 2.11 odds of developing hyperglycemia but this was not significant in the multivariate analysis. A study by Ngah et al showed that a CD4 count < 500 was a risk factor for getting hyperglycemia. (Ngah, Cho et al. 2021) Kalra et al in their study attributed low CD4 count with hyperglycemia to immune restoration after HAART initiation and autoimmune diabetes has recently been reported to develop in some HIV-infected patients after immune restoration during HAART which predisposes to autoimmune disease due to development of antibodies to glutamic acid decarboxylase (Kalra, Kalra et al. 2011)

In this study herbal medicine use showed statisitcal significance at bivariate analysis with a 2.82 odds of getting hyperglycemia but this was not significant at mulitvariate analysis.Fathallah *et al* study reported that drugs caused hyperglycemia by direct cytotoxic effects on pancreatic cells, altering insulin secretion and sensitivity and by increasing glucose production (Fathallah, Slim et al. 2015).

In this study, we noted that 47.7% of participants did not have baseline blood glucose levels, and only about 10% of these participants had been told by health workers that dolutegravir was associated with diabetes which highlighted a knowledge gap in this setting. Having this information would enable these participants to report faster to the health facility in case they noted any signs of hyperglycemia like polyuria, polydipsia, polyphagia and fatigue and intervention done. Zakumumpa *et al* in a national roll-out qualitative study involving 12 health facilities in 4 sub-regions,27 ART clinicians participated in focus group discussions and their assessment was on side effects of DTG, baseline blood sugar levels before beginning DTG,

and evidence of monitoring sugar levels using RBS in patients on DTG based regimen. They reported that most participants did not have a baseline blood glucose levels and that was attributed to lack of awareness among health workers of DTG being associated with hyperglycemia and glucometers to use. (Zakumumpa, Kitutu et al. 2021).

5.3: Study limitations

- From several studies, DTG is associated with hyperglycemia but there are many independent factors that could cause hyperglycemia in HIV positive patients.
- The lack of comparison between participants on DTG and those on non-DTG based regimens to compare risk of developing hyperglycemia makes it difficult to attribute the hyperglycemia directly to the DTG.
- Low hemoglobin level affects HBA1C. We were not able to evaluate hemoglobin levels due to limited funds for our participants and this could have affected our levels of HBA1C.
- More than 50 % of the participants did not have baseline RBS before start of DTG so association of getting hyperglycemia associated with DTG from baseline measurement is difficult.

5.4: Study strength

The sample size of 398 was powered enough to undertake this study.

CHAPTER 6

6.1: Conclusion

HIV positive patients receiving DTG based ART regimens are at increased risk of development of hyperglycemia. Risk factors for hyperglycemia should be identified and blood glucose monitored in all patients receiving DTG.

6.2: Recommendation

- Ministry of Health guidelines should follow up with emphasis that all participants to be started on DTG based regimen must have baseline blood glucose levels and follow up.
- Public Health facilities should provide adequate infrastructure and system for screening and monitoring of blood glucose levels in participants on DTG based regimens.
- All individuals who are HIV positive on DTG with risk factors attained in this study should have frequent monitoring of their blood sugar levels with HBA1C.

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APPENDICES

APPENDIX 1: INFORMED CONSENT FORM (ENGLISH VERSION).

Title of the proposed study:

Prevalence and factors associated with hyperglycemia among HIV positive in and out-patients currently on dolutegravir - based HIV anti-retroviral therapy at kiruddu national referral hospital.

Investigator: Dr. Byereta Happy Lillian, Tel. 0782 429529, 0704 925146; E-mail: hbyereta@gmail.com, Department of Medicine, Makerere University College of Health Sciences

Background and rationale for the study:

Dolutegravir-based (DTG) regimens are rapidly replacing older antiretroviral drugs in low and middle-income countries as first line ART. DTG is preferred due to its efficacy, tolerability and cost-effectiveness. Some patients switched to dolutegravir have been reported to develop high blood sugar. However, evaluation of blood glucose levels is not routinely done in most HIV public clinics because of associated high cost.

The study involved knowing how patients living with HIV and on a Dolutegravir based HAART regimen who presented to the clinic and in patient's wards may have high blood sugar, any findings on history, examination and requesting appropriate laboratory tests to confirm or rule out high blood sugar levels. Your participation is very important because we want to learn more about the challenge of high blood sugar among HIV positive patients taking Dolutegravir based regimen and the associated factors leading to it to improve healthcare.

Description of sponsors;

RASHOTS (Rainier Arnhold Senior House Officer Teaching Support) Project – Established in 2010 to support postgraduate trainees in the department of Internal Medicine, this organization is funded by The Mulago Foundation through a grant obtained by Dr. Robert Kalyesubula, nephrologist and Makerere University-Yale University (MUYU) alumnus, with MUYU assistance. This organization has brought a new level of structure to education and supportive activities for MakCHS residents/SHOs. Over the past seven years, RASHOTS has improved the quality of SHO training and assessment, developed a database to track morbidity and mortality on the internal medicine wards at MNRH, and established a new rotating junior faculty position Chief Resident to further support SHO education.

Dr Andia Irene – Biraro my supervisor is one of the co-directors of RASHOTS.

Purpose:

The information obtained from this study will help streamline a better understanding of the burden, early detection and management of hyperglycemia among HIV positive patients on DTG based regimen in Uganda and the world at large.

Procedures:

You have been identified as a participant in this study because you fulfil the specifications of the patients to be investigated. If you accept to participate, the following will be done: History (Information about you) will be taken, as well as being assisted to fill in a questionnaire. Physical examination will be carried out. A blood sample of about 3mls will be drawn off from one of your arms to run a number of tests inclusive of which will be random blood Sugar and HbA1C. All investigation results will be reported to the primary physician. You will also be reviewed periodically while in hospital.

Who will participate in the study:

HIV positive patients 18 years or older at Kiruddu Communicable Disease Clinic and Kiruddu emergency inpatient unit, currently on a DTG- based ART regimen. Those excluded will be with documented evidence of DM before HAART initiation even when they are on DTG. Duration of the study is 3 months.

How will the study be done?

We shall ask you some questions about yourself and your medical history. You will then be examined. A nurse will remove 3 mls of blood for some tests that will include Random Blood sugar and HbA1C. This will take about 30 minutes in total.

If you agree to participate in the study, you will sign a letter of acceptance.

Risks of blood draw;

Blood withdrawal carries a minimal risk of pain, swelling or even infection at the site of injection. The pain is minimal, reducing a few minutes after the needle has been withdrawn. To minimize pain, bleeding and infection at the puncture site, blood will be taken by a skilled person using aseptic techniques ensuring that a clean swab is applied to the site with gentle pressure. All attempts will be made to have blood drawn once to avoid pricking again.

Benefits:

The investigations will be done for the participant at no cost. Vital observation parameters will also be availed to the primary care team to help improve on the health care rendered to the patients. In addition, you will be informed about your blood sugar status and if indicated, you will be referred for appropriate care.

The results of this study will provide data for future research on prevalence and factors associated with hyperglycemia for patients on DTG-based HIV Antiretroviral therapy in resource limited settings. They will provide evidence to; advocate for tools for routine blood glucose sugar monitoring in a public facility, identify high risk patients not to be started on DTG, closer monitoring or switching patients back to non- DTG regimens earlier, strengthening evidence for guidelines about DTG use.

Rights of the Participant;

Participation is entirely voluntary and participants may join on their own free will and you are free to withdraw from this study at any time without affecting your medical care and without penalty. Information obtained from you will be kept confidential and no unauthorized person will have access to it. Participants' identities will not be used in any reports or publications.

Confidentiality:

The results will be availed to your attending doctors and explained to you. All information obtained will be considered confidential and will not be given to any other person without your permission. All filled questionnaires and laboratory results will be identified using the study numbers and kept in files after data collection and only the local Research Ethics Committee (REC) and Uganda National Council for Science and Technology (UNCST) as entities may have access to private information that identifies the research participants by name.

Reimbursement;

Each participant will receive 10,000 shillings for lunch and to compensate for transport.

Enquiries and Complaints;

Any problems or questions related to the study may be asked at any time during the study by contacting Dr. Byereta Happy Lillian on telephone number 0782 429529 / 0704 925146 or through email at hbyereta@gmail.com

Any unethical or other concerns may be forwarded to the chairperson School of Medicine Research and Ethics Committee (SOMREC) at the College of Health Sciences Prof. Ocama Ponsiano 0772-421190

Dissemination of results:

Research participants will get feedback on findings and progress of the study and any new information that affects the study or data that has clinical relevance to research participants (including incidental findings) will be made available to research participants and/or their health care providers.

The results from this study will shall be disseminated also to the policy makers, Kiruddu National Referral Hospitals and other hospitals in Uganda, Ministry of Health, Makerere University and also published in a peer-reviewed journal.

Ethical approval:

The Makerere University School of Medicine Research and Ethics Committee (SOMREC) have approved this study.

STATEMENT OF CONSENT

.....has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Name …….

Signature/thumb print of participant ……

Date ……

Name …….

Signature of parent/guardian for minors (If applicable) ……

Date …….....

Name……

Signature of witness (if applicable) ……...

Date……

Name……

Signature of interviewer/Person obtaining informed consent …….

Date ……..…….

APPENDIX 2: INFORMED CONSENT FORM (LUGANDA VERSION)

Omutwe gw'okunoonyereza okusabibwa:

Ekigero n'obukonge obwekuusa ku ssukaali w'omumusaayi ow'awaggulu mu balwadde b'akawuka ka mukenenya abali ku bitanda n'abaviira wabweru weddwaaliro abali ku ddagala ly'amukenenya eririmu ekirungo kya Dolutegulaviiru ku ddwaaliro ekkulu Kiruddu.

Anoonyereza: Musawo (Ddokita) Byereta Happy Lilian, Essimu: 0782 429529, 0704 925146. Mayila: hbyereta@gmail.com, Essomero ly'eddagala, Ssettendekero Makerere, ettendekero ly'ebyobulamu (MAKCHS)..

Ennyanjula n'omugaso gw'okunoonyereza kuno.

Amadagala g'akawuka k'amukenenya agalimu ekirungo kya Dolutegulaviiru (DTG) gagenda gasikira ebika byeddagala lyakawuka k'amukenenya ebikadde ku supiidi ey'amangu ennyo mu mawanga agakyaakula obukuzi ng'eddagala lya mukenenya erisookerwaako. DTG ayagalwa nnyo olw'obujjanjabi obwaawaggulu bwaawa, okuba ng'agumibwa mangu abamukozesa, ate nga wa bbeeyi esobolekeka. Abamu ku balwadde abakyuusibwa nebateekebwa ku DTG basangiddwa okuba nga bafuna ssukaali w'omumusaayi ow'awaggulu. Wabula, okukebera Ekigero Kya ssukaali mu musaayi tekutera kukolebwa mu malwaaliro g'olukale/ g'agavumenti agasinga obungi awajjanjabirwa akawuka k'amukenenya olw'ebisale by'okukebera ebiri waggulu.

Okunoonyereza kuno kulimu okumanya engeri abalwadde b'akawuka ka mukenenya abali ku ddagala eririmu DTG abajja mu ka kilinika oba awafunirwa obujjanjabi bwa mbagilawo gyebayinza okubeeramu ne ssukaali w'awaggulu, ebiyinza okusangibwa mu byafaayo byobulamu bwaabwe, okweekebejja omubiri, n'okusaba enneekebejja/ enkebera ezisaanidde okukakasa nti balina sukaali w'omumusaayi ow'awaggulu oba tebamulina. Okweetabaakwo mu kunoonyereza kuno kwa mugaso nnyo kubanga twagala okwongera okuyiga ebisoomooza bya sukaali w'awaggulu mu balwadde b'akawuka k'amukenenya abali ku ddagala eririmu DTG n'obukonge obukyekuusaako, kyongere okutuyamba okukola ennongoosereza ezisaanidde okwongera omutindo ku bujjanjabi obuweebwa abalwadde b'akawuka k'amukenenya.

Ennyanjula y'abafujjirizi b'okunoonyereza kuno.

Enteekateeka ya RASHOTS-(mu bulambulukufu mu lunyaanyimbe/Luzungu kiggwaayo nti Rainier Arnhold Senior House Officer Teaching Support) yatandikibwaawo mu mwaka gwa

2010 okuwagira abayizi abasoma ddiguli yaabwe ey'okubiri nga bagwa mu kiwayi Ky'eddagala ly'omunda**.** Enteekateeka Eno efujjirirwa ekitongole ekiyitibwa mu luzungu" The Mulago Foundation" okuyita mu nsako yensimbi eyafunibwa Dokita Kalyesubula Robert omukugu mu kujanjaba endwadde z'ensigo zaabantu okuva ku MAKCHS era nga y'omu ku baaliko ba mmemba b'ekibiina ekiyitibwa Makerere University-Yale University (MUYU) era abaayambibwaako MUYU.

Enteekateeka eno ereeseewo omutendera omupya ogwensengeka y'okusomesa saako n'okuwagira emirimu gy'abayizi ba ddiguli ey'okubiri ku MAKCHS (oba bayite ba Senior House Officers "SHOs" mu lunyaanyimbe/ Luzungu)

Mu myaka omusanvu egiyise, RASHOTS elongoosezza nnyo omutindo gwensomesa nengezesa y'aba SHO, ekoze ssetterekero w'okulondoola emiwedo gy'abalwadde abafa ku woodi z'ekiwayi ky'eddagala ly'omunda ku ddwaaliro e Mulago, era etaddewo ekifo ekipya ekiyitibwa " akulira ba SHO abakyaali abato mu kiwayi" okwongera okuwagira ensoma y'aba SHO. Omusawo ayitibwa Dokita Andia Irene- o'mu ku bawabuzi bange mu kunoonyereza kuno y'omu kubakulira enteekateeka ya RASHOTS.

Omugaso

Okumanyisibwa okunaava mu kunoonyereza kuno kujja kugabanyizibwaako/ kuweebwa mbagirawo / mu budde eri abasawo mu malwaaliro amalondemu saako n'amalala okweetoloora eggwanga saako nebekikwaatako abenkizo abeenyigira mu nteekateeka z'abalwadde b'akawuka k'amukenenya kiyambeko okukola ennongoosereza ezongezesa entegeera y'omugugu, okuzuula ng'abukyaali, wamu n'enzijanjabamu ya ssukaali ow'awaggulu mu balwadde b'akawuka k'amukenenya abali ku DTG mu Yuganda n'ensi yonna okutwaaliza awamu.

Emitendera gy'okukolamu okunoonyereza kuno.

Olondeddwa okweetaba mu kunoonyereza kuno kubanga olina ebisaanyizo by'abantu abasaanidde okweetaba mu kunoonyereza kuno. Bwokkiriza okukweetabamu, bino wammanga bijja kukolebwa: Ebyafaayoobyo bijja kukubuuzibwa era Ojja kuyambibwaako okujjuza/ okuddamu ebibuuzo ebyaategekeddwa edda ku lupapula. Okukebera omubirigwo nakyo kijja kukolebwa. Omusaayi gw'akipimo Kya miiruzi ng'a kkumi(z'ejjiiko za ssukaali ennene ng'abbiri) gujja kuggyibwa ku gumu ku mikono gyo gutuyambeko okukola okugezesa/ enkebera ezenjawulo nga mwemuli neezo ezikebera oba olina obulwadde bwa ssukaali.

Ebinaava mu kugezesa/kukebera kuno byonna bijja kutegeezebwa eri dokitawo omukulu akujjanjaba. Era Ojja kukeberebwangako buli luvannyuma lw'ebbanga eggere ng'oli mu ddwaaliro.

Ani aneetaba mu kunoonyereza kuno?

Abalwadde abalina akawuka k'amukenenya, nga balina emyaka 18 egyobukulu oba okusingawo nga bali ku kilinika y'eddwaliro lya Kiruddu ekola ku ndwadde z'olukonvuba (Kiruddu communicable disease clinic) ne woodi y'eddwaliro Kiruddu ekola ku bujjanjabi obwa mbagirawo (Kiruddu emergency inpatient unit'") nga bali ku ddagala lyakawuka k'amukenenya eririmu DTG. Abalwadde abanajjibwa mu kunoonyereza kuno beebo abanaaba n'obulwadde bwa sukaali obwaakakasibwa edda era nebuteekebwa mu buwandiike ngatebannatandika ddagala ly'akawuka k'amukenenya nebwebaba nga Bali ku DTG.

Ebbanga ly'okunoonyereza kuno lya myezi esatu

Okunoonyereza kuno kunaakolebwa kutya?

Tujja kukubuuza ebimu ku bibuuzo ebikukwaatako ggwe ng'omuntu wamu n'ebyaafaayo by'obujjanjabi bwo. Tujja kuzzaako okukebera/ okukweekebejja omubiri. Nnansi omu ajja kukuggyako omusaayi ku Mukono, ekipimo Kya miiruzi kkumi (gwenkana ng'ejjiiko za ssukaali ennene enzijuvu bbiri) gukozesebwe okukebera ebintu ebyenjawulo ng'amwotwaalidde n'okukebera obulwadde bwa ssukaali. Bino byonna bijja kutwaala obudde bwa ddakiika ng'amakumi asatu.

Bwokkiriza okweetaba mu kunoonyereza kuno, Ojja kuteeka omukonogwo ku bbaluwa elaga okukkirizakwo.

Obutyaabaga obuli mu kujjako omusaayi

Okukujjako omusaayi kuyinza okuleetawo obutyaabaga butono nnyo, okugeza ng'obulumi, okuzimba, oba n'okuyingiza mu mubiri obuwuka obulwaaza nga buyita mu kitundu ky'omubiri ewafumitiddwa empiso. Obulumi butonno nnyo, era bukendeerera ddala ngawayiseewo eddakiika ntono ngempiso efumise emaze okujjibwa mu mubiri. Okugezaako okukendeereza ddala ku bulumi obwo, omusaayi okutiiriika, saako n'okuyingiza obuwuka obulwaaza mu mubiri, omusaayi gujja kuggyibwaako omuntu omukugu ennyo mu kukola ekikolwa kino, era ajja kukozesa emitendera n'obukodyo obwenkizo bwonna obugobererwa okusobola okutangira akawuka konna okuyingira mu mubiri nga kayita ewafumitiddwa. Ekitundu ekifumitiddwa kijja kunyigibwako mpolampola (kukola ka masaagi) oyo afumise okugezaako okukendeeza

kubulumi amangu. Buli kisoboka kijja kukolebwa okugezaako okulaba nga omusaayi guggyibwaako omulundi gumu gwokka okweewala okufumita omuntu emirundi egisukka mu gumu.

Ebyokuganyulwa :

Okukebera okwenjawulo kwonna okunaakolebwa eri eyo eyeetaba mu kunoonyereza kuno kujja kuba Kwa bwereere. Ebyeetaagisa ebyenkizo mu kulondoola/ kweetegereza obulamu bw'omulwadde nabyo bijja kuweebwa abo abavunaanyizibwa ku kulabirira omulwadde kiyambeko okwongera ku mutindo gw'obujjanjabi obuweebwa abalwadde. Ekirala, Ojja kutegeezebwa ku mbeera/ ekipimo Kya sukaali wo ow'omumusaayi era ekipimo ekyo bwekitaabe mu mbeera nungi, ojja kulagirirwa wa w'oyinza okufuna obujjanjabi obweetaagisa.

Ebinaava mu kunoonyereza kuno bijja kuteekawo Ebiwandiiko ebyenkizo ennyo eri okunoonyereza okulala okulikolebwa jebujja nga kukwaata ku kigero n'obukonge obwekuusa ku ssukaali w'omumusaayi ow'awaggulu mu balwadde b'akawuka ka mukenenya abali ku ddagala ly'amukenenya eririmu ekirungo kya DTG mu nsi ezikyaakula. Okutegeera Ekigero Ky'abantu abalina sukaali owawaggulu kijja kuwa obukakafu obunaasinziirwaako okulwaanirira okuteekawo ebikozesebwa okukebera n'okugoberera ekipimo ky'assukaali mu musaayi gw'abantu mu malwaaliro agoolukale, okuzuula abalwadde abali mu katyaabaga kaawaggulu baleme kutandisibwa ku DTG, okutunuulira n'eriiso ejjoji oba okukyuusa amangu abalwadde abeekika Ekyo okubazza ku ddagala lya mukenenya eritaliimu DTG, wamu n'okwongera okugumya obukakafu mu bigobererwa mu kukozesa DTG.

Eddembe ly'abaneetaba mu kunoonyereza kuno.

Okweetaba mu kunoonyereza kuno kwa bwannakyeewa era abakweetabamu bakikola nga Kya kyeeyagalire. Abakkiriza okukweetabamu era balina eddembe okuva mu kunoonyereza kuno essaawa yonna webaba baagalidde era nga tewali kibonerezo kijja kubaweebwa olwookusalawo bweekutyo. Obubaka bwonna bwetunaafu a okuva gyooli bujja kukuumibwa nga bw'akyaama era tewali muntu yenna atalina lukusa lwakubumanya ajja okuba nga abutuukako. Endaga buntu z'abaneetaba mu kunoonyereza kuno tezijja kukozesebwa mu alipoota yonna oba obuwandiike obw'olukale.

Okukuuma ebyaama:

Ebivudde mu kukebera okwenjawulo bijja kuweebwa abasawo abakujjanjaba era bijja kukunnyonnyolwa.Ebikuggyiddwaako byonna bijja kutwaalibwa nga byakyaama era tebijja kuweebwa muntu mulala yenna awatali lukusa kuva wuwo.

Empapula zonna eziriko ebibuuzo ebyaanukuddwa wamu neebivudde mu kukebera mu labalatole bijja kulambibwa n'ennamba z'okunoonyereza era biteekebwe mu Zi Ffayiro ng'okukungaanya obubaka kuwedde.

Akakiiko k'okussomero ly'eddagala e Makerere akakwaasisa empisa z'okunoonyereza (SOM-REC) wamu n'akokumutendera gwe ggwanga eddamba Yuganda (UNCST) bwebukiiko bwokka obuyinza okufuna olukusa olutuuka ku bubaka obwekyaama obulimu endaga buntu z'abantu abanaaba beetabye mu kunoonyereza kuno.

Okuddizibwa ssente ezisaasaanyiziddwa

Buli muntu aneetaba mu kunoonyereza kuno ajja kuweebwa ssente omutwalo gw'ayuganda gumu (10,000) gwakukozesa ku bisale by'entambula wamu n'ekyemisana.

Ebibuuzo n'okweemulugunya

Ebizibu byonna oba ebibuuzo ebikwaata ku kunoonyereza kuno biyinza okubuuzibwa akaseera konna ng'okunoonyereza kuno kukolebwa ng'otuukirira Dokita Byereta Happy Lilian ku nnamba y'essimu 0782 429529 / 0704 925146 oba ng'oyita ku Mayila: hbyereta@gmail.com

Empisa zonna ezitali nungi oba okweelaliikirira kwonna kusobola okusindikibwa eri ssentebe w'akakiiko akakwaasisa ebyempisa mu kunoonyereza ak'essomero ly'eddagala(SOM-REC) ku ttendekero ly'ebyobulamu ku ssettendekero Makerere Ssaabakenkufu Ocama Ponsiano ku nnamba yessimu 0772-421190

Okusaasaanya ebinaaba bivudde mu kunoonyereza kuno

Abaliba beetabye mu kunoonyereza kuno bajja kufuna obubaka ku binaaba bizuuliddwa mu kunoonyereza kuno wamu n'entambula yaakwo. Okumanyisibwa okupya kwonna okuyinza okukyuusa okunoonyereza kuno oba okulina eky'amakulu eri abaliba beetabye mu kunoonyereza kuno (ng'otwaliddemu n'ebiriba bisangiddwa ku ggwiiso/ngabibadde tebisuubilwa) bijja kutegeezebwa abo abaliba beetabye mukunoonyereza kuno oba abasawo ababawa obujjanjabi.

Ebinaava mu kunoonyereza kuno era bijja kuweebwa abakozi b'amateeka, eddwaliro ekkulu Kiruddu n'amalwaaliro amalala mu Uganda, ekitongole ky'ebyobulamu, ssettendekero Makerere, era biwandiikibwe mu lukale ngatuyita mu ssekitabo eyeekenneenyerezebwa.

Olukusa okukola okunoonyereza

Akakiiko akakwaasisa empisa nengeri y'okukolamu okunoonyereza ak'essomero lye ddagala (SOM-REC) ku bbanguliro ly'abasawo erya ssettendekero Makerere kakakasizza era nekawa olukusa okunoonyereza kuno kukolebwe.

Ekirayiro ky'okukkiriza okweetaba mu kunoonyereza kuno

.....

Annyinnyonnyodde ekigenda okukolebwa,

Obutyaabaga wamu n'okuganyulwa ebikulimu, saako n'eddembe lyange mu kunoonyereza kuno. Ntegeera nti okusalawo kwange okweetaba mu kunoonyereza kuno tekijja kukyuusa mu ngeri jenfunamu bujjanjabi bwange eyaabulijjo. Mukukozesa obubaka buno, endaga buntu bwange zonna zijja kusigala nga zaakyaama. Nkimanyi nti nsobola okuva mu kunoonyereza kuno akaseera konna bwemba njagadde. Ntegeera nti okuteeka omukono gwange ku kiwandiiko kino, ssejjaako yadde neerimu ku ddembe lyange wabula ndaga bulazi nti bantegeezezza ebikwaata ku kunoonyereza kuno mwengenda okweetaba kyeeyagalire nga tewali wadde n'omuntu omu ankase. E'mu ku kkopi z'ekiwandiiko kino ejja kumpeebwa.

Erinnya……

Omukono/Ekinkumu kyakkirizza okweetaba mu kunoonyereza kuno……..…

Ennaku z'omwezi …….....

Erinnya ……

Omukono gw'omuzadde/omukuumi w'omwana (bwekiba kyekisoboka).....

Ennaku z'omwezi……

Erinnya.....

Omukono gw'omujulirwa (bwekiba kyeekisoboka)…….....

.Ennaku z'omwezi. .....

Erinnya …….

.

Omukono gw'omunoonyereza asaba okusalawo okutegeeze okuva eri

omulwadde.....

Ennaku z'omwezi……...

APPENDIX 3: ELIGIBILTY ASSESSMENT FORM

All the participants to be enrolled in the study must meet the following eligibity criteria, based on the inclusion / exclusion criteria detailed in this form.

A, Study information

Title	Prevalence and factors associated with hyperglycemia among HIV positive patients in out and in patients at Kiruddu National Referral Hospital
Protocol number	
Principal Investigator	Dr Byereta Happy Lillian.

B, Participant information

Study identification number		
Gender	Male	female

C, Inclusion/ Exclusion criteria

Inclusion criteria (tick as appropriate)	**YES**	**NO**
1. Adult patient >18years of sound mind		
2. On follow up at Kiruddu NRH		
3. Has consented to participate in the study		
4. On DTG based ART regimen for not less than 3 months.		
5. No documented history of Type 1 DM, Type 2 DM or any use of hypoglycemics.		

Exclusion criteria (tick as appropriate)	**YES**	**NO**
1. On hypoglycemic or cancer chemotherapy		
2. Has End stage renal disease or uncontrolled hypertension		
3. Is expectant at the time of recruitment.		

All subject participants must get supporting documentation to confirm subject eligibility. This will be confirmed from the subject self-report, laboratory test results, patients' database / file from the clinic.

D, Statement of eligibility

The subject is (tick as appropriate)

Eligible…….

Not Eligible……

Date;

……

……..

Name;

……

……

Signature;

……

……..

APPENDIX 4: DATA COLLECTION TOOL

A study to determine the prevalence and factors associated with hyperglycemia among HIV positive in and out patients on Dolutegravir based ART regimen at Kiruddu Hospital.

A. **BIODATA;**

1. Date …….
2. Patient IP No…….
3. Respondent; Patient…….……..
   NOK…….……...
4. Current Address.…….....
5. Phone number for Patient/NOK…….…….…….
6. Gender; Male …… Female …….
7. Age (in years) ……
8. Marital status single married separated widowed
9. Education level informal primary secondary tertiary
10. Employment status; Unemployed Employed Informal Formal

B. **CLINICAL DATA**

11. Symptoms; Polyuria, Polydipsia, Polyphagia, fatigue, DIB.
12. Other symptoms; ……
13. General condition Fair General Condition Sick-looking Wasted
14. Weight (kg)……. Height(cm)……BMI……
15. Blood pressure ……
16. GCS……
17. Baseline RBS before stating
    DTG…….…….……
18. Any other important / abnormal findings ……
19. Family history of diabetes mellitus or hyperglycemia…….
20. Physical activity; None Minimal Moderate Active
21. High fat diet …….
22. Alcohol use (CAGE); Yes……No……CAGE;……..
23. Smoking (Pack years) Yes……. No…….Pack years;…….
24. Diagnosis on admission/review……
25. Cor-morbidities ……

C. **HIV DATA AT TIME OF PRESENTATION**

26. Date of HIV diagnosis ……..
27. Current treatment centre…….
28. Last date of review at treatment Centre.…….
27. Clinical state on last date of review …….
28. WHO stage ……
29. Most recent CD4 cell count and date……
    Low < 200, High > 200, No CD4 Count done
30. Viral load (copies /ml) and date…….
    Low <1000, High > 1000, No VL done
31. Adherence; Good > 95%, Average 50% - 95% Poor < 50%
32. DTG – ART based Regimen…….
33. Duration on DTG – Based ART (months) …….
34. Previous HAART regimen and date stopped if any.……
35. Duration on previous HAART regimen…….
36. Reason for discontinuation; adverse effects specify ……
    Treatment failure WHO guidelines / Tx optimization
37. Patient education/counseling on possible side effects, adherence, nutrition, lifestyle modifications of DTG; Yes…… No…...….
38. Co-prescribed medications (corticosteroids, beta blockers, thiazides, metformin, chemotherapy etc) …….
39. Have you ever been with herbal remedy on your current medications? Yes NO
40. Number of Blood sugar levels done and documented since DTG was started…….
41. Monitoring of plasma glucose (last done when) …….
42. Concurrent opportunistic infections; yes …… No .....
    TB TOXOPLASMOSIS CCM OTHERS
43. Patient outcome; Healed…...Died……Hospitalized……Stable in Clinic…….

D.LABORATORY FINDINGS

44. Current RBS …….
45. Current HbA1c……

Name of interviewer…….

Signature…….

APPENDIX 5: BUDGET FOR MY RESEARCH PROJECT

A.STATIONARY					
No	Item	Quantity	Unit cost(Ug, shs)	Total Cost (Ug, shs)	Justification
1.	Box file	5	6,000	30,000	For safe custody of RBS results
2	Data collection tools and consent forms	1	750,000	750,000	For all paperwork pertaining to the study
3	Stapler	1	10,000	10,000	Keeping the documents in order
4	Punching machine	1	10,000	10,000	To keep them in the file
5	Registry books	2	4,000	8,000	To register the study participants
6	ID labels	3	3,500	10,500	For patient numbers
7	Pens	9	500	4,500	For documentation of all study information
B. HUMAN RESOURCE					
8	Biostatisticians	1	700,000	700,000	For data analysis
9	IRB fees	1	100,000	100,000	As an IRB requirement research
10.	2 research assistant	1	1,100,000	1,100,000	Recruit in-patients into the study
11.	Patient fees for participating	398	10,000	3,980,000	Recruit out - patients into the study

12.	Calls and sms	4	50000	200,000	Call participants for results
C.SUPPLIES					
10	Vacutainers (purple top)	4	25000	100,000	To carry out blood sugar tests.
11	Syringes	5ml	18000	90,000	To collect blood.
12	Gloves	4 boxes	25000	100,000	To collect blood samples
13	Cotton wool	2	6000	12,000	To collect blood samples
14	Savlon	4	4000	16,000	To collect blood samples.
15	HbAlc	398	20,000	7,960,000	For testing blood sugar levels
Grand total (Ug shs)				**15,001,000**	

APPENDIX 6: TIMEFRAME AND WORKPLAN

- **Submit proposal to Department of Medicine Scientific Review Committee; 26th March 2021.**
- **Present proposal to Department of Medicine Scientific Review Committee; March 2021**
- **Submit proposal to IRB: March 2022**
- **Start data collection and analysis; May 2022**
- **Complete data analysis; August 2022**
- **Manuscript preparation completed; September 2022**
- **Submit to peer-review; October 2022**