PREVALENCE OF DOLUTEGRAVIR ASSOCIATED HYPERGLYCEMIA AND ITS COVARIATES AMONG PERSONS LIVING WITH HIV ON TREATMENT AT KENYATTA NATIONAL HOSPITAL

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DEDICATION STATEMENT

This work is dedicated to the Almighty Father for his mercies upon me throughout the study period; my beloved husband Elisha for the encouragement, patience, support and understanding; and to our children Tonny, Chelsea and Alicia for believing in me that I could do it.

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TABLE OF CONTENTS

ABBREVIATION AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
BMI	Body Mass Index
CCC	Comprehensive Care Centre
CNS	Central Nervous System
CPE	CNS Penetration Effectiveness
CYP450	Cytochrome P450
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DTG	Dolutegravir
EFV	Efavirenz
FDA	Food and Drugs Administration
FPG	Fasting Plasma Glucose
FTC	Emtricitabine
GLUT-4	Glucose Transport-4
HAART	Highly Active Antiretroviral Therapy
HbA1c	Glycosylated Hemoglobin A1c
HHS	Hyperosmolar hyperglycemic State
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
Kg	Kilogram
KNH	Kenyatta National Hospital
M	Meter
Mg/dL	Milligrams per deciliter
Mmol/L	Millimoles per Litre
MOH	Ministry of Health

MS	Metabolic Syndrome
NNRTs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleos(t)ide Reverse Transcriptase Inhibitors
OGTT	Oral Glucose Tolerance Test
PI	Protease Inhibitor
PLHIV	Persons Living with HIV
QC	Quality Control
RAL	Raltegravir
RBS	Random Blood Sugar
TDF	Tenofovir Disoproxil Fumarate
USNA-ACCORD	United States North American AIDS Cohort Collaboration on Research and Design
WHO	World Health Organization

LIST OF FIGURES

LIST OF TABLES

OPERATIONAL DEFINITIONS OF TERMS

Fasting plasma glucose – Blood glucose concentration after fasting for at least eight (8) hours.

HbA1c– Measure of proportion of one of the four glycosylated hemoglobin A fractions (A1c), used as a retrospective index of glucose control over time.

Hyperglycemia - A disorder characterized by an elevation in the concentration of plasma glucose, commonly seen in diabetics. For purposes of this study, the cut-off values were random blood sugar (RBS) ≥7.2mmol/L and/or HbA1c ≥6.1%.

Postprandial glucose concentrations - Plasma glucose concentration of at least two hours after a meal.

Random blood sugar – Blood glucose level at a random time of the day.

Treatment optimization- Introduction of better medicines and patient centered approaches in HIV management, to maintain viral suppression, without limiting future treatment options.

ABSTRACT

Background

The introduction of dolutegravir based antiretroviral therapy has provided a potent treatment option for persons living with the human immunodeficiency virus. However, there is growing evidence from clinical settings that use of dolutegravir can result in significant hyperglycemia. The prevalence of dolutegravir-associated hyperglycemia in our population remains unknown. Identification of dolutegravir-associated hyperglycemia is necessary for reducing morbidity and mortality associated with uncontrolled plasma glucose levels among patients on antiretroviral therapy.

Objective

To determine the prevalence of dolutegravir associated hyperglycemia and its covariates among adult persons living with human immunodeficiency virus on treatment and follow-up at Kenyatta National Hospital.

Methodology

A cross-sectional descriptive study was conducted at Kenyatta National Hospital comprehensive care center from July through to September, 2020. The study targeted adult persons (>18 years) on dolutegravir-based antiretroviral therapy for at least 3 months. Pregnant mothers, diabetics or patients with a documented diagnosis of diabetes were excluded from the study. Consecutive sampling technique was used to obtain a representative sample of 358 participants, who consented to the study. Data on prevalence of dolutegravir associated hyperglycemia and its covariates was collected using laboratory measurements of random blood sugar and glycated hemoglobin levels. Researcher administered structured questionnaires and IQ-care patient data base were also used to obtain other information relevant to the objective of the study.

The main study outcome was hyperglycemia. A case/ non-case method was employed to calculate the prevalence of dolutegravir-associated hyperglycemia and results presented in frequency tables, and bar charts.

Logistic regression analysis was conducted to establish variables that were independently associated with hyperglycemia development in this population. A p-value of < 0.05 was considered statistically significant.

Results

The population studied was largely female (62%). The mean age of participants was 43.7 (SD 10.6) years. More than half of the population were in the middle-age bracket (41-60 years, 63.6%). Hyperglycemia was observed in 200 (55.9%), measured via glycated hemoglobin and/or random blood sugar. On bivariate analysis advanced age (OR=1.7; 95% CI, 1.1 – 2.7); female gender (OR= 1.6; 95% CI, 1.1 – 2.5), overweight (OR= 1.8; 95% CI, 1.1 – 2.9) and obesity (OR= 3.1; 95% CI, 1.7 – 5.6) were found to be associated with hyperglycemia development in this study population. However, on multivariate analysis, only age >40 years, overweight and obesity were significantly associated with development of hyperglycemia (aOR=1.7; 95% CI, 1.1 – 2.7; p= 0.026), (aOR=1.7; 95% CI, 1.1 – 2.8; p = 0.026) and (aOR=3.1; 95% CI, 1.7 – 5.5; p<0.001), respectively.

Conclusion

The study showed a consistent hyperglycemic risk for patients on dolutegravir and confirmed the usefulness and safety of glucose monitoring plan for patients on dolutegravir. Early diagnosis of dolutegravir associated hyperglycemia is important in providing optimal effective treatment while preventing complications for patients on antiretroviral therapy. The study has also highlighted the importance of routine body weight monitoring for all patients on dolutegravir.

CHAPTER ONE: INTRODUCTION

1.1 Background

The Human Immunodeficiency Virus (HIV) remains a global public health concern. Worldwide, by December 2018, approximately 37.9 million persons were infected with HIV, of which about 23.3 million (62%) people were on antiretroviral therapy (ART) (1). In Kenya, approximately 1.6 million people are infected with HIV, of whom 69% and 61% of adults and children, respectively, were on ART by December 2018 (2). Two primary goals of ART are to suppress viral replication and to preserve and restore the number of functional immune cells (3).

The World Health Organization (WHO) recommends adoption of antiretroviral regimens with high potency, lower incidences of adverse events, high genetic barrier to resistance, improved efficacy across different populations. To this end, dolutegravir (DTG) based highly active antiretroviral therapy (HAART) regimens were recommended as the preferred first- and second-line treatment for all populations. It was realized that utilization of optimized drug regimens could improve treatment durability and quality of care for people living with HIV (PLHIV) (4).

Dolutegravir remains the latest ART agent approved by Food and Drug Administration (FDA) for the management of HIV-1 infection, used in combination with other antiretrovirals (ARVs). Dolutegravir, an integrase strand transfer inhibitor (INSTI) possesses unique properties like un-boosted daily dosing, improved barrier to resistance and minimal cross resistance to the first generation INSTIs (5).

Although a number of studies have shown that DTG possesses improved safety profile, tolerability, effectiveness and durability compared to efavirenz, currently there is lack of data to support the switching of patients from their current regimens directly to DTG based regimens in situations of detectable or unknown viral load. More trials may be required for better understanding of the consequences of this treatment switch (6). WHO fully supports the transition to dolutegravir-based regimens, to optimize ART, especially in regions with suspected pre-treatment failure to either efavirenz or nevirapine, of more than 10%, as commonly seen in Southern and Eastern Africa. (7).

The findings of a randomized controlled trial done in Cameroon to evaluate a DTG- over an EFV 400mg-based regimen as first line treatment involving 616 patients, followed over 48weeks also supported the use of DTG based regimen as a preferred first line to preserve future treatment options, having established that DTG was non-inferior to EFV 400mg in the study population. However, the overall safety and tolerability of both drugs was comparable in both arms (8).

In Kenya, based on the current ART guidelines, the preferred first-line regimen for adolescents and adults ≥ 15 years or ≥ 35 kg body weight is DTG combined with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). Based on WHO recommendations (9), the Ministry of Health (MOH) currently recommends that all virally suppressed patients on first line treatment be switched to a DTG based regimen, including children weighing above 20 kilograms (kg), and that efavirenz (EFV), combined with TDF and 3TC be reserved only for expectant mothers and women of childbearing potential, not on effective contraceptives (3). However, as with all medications, treatment decisions should be based on informed healthcare team discussions, with the healthcare provider striking a balance between benefits and potential risks (4).

Recently, some reports associated the use of DTG with hyperglycemia development (10,11). Hyperglycemia is clinically defined as a random plasma glucose >11.1 mmol/L or fasting serum glucose level of>7.0 mmol/L and/or proportion of glycosylated hemoglobin (HbA1c) of ≥6.5% (3,12).

Data on prevalence of hyperglycemia and diabetes associated with ART among PLHIV is very scarce, with those reported mainly arising from use of PIs (13,14) and few cases from DTG. Unlike hypoglycemia, persistent hyperglycemia is often benign, persisting without any clinically significant signs and symptoms. Uncontrolled hyperglycemia is usually associated with clinical adverse events, and it has been recognized to enhance oxidative stress that contributes to increased risk of coronary and renal complications in affected patients(13).

Prolonged use of ART is associated with several metabolic syndromes that can all manifest with hyperglycemia, depending on the ART regimen used (15). Some newly introduced medications for HIV management have recently been identified to either elicit hyperglycemia in non-diabetics or worsen blood glucose control in diabetic patients.

Reports have linked protease inhibitors use with the pathogenesis of insulin resistance and hyperglycemia development, and a causal relationship was reported in about 5 % of HIV patients (11). A study reported an increased insulin resistance and the development of overt diabetes with use PIs, and found a 7% incidence of new-onset diabetes as diagnosed by random blood sugar and OGTT. A conclusion was made that PI–associated diabetes involved peripheral insulin resistance, relative to high levels of glucagon and abnormal BMI. When PIs were discontinued and replaced with other medications in this study population, plasma glucose normalized and hyperglycemia reversed, confirming the role of PIs in hyperglycemia pathogenesis (14).

One study directly linked the use of PIs to pure hyperglycemic hyperosmolar syndrome (HHS). It is therefore important to regularly monitor all patients undergoing ART for new-onset hyperglycemia (13). A number of cases of dolutegravir use and hyperglycemia development after a short period of time have also been reported, the mechanism not well understood.

1.2 Problem Statement

Introduction of HAART has led to sustained HIV-1 replication suppression, but also development of metabolic syndrome, conferring an increased risk of morbidity and mortality due to premature cardiovascular complications (15). A number of abnormalities in both lipid and glucose metabolism have been frequently reported with newer antiretrovirals (16).

Since the approval and introduction of DTG in the Kenyan treatment guidelines as first line regimen, a number of patients are already on the drug, with an intention of switching all patients >20kg to DTG-based regimens for treatment optimization.

From the Ministry of Health Antiretroviral Drugs Supply Chain Management Tool, KNH: Web ADT Version 3.4.1.data base, about 62% of the patients on HAART were already on DTG by the end of 30 November, 2019. However, there is no study done nor published in Kenya or Sub-Saharan Africa regarding association between DTG use and hyperglycemia development as claimed by some observational studies in different populations.

The study therefore sought to assess the risk of new-onset hyperglycemia and documented the prevalence of DTG associated hyperglycemia among PLHIV on HAART at Kenyatta National Hospital.

1.3 Justification of the study

Multiple studies have established that regular monitoring and strict glycemic control (HbA1c <7.0%) prevents development of diabetes mellitus and its complications(17).Other studies have also indicated that hyperglycemia remains a clinically independent risk factor for myocardial abnormalities in nondiabetics (17).

A persistent high fasting plasma glucose>6.1 mmol/L and glycated hemoglobin >6.1% , induced by some of the ART regimens, have been associated with a 2-fold increased risk of death from cardiovascular diseases(17).Studies have suggested the need for stricter glycemic control for prevention of both macrovascular and microvascular complications among patients on DTG based regimens (10). The findings of this study are intended to inform baseline and follow-up investigations, monitoring parameters and management of patients on DTG based ART, thereby reducing the likelihood of hyperglycemia and its complications.

1.4 Research Questions

1. What is the prevalence of hyperglycemia in patients receiving dolutegravir based regimen at KNH?
2. What are the patient factors associated with the development of hyperglycemia among patients on DTG?
3. What are the healthcare provider factors associated with hyperglycemia development in this patient population?

1.5 Objectives

1.5.1 Main Objective

To determine the prevalence of dolutegravir associated hyperglycemia and its covariates among adult persons living with HIV on antiretroviral therapy at Kenyatta National Hospital.

1.5.2 Specific Objectives

1. To determine the prevalence of dolutegravir associated hyperglycemia.
2. To determine patient related factors associated with development of hyperglycemia in the study population.
3. To determine healthcare provider factors associated with development of hyperglycemia in the study population.

1.6 Significance and anticipated output

Given that ART is long-term in PLHIV, these patients are pre-disposed to drug induced toxicities arising from ART. Strict baseline investigations and monitoring of patients on DTG and protease inhibitors, the recommended first- and second-line therapies respectively, for development of drug-induced hyperglycemia becomes important for improved clinical outcomes and minimize hyperglycemia associated complications.

Regular monitoring of blood sugar is one way of ensuring that the level remains within the acceptable range, as patients continue taking their medications. Early detection of hyperglycemia improves treatment outcomes and minimize associated complications. Patients and/or their care givers will also be sensitized on regular blood sugar monitoring, early detection and management of hyperglycemia by their care providers

1.7 Delimitations

This was a real-life study, conducted among patients on care and follow-up at KNH CCC for at least three months. Therefore, the clinical data was readily available at the IQ-care data base, to confirm information given by patients, or those that they could not recall.

1.9 Conceptual Framework

Hyperglycemia is a dependent variable that arises from uncontrolled plasma glucose levels. There are various independent variables that also impact on plasma glucose levels among patients on DTG, consequently resulting in observed complications associated with poor glycemic control. The variables cut across care providers and patients, with DTG intervening in the hyperglycemia development pathway.

Healthcare provider factors include the prescribed medications such as DTG, inadequate patient education on methods of glycemic control and irregular blood sugar monitoring. Patient-specific non-modifiable factors include age and gender. Modifiable factors such as dyslipidemias, obesity and sedentary lifestyle, cardiovascular complications such as high blood pressure and renal and liver insufficiencies also influence plasma glycemic states (18). All these variables interact in a complex way to influence glycemic control among patients on HAART (Figure 1.1).

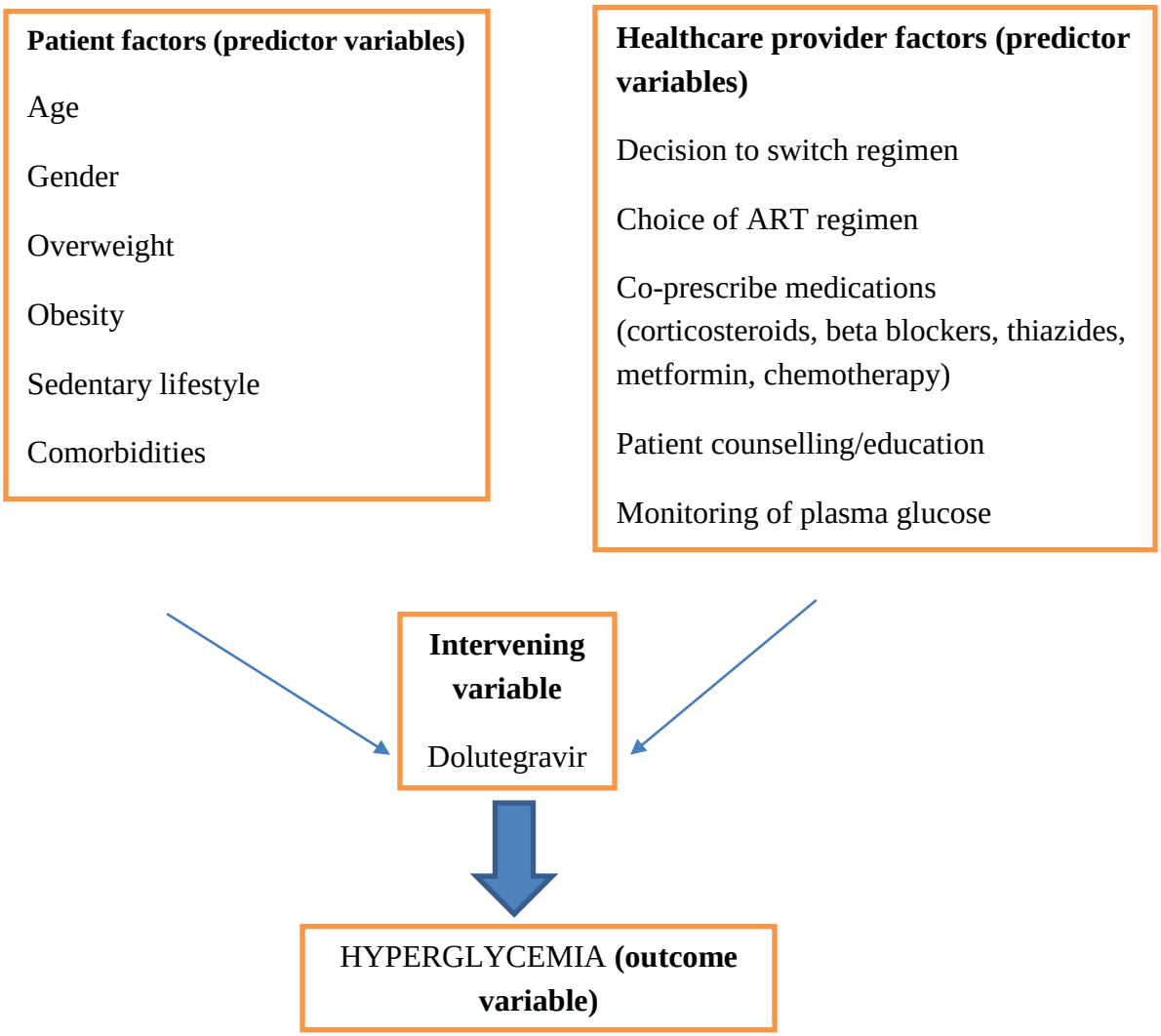

Figure 1.1: Conceptual framework

CHAPTER TWO: LITERATURE REVIEW

2.1 Antiretroviral Therapy, Treatment Goals and Considerations

Antiretroviral therapy has led to a marked reduction in HIV-related morbidity and mortality, by transforming the infection into a more manageable condition(19). Two primary goals of ART are to maximally suppress viral replication, thereby delaying selection of drug resistance mutations, and to preserve and restore immune function(3).

To achieve viral suppression, a combination of ARVs is required, a minimum of three drugs from different antiretroviral medications classes (3). The initial antiretroviral combination therapy consisted of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and another third drug. This can be a NNRTI, a protease inhibitor or an integrase inhibitor. There is no clear evidence that definitively recommends one class over the other, and selection in most cases is dependent on patient-specific factors and provider preferences (20).

The majority of recommended regimens have relatively comparable efficacy, but usually vary in side effects profile, pill burden, potential for drug-drug interactions and propensity to select for resistant mutants if adherence to ART is suboptimal (19). Before initiation of ART, the baseline patient characteristics, potential side effects, patient co-morbidities, possible drug-drug interactions, regimen convenience as well as any information regarding drug resistance should be considered. This guides the choice and design of patient-specific regimen, enhances adherence and supports long-term treatment success (21).

In recent years, integrase strand inhibitors have increasingly dominated treatment developments in management of HIV-1 infection, with dolutegravir being approved for use in 2013 (22).

To optimize antiretroviral therapy, the current clinical ART guidelines recommend that all virally suppressed patients on first line ART be switched to DTG based regimen, even if they are currently tolerating their regimen well, except for a few patient populations. DTG is currently the preferred first-line ART, used in combination with other ARVs for children >20kg, adolescents and adults (3).

2.2 Pharmacology of dolutegravir

Dolutegravir acts by inhibiting catalytic activity of HIV integrase, the enzyme that is responsible for insertion of the viral genomic material into the host cell DNA, usually a vital step in HIV replication (23). Specifically, it inactivates the integrase enzyme by binding magnesium on its active site (24).

It is an orally administered once daily pill, rapidly absorbed, with a half-life of about 12 hours. It requires no pharmacological boosting, and its antiviral activity is strongly correlated to its trough concentrations (25). It has minimal urinary excretion, with hepatic glucuronidation by UDP-glucuronosyltransferase 1A1 being the predominant metabolic pathway (26).

2.3 Role of dolutegravir in antiretroviral therapy

DTG is the latest FDA approved ART agent, recommended by WHO for management of HIV-1 infection in adolescents and adults (5). Some of its known unique properties include superior efficacy, un-boosted daily dosing, tolerability, high barrier to resistance, especially in treatment naïve patients; and treatment durability, compared to the existing first-line regimens (7). Owing to the favorable DTG characteristics, its use for treatment of HIV-1 has rapidly increased since 2013 (27).

Clinical trials evaluating dolutegravir as a 50-mg daily dose in both treatment- naive and experienced patients concluded that combining DTG with abacavir (ABC) and 3TC was superior to efavirenz (EFV) combined with emtricitabine (FTC) and TDF. It was also found to be superior to both PI based regimens, regardless of baseline viral load, and to the first generation INSTI, raltegravir at 400mg twelve hourly (5).

DTG-based regimens are now the recommended preferred first- and second-line treatments, when combined with other ARVs, for all populations. The WHO fully supports optimization of ART by use of DTG-based regimens, especially in regions with suspected pre-treatment drug resistance to NNRTIs of more than 10% (7).

Based on the current National ART guidelines, the preferred first-line regimen for adolescents and adults ≥ 15 years or ≥ 35 kg body weight is DTG combined with3TC and TDF or ABC (3).

As supported by the WHO, the current MOH recommendation and practice is that all virally suppressed patients on first line treatment be switched to a DTG-based regimen, including children weighing above 20kg, with exception of pregnant women, adolescents and women of childbearing age, not on effective contraception (28).

2.4 Dosing of dolutegravir

The recommended dosing is standard in all the populations, at 50 mg once daily, preferably in the morning. For patients on rifampicin, or with suspected or confirmed INSTI resistance, the recommended dose is 50mg twelve hourly (Table 1) (3)**.**

Table 2.1: Dosing and administration of dolutegravir

AGE/WEIGHT	DOSE (mg)	FREQUENCY	REMARKS
≥ 15 years or ≥ 35kg body weight	50	24 hourly	Preferably taken in the morning, as a fixed dose formulation
≥ 15 years or ≥ 35kg body weight	50	12 hourly	Patients on rifampicin, a fixed dose in the morning, and a DTG tablet after twelve hours.
≥ 15 years or ≥ 35kg body weight	50	12 hourly	Confirmed first generation INSTI resistance
Children and adolescents>20kg and < 35kg	50	24 hourly	MOH currently recommends use of 50mg DTG tablet 24-hourly, just like adults with no history of INSTI resistance
Children below 20 kg, pregnant mothers, reproductive women not on contraceptives	-	-	Not recommended

2.5 Drug interactions with dolutegravir

Dolutegravir rarely induces or inhibit cytochrome P450 isoenzymes, therefore has modest drug interaction profile. Its mode of action involves inhibition of integrase enzyme by binding the magnesium on its active sites, therefore prone to chelation-type drug interactions, when given concurrently with di- and/or trivalent metal cations. Antacids and mineral supplements, frequently taken by PLWHIV significantly lower the dolutegravir plasma levels, and if must be given, a two hours separation before, or a six hours post dolutegravir dose should be considered(24,25).

Another study recommended close monitoring and where necessary, dose adjustments of metformin when co-administered with DTG. It revealed a significant increase in metformin serum concentrations when administered at the same time with DTG, which inhibits OCT2 and toxin extrusion transporter 1 (MATE 1), both of which are involved in the disposition of metformin (29). However, the relevance of metformin dose adjustment was disputed by another study involving HIV infected diabetic patients on DTG (30).

2.6 Adverse effects of dolutegravir

Despite reports of better tolerability and effectiveness of DTG than EFV, safety concerns have already been raised in some clinical settings (31).These concerns are arising now as the medication is being used by many patients and for longer periods of time, than was tenable in clinical trials (32).

Most of the documented adverse effects from trials involve the nervous, hepatorenal, gastrointestinal, and immune systems. Neurotoxicity, headache, insomnia, increased serum creatinine, nausea, diarrhea and hypersensitivity reactions were some of the commonly reported adverse effects. A few cases of dolutegravir-induced hyperglycemia have also been reported (10,11).

Neurotoxicity led to discontinuation of the drug in a number of patients. In a retrospective analysis of more than 1700 patients, looking at the potential neurotoxic effects of INSTIs, about 6% of patients on dolutegravir were discontinued due to neuropsychiatric symptoms within a year of initiation (32,33).

Four patients were reported to have experienced an onset of psychiatric troubles or an exacerbation of psychiatric symptoms after starting DTG.
Of the four, three patients recovered after discontinuing DTG. It was hypothesized that the direct CNS toxicity was related to DTG's high CNS penetration effectiveness (CPE) (34).

In another cohort study in Netherlands involving 556 patients on DTG, after a median 225 days of follow-up, DTG was stopped in 85 patients (15.3%). Among those stopped, intolerability comprised 13.7%, while 5.6% of DTG discontinuation were due to insomnia and sleep disturbances.

The neuropsychiatric symptoms (anxiety, psychosis and depression) that predominantly resulted in switching from DTG regimen, comprised 4.3% of the discontinuations (35). Other studies cited female gender, increased age and obesity to be associated with development of the observed neuropsychiatric adverse effects in patients on DTG (36).

Among the under-published adverse effects of DTG is hyperglycemia. Several case reports have been documented, associating the use of INSTIs in general, with hyperglycemia. A 44-year-old male HIV patient, with hemophilia A, who was switched from EFV to raltegravir, was reported to have developed DM four months after the switch. When raltegravir was withdrawn and the patient switched back to EFV, it was reported that the HbA1c levels normalized, and the patient stopped exogeneous insulin completely (37).

DTG- induced hyperglycemia was also reported in a case study involving 48-year-old transgender patient initially on EFV/FTC/TDF, then switched to DTG/FTC/TDF. After one month of DTG use, her random blood sugar was 467mg/dL (25.94mmol/L). Two months later while still on DTG, she presented with symptoms consistent with hyperosmolar hyperglycemic state. At the time, her glycated hemoglobin had risen from 5.9% during initiation to 12.9%, with a plasma glucose reading of 1700mg/dL (94.4mmol/L). Several other laboratory abnormalities were also noted (11).

A rather similar case of DTG induced hyperglycemia was reported in an African-American male. Although the patient had other co-morbidities, he had normal glycemic control during DTG initiation, but three weeks later, both plasma glucose and HbA1c had risen from 65mg/dL and 6.2%, to 949mg/dL and 14.9% respectively (10).

In both cases, there was no evidence of other identified triggers of hyperglycemia, and the glycemic control markedly improved after discontinuation of DTG (10,11).

Similar cases were reported in other observational studies. A group of researchers reported cases of 3 patients, 2 men and a woman, all >44 years old, who developed acute hyperglycemia, as measured by plasma glucose and HbA1c levels, while receiving INSTI based regimens. All the three patients had metabolic syndromes, but had normal levels of HbA1c during initiation of the drugs. The 44- and 55-year-old man and woman, on elvitegravir (EVG) and DTG respectively, developed diabetic ketoacidosis (DKA) more than 12 months after initiation. The third patient, a 66-year old man on DTG developed hyperosmolar hyperglycemic state within 6 months of therapy (38).

A cohort study involving 2260 PLHIV reported weight gain with DTG use. The study was analyzing reasons for discontinuation of DTG-based regimen and established that out of 517 patients who discontinued treatment, 7% were due to abnormal weight gain ranging from 4 to 12kg (39).

This was supported by another study that assessed changes in weight in virologically suppressed patients, switched from EFV-based to INSTI-based regimens. After 18 months of INSTI therapy, from the 136 patients switched to INSTIs, the most weight gain was noted among patients on DTG, compared to other INSTI-based regimens; with an average weight gain of 2.9kg, compared to 0.9kg noted among patients switched to DTG-based and those who continued with EFV-based regimens respectively(39).

Dolutegravir use have been associated with increased BMI and worsening of insulin resistance. This was supported by the US NA-ACCORD study that observed that, after 3 years of INSTI therapy, there was an increase in body mass index of between 25 $kg/m^2$and 29.9 kg/m^2 in 22% of patients who initially had normal body mass index ranging between 18.5$kg/m^2$to 24.9 kg/m^2.

The same study observed obesity (BMI >30 kg/m^2) in 18% of the patients who were initially overweight. The increases in both cases were largest in women and blacks (40).

2.7 Mechanisms of dolutegravir - induced hyperglycemia

The exact mechanism of how dolutegravir causes the development of hyperglycemia is not clear, but some mechanisms have been hypothesized. A study reported that DTG has the ability to chelate magnesium at the active site of integrase enzyme. Low magnesium levels affect glucose transport by GLUT-4 receptor resulting in increased glucose production by the liver. Inhibition of insulin release and signaling transduction also contributes to insulin resistance (10,11).

Modulation of insulin action is dependent on the concentration of intracellular magnesium concentration. From the results of a study establishing the role of magnesium in insulin action, low intracellular magnesium concentration, as seen in non-insulin dependent DM and hypertensive patients, interferes with the activity of tyrosine-kinase at the insulin receptor level, resulting in intracellular calcium level increase. Hyperglycemia then results due to impaired insulin action(41).

A cross-sectional comparative study involving 192 patients with metabolic syndromes (MS) in one arm and 384 control subjects on the other arm, all matched for age and gender found an association between low serum magnesium levels, DM as well as high blood pressure. In this study, MS was defined by presence of hyperglycemia, high blood pressure (≥160/90 mmHg), dyslipidemia and obesity. Low plasma magnesium concentration was reported in 65.6% and 4.9% of participants with and without MS respectively, $p<0.00001$. However, high blood pressure and dyslipidemia were found to be strongly associated with low serum magnesium concentrations, compared to hyperglycemia (42).

Another evidence suggested that DTG, is linked to greater weight gain in people initiated on it, hence insulin resistance. However, the reasons for this are still not well understood (43).

Other studies established a causal relationship between INSTIs, specifically dolutegravir and raltegravir; and changes in the structure of fat cells that can promote obesity. Elevation of free fatty acids seen in insulin resistance results in inhibition of glucose uptake by skeletal muscles, stimulation of hepatic gluconeogenesis and hyperglycemia.

Some cohort studies and clinical trials also established an association between use of DTG and the likelihood of substantial weight gain, causing insulin resistance. In these studies and trials, the mechanism of fat gain and interference with metabolism by INSTIs was not clear, but a French research group suggested direct effects on adipose tissues, promoting weight gain (44). These studies revealed that DTG exposure was associated with greater adipocyte differentiation and greater expression of markers associated with lipid storage. It established that cells exposed to DTG had increased levels of lipid accumulation, lower levels of leptin and adiponectin, and reduced uptake of glucose, compared to control samples (44).

The weight gain observed in patients on DTG was supported by findings from two studies done in Africa, NAMSAL study (Cameroon) and ADVANCE study (South Africa). In the former, after 48 weeks of follow-up of 613 adult patients on DTG and EFV based regimens, those on the DTG arm had gained a median of 5kg with a +1.7 BMI increase, compared to those on EFV arm, with a median of 3kg weight gain, with a +1.2 BMI increase ($p < 0.001$). The study reported a significant proportion of patients on DTG arm that gained adequate weight to be classified as obese, compared to EFV arm (12% vs 5%) respectively ($p <0.01$)). The ADVANCE study had similar findings, a greater weight gain of +3kg in DTG arm, compared to + 1kg in the EFV arm, after following 1053 adults and adolescents for 48 weeks (45).

2.8 Risk Factors Associated with dolutegravir induced-hyperglycemia during therapy

Besides the documented risk factors for development of hyperglycemia in diverse populations, a number of factors have been found to play important roles in its development among PLWHIV on HAART.

2.8.1 Patient specific factors

These include; HIV infection itself, the viral load, CD4 T- cell count, duration of HIV infection, long term exposure to HAART (46,47). Studies have hypothesized that an interaction between HIV infection, ART and chronic inflammation seen in this population can significantly contribute to development of hyperglycemia. Other contributing factors include older age, male gender, microbial co-infection, especially with hepatitis B or C virus, co-morbidities and concurrent medication use, especially those that interfere with normal glucose homeostasis (47).

Studies have reported obesity and weight gain as important risk factors for development of insulin resistance and type 2 DM, among other metabolic syndromes. This is evidenced by changes in both inflammatory cells and biochemical markers seen in HIV infection, where the sub-acute and chronic state of inflammation usually accompanies both hepatic and adipose tissue excess lipid accumulation (48).

Another study involving 16,000 individuals in Taiwan, investigating an association between serum triglycerides (TGs) and HbA1c, one of the biomarkers of glycemic control, examined possible relationship between circulating TGs and HbA1c. Their findings confirmed that a single-unit (mg/dL) increase in serum triglyceride was associated with a significant increase of approximately 10 units of glycated hemoglobin ($p = 0.029$, 95% CI =1.05-18.95), and concluded a relationship between higher serum triglycerides and elevated glycated hemoglobin proportion (49).

2.8.2 Healthcare provider associated factors

These include, but not limited to inadequate patient education on methods of glycemic control, irregular blood sugar monitoring and the co-prescribed medications. Chronic illnesses such as HIV require healthcare systems that support chronic care and regular patient monitoring, and their management should be integrated in comprehensive care centers, including at the primary care level.

The guidelines recommends that for monitoring parameters unable to be performed at the care site, all possible arrangements should be made to have them done at a regional reference laboratory (3).

Studies have shown that the care provider attitude, beliefs and knowledge about hyperglycemia and its complications also influence its management(50). A study looking at the role of psychological motivation and patient education in regular glucose monitoring established that achieving and maintenance of near-normal plasma glucose levels require regular patient education and motivation in adoption of a variety of healthy behaviors. This requires participation of both the patient and the caregiver (51).

Clinicians have an influence on the patient's perception on his/her health status through effective communication skills, especially if these are integrated in a healthcare system. Once barriers to achievement of normoglycemia are identified, measures necessary can be taken by both clinicians and the patients to improve the glycemic control and prevent development of hyperglycemia and its complications (50).

This was supported by another study looking at mechanisms underlying relationship between health literacy and glycemic control in Americans. The study established that patients with stronger health literacy skills demonstrated better glycemic control (52).

Results of regular monitoring are useful in assessment of treatment efficacy and guides adjustment in medical nutrition therapy, physical activity, medications and doses required to achieve optimal glycemic control (51). Kenyan ART guidelines recommend evaluation of blood glucose, either fasting or random blood sugar at baseline for all HIV patients, and then annually if baseline screening is normal.

However, for patients with pre-diabetes, their blood sugars, FBS and/or HbA1c should be monitored every 3 months besides lifestyle modifications (3).

Other studies recognize that regular monitoring for new onset hyperglycemia in all patients at risk of hyperglycemia development from their prescribed medications is important(12).

A study evaluating the impact of pharmaceutical care interventions on glycemic control in Jordan demonstrated improved glycemic control and lipid profile among participants and suggested benefits of integration of clinical pharmacist services into the healthcare team in management of patients at risk of hyperglycemia(53).

2.9 Literature gap

Since the introduction of dolutegravir in the Kenyan Antiretroviral therapy clinical guidelines, a number of patients are being switched to DTG-based regimens as per the MOH recommendations. The prevalence of dolutegravir associated hyperglycemia among patients on HAART at Kenyatta National Hospital is unknown. So far, there is no published data on the same in Kenya nor Sub Saharan Africa.

This study therefore seeks to fill this gap and inform measures that need to be taken to closely monitor all patients on DTG for prevention and/or early recognition and management of DTG associated hyperglycemia.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

A hospital setting cross-sectional study was conducted in the KNH comprehensive care center. The design was the most appropriate for descriptive analysis and for evaluating the burden of a condition in a specified population in a given point in time(54).

3.2 Study Site

The study was conducted at Kenyatta National Hospital, a referral healthcare facility in Kenya, that also serves as a teaching hospital for various medical training institutions. The health facility is strategically located around Upper Hill area, along Hospital road, immediate west of Upper Hill area, near the central business district of Nairobi. Nairobi County is the most densely populated county in Kenya. KNH is a tertiary care hospital, one of the largest healthcare facility Africa, with a bed capacity of about 1800 and about 50 wards. It has about 22 outpatient specialized clinics offering specialized healthcare services, not only to patients from Nairobi, but also referrals from other counties. Comprehensive Care Clinic (CCC) is located at the ground floor, off Hospital Road, opposite Kenyatta National Hospital post office. The clinic runs from Monday to Friday, from 8am to 5pm, with more than 300 patients being reviewed on a daily basis, others coming specifically for medication re-fill; as per average daily work load statistics.

3.3 Study Period

The data collection for this study was carried out between 30th July, 2020 and 2nd Sept. 2020.

3.4 Target Population

This study targeted adult (> 18 years) patients receiving dolutegravir based HAART regimen, enrolled and on follow-up at the CCC at Kenyatta National Hospital, coming for their clinic and/or pharmacy appointment(s).

3.5 Study Population

These included all HIV patients enrolled at KNH comprehensive care clinic, on dolutegravir, combined with appropriate backbone for at least 3 months. The patient was either treatment naïve or switched from a previous regimen to DTG-based regimen, and had come to the clinic for either review or medication re-fills. He/she must have also consented in writing to participate in the study and willing to proceed to clinic laboratory for sample collection for both random blood sugar and HbA1c measurements.

3.5.1 Inclusion Criteria

Participant was included in the study if:

- He/she was an adult patient (>18 years) of sound mind, on follow-up at KNH CCC and on dolutegravir-based regimen for not less than 3months.
- An informed written consent was obtained.
- He/she had no documented diagnosis of diabetes mellitus type 1 or type 2, or history of DM at the time of study.
- He/she was not on any hypoglycemic agent(s).

3.5.2 Exclusion Criteria

Participant was excluded from the study if:

- He/she was previously on protease inhibitor-based regimen.
- He/she was on cancer chemotherapy and/or other non-HAART hyperglycemia inducing agents.
- He/she had end stage renal disease or uncontrolled hypertension
- She was pregnant at the time of recruitment.

3.6 Case definitions

Cases were defined as laboratory reports of hyperglycemia, from RBS and HbA1c measurements, based on Kenyatta National Hospital reference ranges (appendix VIIB). Hyperglycemia diagnosis was made by glycosylated hemoglobin (HbA1c) measurement≥6.1% and/or a random blood glucose ≥ 7.2 mmol/L.

3.7 Sample Size Determination and Sampling Technique

3.7.1 Sample size

Approximately 9,555 adult active patients were on HAART at KNH clinic by November 2019. From this population, about 5891 (62%) were on DTG-based regimen, of whom 3303 were female, and 2588 were male. A representative sample of 358 adult patients was drawn from this population.

Due to lack of published data on prevalence of DTG associated hyperglycemia in blacks, and since the mechanisms of development of hyperglycemia in both DTG and PIs use are rather similar (55), an assumption was made that the prevalence of DTG associated hyperglycemia was approximately the same as that of PIs (37.0%), as reported from a South African study in blacks (56). The prevalence of protease inhibitors associated hyperglycemia was therefore used as proxy, and the sample size determined using Cochran formula for calculating sample size in descriptive studies (57).

$$n = \frac{Z^2 p(q)}{e^2} = \frac{1.96^2 \times 0.37 (1-0.37)}{0.05 \times 0.05} = 358.2 \text{ persons}$$

$$\approx 358 \text{ persons}$$

Where: **n** = sample size, **Z** = statistic for 95% level of confidence, value =1.96.

p = estimated proportion of adult patients on DTG-based regimen at the clinic, 37%.

q = 1-p**, e** = level of precision which in this study will be set at 5% (0.05)

3.7.2 Sampling Technique

A consecutive sampling technique was employed. After a thorough explanation of the participation conditions, every participant who met the inclusion criteria, and was willing to participate was enrolled in the study. Consecutive sampling was applied to get the desired sample size of 358 participants. Approximately 57 PLHIV on DTG-based regimen were visiting the clinic per day during working hours for services.

3.8 Patient Recruitment

Recruitment of the participants was done by the principal investigator (PI), assisted by research assistants within the clinic, which included a medical officer intern, laboratory technologist, a pharmacist intern and a data clerk. They were briefed on the objectives of the study and its requirements; and their support sought. At the patient's exit point, in a separate room, the purpose of the study and study objectives were explained and patient taken through the consenting process. Concerns from the participants relevant to the study were addressed as they arose. Assessment of eligibility for participation was done using eligibility assessment form (appendix I), and a written and signed informed consent obtained from each and every participant.

Those unable to read and/or write, and therefore unable to fill the consent form (appendix II) were assisted by the principal investigator or research assistants. Those included in the study were briefed on what was meant by random blood sugar and HbA1c and their implications on their health. All eligible participants were given unique identity codes, used for identification throughout the study and data analysis period. All the medications the participant was on were also documented as reported by the patient.

3.9 Data Collection

3.9.1 Research instruments

The main data collection tools included a calibrated glucometer in working condition (ACCU-CHEK Instant; SN: 95902758012, LOT No. 20171073, REF: 07819315340, expiry date: 18th May 2021), used together with valid glucometer strips (ACCU-CHEK Instant; SN: 529283051913, LOT No. 300919, Man. date: 13th Dec. 2019, expiry date: 11th June, 2021).

HbA1c measurements were done using a calibrated HbA1c machine (DIRUI CS 300B Auto-Chemistry Analyzer, SN: S150300BCS0341MA), used with approved reagents (DIRUI HbA1c, Lot. No. 20200225, expiry date,24th Feb. 2022), calibrator (Stanbic Direct HbA1c Calibrators, Lot. No. 192191, expiry date,31st Jan. 2022) and control (Stanbic Direct Glycohemoglobin CTRLS, Lot no. 201041, expiry date, 31st Oct. 2021). All procedures were as per approved KNH laboratory medicine standard operating procedures (appendix VI).

To mitigate against obstacles such as language barrier and low literacy levels, structured questionnaires (appendix III), administered in the form of researcher-guided interview were also used to collect participants demographic characteristics and clinical data. The IQ-Care patients data base at CCC was used to obtain clinical data and other information relevant to the study.

3.9.2 Data collection Techniques

3.9.2.1 Sociodemographic and clinical data

Structured questionnaires were used for collection of all the necessary information relevant to this study. They were structured to have sets of closed-ended questions, that were administered to participants by the researchers after recruitment. The PI and the research assistants filled the questionnaires by indicating participant responses onto the spaces provided.

Where the current weight could not be established, the last measured height and weight (within 3-6 months), obtainable from the data base, were used to determine the current BMI, that was used for comparison with the BMI during initiation of DTG.

Both values were recorded in the questionnaire. Age, sex and level of physical activity at leisure time, and any other patient information relating to their co-morbidities, including medications used were all documented, as either reported by the patient, or abstracted from the patient's data base, using the data abstraction form (appendix IV).

3.9.2.2 Laboratory data

HbA1c and random plasma glucose measurements were done at the clinic's laboratory as per Kenyatta National Hospital Laboratory Medicine standard operating procedures (SOPs) and quality control protocols for glycated hemoglobin enzymatic assay (58) and finger prick blood glucose testing (59) respectively (appendix V).

These were done at the clinic laboratory and the results were considered valid only if documented as HbA1c or RBS by the laboratory staff. Results were collected on a daily basis by the PI assistant and fed onto the questionnaires. Values of RBS and HbA1c $\geq$ 7.2mmol/L and $\geq$ 6.1% respectively, were considered hyperglycemia.

3.9.3 Study Variables

The primary outcome variable was hyperglycemia as per the KNH glycemic ranges (appendix VII B). This was the dependent variable, which was determined from the laboratory results of plasma glucose and proportion of glycated hemoglobin. The predictor (secondary) variables were the healthcare provider and patient factors, both modifiable and non-modifiable.

The healthcare provider factors considered included-prescribed medications used together with HAART, that could affect glucose homeostasis; inadequate patient education on glycemic control, healthy lifestyle and side effects of drugs. Lack of screening for blood sugar at baseline as recommended in the guidelines, during initiation of DTG and irregular monitoring of plasma glucose for patients on DTG could all have contributed to the undetected hyperglycemia. The modifiable patient factors considered in this study included overweight, obesity, sedentary lifestyle, herbal medicine, alcohol use, smoking, dyslipidemias, cardiovascular complications like high blood pressure, renal and hepatic insufficiencies.

The non-modifiable patient factors included age, sex, and gender. Data on these predictor variables were sourced through questionnaire-guided interview and clinical data from the data base.

3.10 Quality assurance of data

3.10.1 Training of research assistants

The principal investigator (PI) identified research assistants from the healthcare team, with basic knowledge on HIV/AIDS care. The PI explained in details the nature, objectives and purpose of the study, before commencement of data collection. The assistants included a medical laboratory technologist, a pharmacist intern, a medical officer intern and a data clerk.

The explanation entailed a practical demonstration on utilization of data collection tools, accurate data entry and safe storage of data. Ethical considerations and overall conduct expected of a scientific research were explained by the PI. Their competence was assured by the PI during piloting of the data collection tools before commencement of data collection.

3.10.2 Pilot study

Data collection tools were piloted using 10 patients from the target population, who after explaining the purpose of the study and consented, willingly agreed to participate in the study.

10 copies of the questionnaires intended to be used in the study were administered to the participants, blood samples taken and coded, then and blood sugars measurements done for both RBS and HbA1c at the CCC laboratory. For reproducibility of HbA1c results, the same coded blood samples were subjected to same analytical procedures at a different biochemistry laboratory in the main hospital (laboratory number 16). The differences in the results obtained in both laboratories were insignificant (± 0.03). All the tools were therefore found to be suitable for achievement of study objectives and adopted for use in data collection.

3.10.3 Validity

Validity of the study was assured by strict adherence to laid down good laboratory practices, accuracy and completeness in documentation of laboratory results (coding and specification of RBS and HbA1c results), neatness and completeness of questionnaires, as well as accuracy of data abstraction from patient's clinical records to enable collection of all the relevant data, with regard to study objectives. The questions were made simple, clear and concise, and guided by the study objectives.

3.10.4 Reliability

Data collection tools were pre-tested during the pilot study, for reproducibility and reliability of the results before the actual study.

3.11 Data management

Each of the participants' filled questionnaire bore a unique code for identification purposes, and coded data entered into each participant's form on an excel sheet. This was done and backed up on a hard drive on a daily basis after assuring accuracy and completeness.

3.12Statistical analysis

Data analysis was done using Stata version 13 software (Stata Corp, USA). Results obtained were presented in in form of tables, bar charts and graphs.

At commencement of data analysis, the Shapiro Wilk test was conducted on all continuous variables to check for normal distribution. Those that were not normally distributed were summarized as median and inter-quartile range (IQR). Categorical variables were summarized as frequencies and percentages. Inferential statistics was conducted to compare the distribution of variables across participants with hyperglycemia versus those without hyperglycemia, and also those patients with co-morbidities vs those without comorbidities. A multivariate logistic regression analysis was used to determine the independent predictor variables of hyperglycemia development in the study population and also to adjust for potential confounding factors.

Age, sex, BMI, level of physical activity, presence of comorbidities, duration of DTG therapy and type of DTG regimen were some of the patient variables included in the regression model. Preliminary analysis was done based on all participants who met the criteria for inclusion in the study. The association between the variables was tested using chi-square test as well as the p-value. The statistical test was two tailed and performed at a 95% statistical level of significance.

To establish the temporal relationship between patient and healthcare provider factors in regard to development of hyperglycemia, definition of cases was restricted to those with hyperglycemia diagnosis. BMI measurements, socio-demographic as well as clinical data were considered as covariates of interest in these patients.

3.13 Ethical considerations

3.13.1 Ethical approval

This was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC); study refence number P77/02/2020, prior to conducting the study (appendix VIII). Institutional and departmental approvals were obtained from KNH Research & Programs department and KNH Comprehensive Care Center respectively (appendix IX A and IX B).

3.13.2 Informed consent

All eligible participants were guided through information regarding the study. The purpose of the study and their role in its success was explained in details. Once this was well understood, the participant was taken through the consenting process, and a consent form (appendix IIA and IIB) provided to be filled, in either English or Swahili language, and signed.

Prior to participation, it was made clear to all the participants that participation in the study was purely voluntary, without any immediate benefit nor incentive, and that any of them was at liberty to decline to participate in the study at any stage, without any prejudice befalling them. Every participant was free to ask any question relevant to the study in the course of the interview, and all these were addressed as appropriate.

A number of participants requested to be alerted on their glycemic status, especially if above normal and therefore the need for intervention.

They were also informed that they were free to contact the KNH/UoN-ERC in case they had any concerns regarding their rights as study participants.

3.13.3 Confidentiality

Study unique identifier codes were generated, assigned and used instead of patient names, during data collection and analysis. This was to ensure concealment and safeguarding of participant's identity. All data collection materials were safely kept in an identified lockable cabinet. The database was password protected at all times, only accessible with permission from the PI. The data obtained were used only for the purpose of the study.

However, patients that were diabetic as per the diabetic treatment guidelines were contacted and advised accordingly to liars with their clinicians for further medical check-ups.

3.13.4 Risks involved

This was a low risk study, involving pricks to obtain blood samples for plasma glucose and glycated hemoglobin measurements. Risk of infection spread during the procedures, especially in this period of COVID-19 pandemic, were minimized by observing standard infection control measures. Such measures included handling of one patient at a time, with the rest keeping at least 1.5metre social distancing; wearing of hand gloves, wearing of face masks by both patients and care providers and disinfection of the skin before each sample withdrawal. Both patient's privacy and confidentiality were maintained at all times during the study.

3.13.5 Benefits from the study

The study offered no immediate benefits to the participants nor the care givers, but the findings were meant to provide long term benefits, in terms of improved clinical outcomes for the participants.

Those requiring immediate clinical intervention were contacted and appropriately advised to liars with their clinicians for further medical check-up.

It is was intended that the findings from this study would be used to design prospective studies, whose findings may inform clinical guidelines changes on treatment initiation and monitoring of patients on dolutegravir and prevention of drug-associated adverse effects.

3.14 Data dissemination Plan

These findings on the prevalence of DTG associated hyperglycemia and the accompanying recommendations made will be shared with the healthcare team at the CCC clinic in form of a power point presentation.

A manuscript has been prepared and sent for review and publication. The same information is scheduled to be presented in scientific seminars/conferences and to relevant clinical teams during the continuous medical educations (CME).

3.15 Source of funding

Kenyatta National Hospital funded the study to its completion, from the Hospital Research and Programs Fund kitty.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter describes the results obtained from analysis of the data collected from a sample of 358 participants on dolutegravir-based antiretroviral therapy at KNH CCC. Descriptive, inferential and logistic regression analyses were conducted on the sample to determine the prevalence of DTG associated hyperglycemia and its covariates on the development of hyperglycemia. A report of the sociodemographic, patient and health provider factors that affect hyperglycemia was done among the study population.

Table 4.1: Sociodemographic traits of patients on dolutegravir

Variable	Category	Frequency (N=358)	Percentage (%)
Age (years)	18 – 40	116	32.4
	41 – 60	226	63.1
	>60	16	4.5
Sex	Male	136	38.0
	Female	222	62.0
Marital status	Single	138	38.5
	Married	220	61.5
Education	Informal	8	2.2
	Primary	69	19.3
	Secondary	143	39.9
	Tertiary	138	38.5
Employment status	Unemployed	73	20.4
	Self-employed	122	34.1
	Formal	120	33.5
	Informal	43	12.0

4.2 Sociodemographic characteristics of the population

Summary data analyses from the sample are presented in Table 4.1. The population studied was largely female (n=222, 62.0%). The mean age of the patients was 43.7 (SD 10.6) years. The minimum age was 18 years while the maximum age was 72 years. More than half of the population comprised participants in the middle-age bracket (41-60 years, 63.6%).

Young adults (18-40 years) and the elderly (>60 years) made up 32.4 % and 4.5% of the population respectively.

Most participants were married (n=220, 61.5%). The majority had acquired up to secondary (n= 143, 39.9%) and tertiary (n=138, 38.5%) level education. The self-employed and those in formal employment comprised the majority (n=122, 34.1% and n=120, 33.5%) respectively. The rest were either unemployed (n=73, 20.4%) or in informal employment (n=43, 12%).

4.3: Patient-specific characteristics of the population

Summary of this data is presented in Table 4.2. The mean Body Mass Index (BMI) of the studied population was 26.6 (SD 5.5) kg/m^2, while the median BMI was 25.8 (IQR 22.6 – 29.6) kg/m^2. The minimum BMI was 14.5 kg/m^2 while the maximum BMI was 51.8 kg/m^2. More than 50% of the participants were either overweight (n=127, 35.5%) or obese (n=81, 22.6%). The BMI of 39.1% (n=140) of the population was within the normal range, with a few participants (2.8%) having a low BMI.

Majority of the participants reported some level of physical activity, only 9 (2.5%) denied being involved in any kind of activity. Most patients (n=352, 98.3%) were non-smokers, the smoking population comprising only 1.7% (n=6). Current alcohol use was reported among 27 participants (7.5%), others had either stopped when started on HAART, or denied having ever used.

Table 4.2: Patient – specific characteristics of the population

Variable	Category	Frequency (n=358)	Percentage (%)
BMI (Kg/m^2)	<18.5	10	2.8
	18.5-24.9	140	39.1
	25.0-29.9	127	35.5
	>=30.0	81	22.6
Level of physical activity	None	9	2.5
	Minimal	72	20.1
	Moderate	140	39.1
	Active	137	38.3
Smoking status	Yes	6	1.7
	No	352	98.3
Alcohol use	Yes	27	7.5
	No	331	92.5

BMI = Body Mass Index

4.4: Clinical characteristics of the population

This information is summarized in Table 4.3. As per the treatment guidelines recommendations, most participants (n=317, 88.5%) were virally suppressed (HIV-1 RNA < 1000 copies/ml) prior to switch to DTG, with only 4.2% of the study population having viral loads (VL) > 1000copies/ml. The information on VL counts during the switch for a few participants (n=26, 7.3%) could not be traced, and were therefore considered not done. A number of participants had their CD4+ cell count done during DTG initiation, the majority having > 200 cells/mm^3 (n=176, 49.2%). Those with <200 cells/mm^3 comprised 10.6%, while the CD4+ information for the rest of the participants (n=144, 40.2%) could not be traced, therefore considered not done.

The baseline blood pressure, as per JNC 9, was used to categorize patients as either normotensive (≤150/90mmHg) or hypertensive (>150/90mmHg) during DTG initiation. Majority of patients were normotensive (n=321, 89.7%), with only 10.3% being hypertensive (n=37).

Comorbidities documented as affecting the study population during DTG initiation, that could also have impact on participants' glycemic control are presented in figure 4.2.

Most participants (n=348, 97%) had no documented nor reported co-morbidities during DTG initiation, with only 10 (2.8%) having documented co-existing illnesses, on which they were being followed up on. Of the documented comorbidities, hypertension was relatively prevalent (n=5,1.4%), followed by tuberculosis (n=2,0.6%), the rest (arthritis, hepatitis C and asthma) being distributed in equal proportions (n=1, 0.3%).

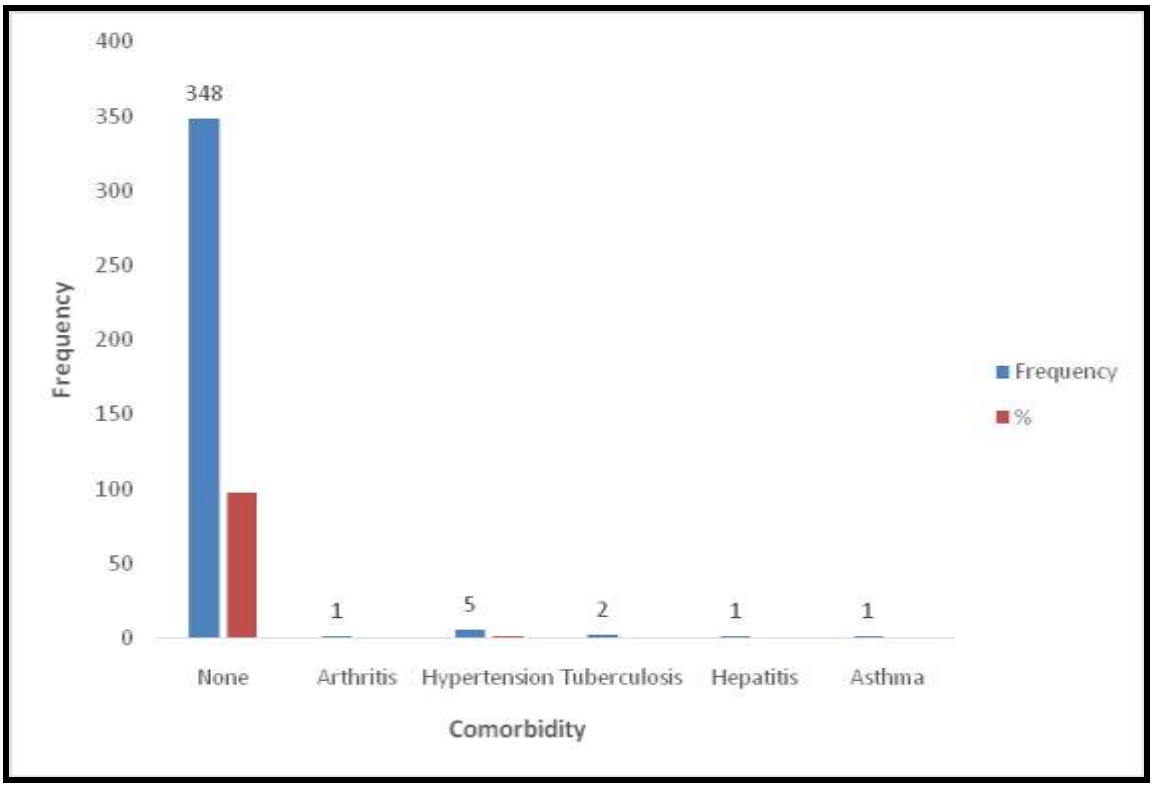

Figure 4.1: Patients comorbidities at initiation of dolutegravir

Table 4.3: Patient related baseline clinical characteristics

Variable	Category	Frequency (n=358)	Percentage (%)
Viral load	Low VL (<1000 copies/ml)	317	88.5
	High VL (>1000 copies/ml)	15	4.2
	No VL done	26	7.3
CD+ count (cells/mm^3)	Low CD4+ (<200 cells/mm^3)	38	10.6
	High CD4+ (>200 cells/mm^3)	176	49.2
	No CD4+ count done	144	40.2
Blood pressure (mmHg)	Normotensive (≤150/90)	321	89.7
	Hypertensive (>150/90)	37	10.3
Comorbidity	None	348	97.2
	Arthritis	1	0.3
	Hypertension	5	1.4
	Tuberculosis	2	0.6
	Hepatitis	1	0.3
	Asthma	1	0.3

4.5: Patients antiretroviral medication use history

This information is summarized in Figure 4.2. Most patients were switched to DTG/TDF/3TC (n=351, 98%) from their previous ART regimens, with only 33(9.2%) being directly initiated on the same regimen as their first line therapy. A few patients were either switched to DTG/ABC/3TC (n= 4, 1.1%) or DTG/AZT/3TC (n=3, 0.8%). The most common first regimen, before the first switch was EFV/TDF/3TC and of all the patients switched to DTG regimens, the majority (n=243, 67.9%) were switched from EFV/TDF/3TC.

Those switched from NVP/AZT/3TC, NVP/TDF/3TC and EFV/TDF/3TC comprised 33(9.2%), 30(8.4%) and 16(4.5%). The rest were switched from either EFV/ABC/3TC (n=2, 0.6%) or NVP/ABC/3TC (n=1, 0.3%).

The main reason for regimen switch was treatment optimization (n=315, 88.0%). Some patients were switched due to treatment failure (n=4, 1.1%) and a few others (n=3, 0.8%) due to adverse drug events, of great importance being CNS effects. The rest (n=36, 10.7%) were on DTG as their first line regimen and/or for unspecified reasons, and therefore categorized as 'other'.

The mean duration of DTG use by participants was 11.7 (SD 6.2) months, whereas the median duration of use was 10.0 (IQR 7.0 – 16.0) months. The minimum duration of use was 3 months while the maximum was 33 months. Majority of patients had been on DTG for less than 12 months (n=202, 56.4%). Those who had been on DTG for 12- 24 and > 24 months comprised 39.9% (n=143) and 3.6% (n=13), respectively.

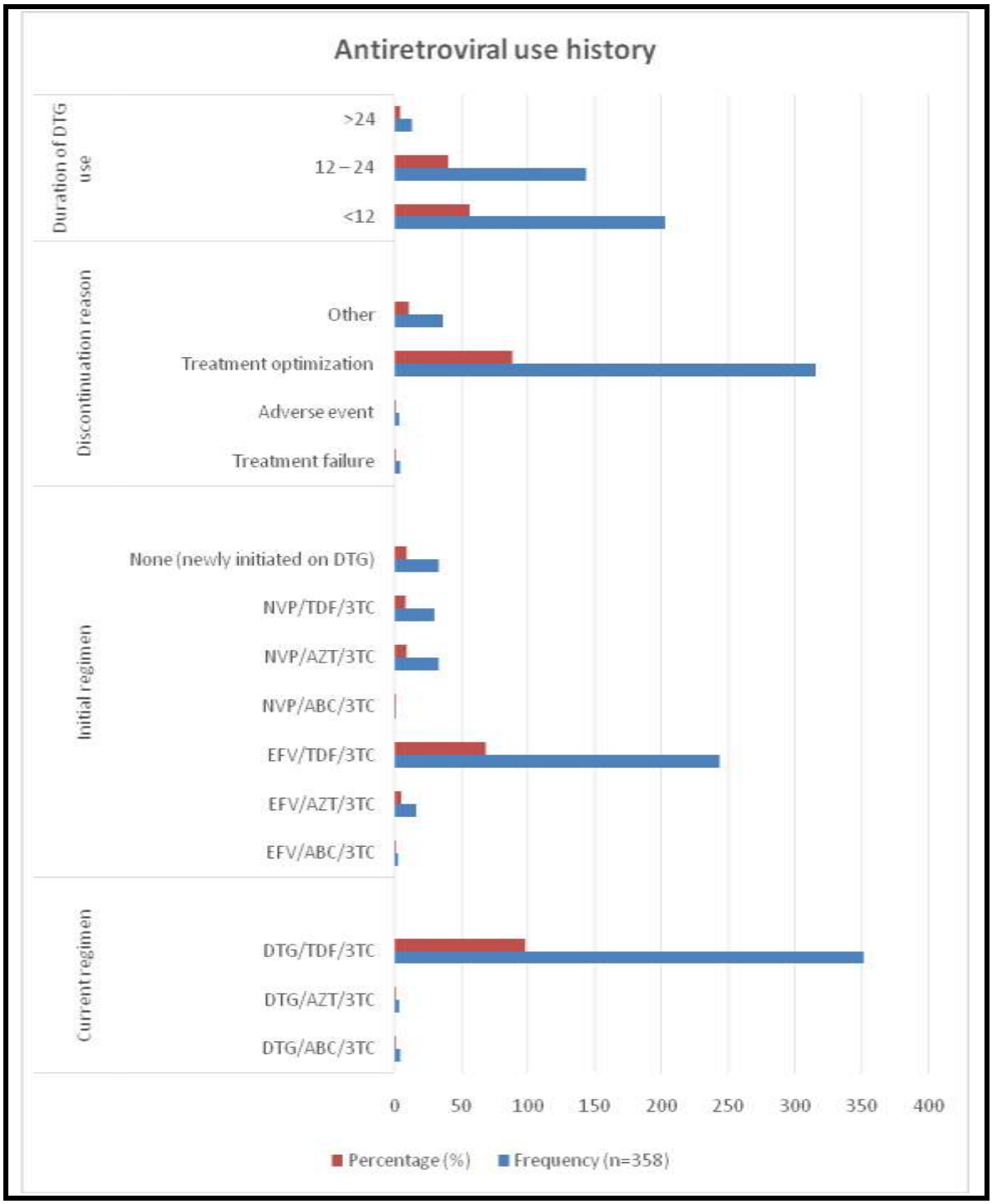

Figure 4.2: Antiretroviral use history

4.6: Patients current comorbidity/co-medication status

This information is summarized in Table 4.5. Majority of patients reported no existing co-morbidities (n=308, 86.0%). Forty-two (11.7%) had documented cardiovascular system (CVS) disorders, on which they were being followed-up in various clinics, on medications and stable. Of the reported cardiovascular disorders, hypertension was the leading (n=39, 92.9%). There was also one (2.8%) reported and documented case of liver disease (hepatitis C infection). The rest (n=7, 2.0%) reported other disease conditions of little significance in hyperglycemia development, such as arthritis, asthma, peptic ulcer disease, among others.

Apart from the conventional medications co-administered with DTG-based regimens, few patients (n=5, 1.4%) reported concurrent use of herbal remedies. The rest denied current use of any herbal remedy.

Table 4.4: Current patient comorbidities/ co-medications

Variable	Category	Frequency (n=358)	Percentage (%)
Blood pressure	Normotensive (≤150/90)	319	89.1
	Hypertensive (>150/90)	39	10.9
Present known chronic disorders	Liver disorder	1	2.8
	Cardiovascular disorders	42	11.7
	Others	7	2.0
	None	308	86.0
Herbal remedy use	Yes	5	1.4
	No	353	98.6

4.7: Prevalence of dolutegravir associated hyperglycemia.

This section sought to determine the overall prevalence of dolutegravir associated hyperglycemia, and the information is summarized in Table 4.6. 358 participants were assessed and their glycemic status evaluated via both random blood sugar (RBS) and HbA1c measurements.

Eight (2.2%) and 199 (55.6%) participants were found to be hyperglycemic via RBS and HbA1c, respectively. The cutoff points were RBS ≥7mmol/L and HbA1c ≥6.1%. As per the protocol, a patient was considered hyperglycemic if the measurements, RBS and/or HbA1c was positive for hyperglycemia. In this study population, the majority (n=200, 55.9%) were hyperglycemic. The rest (n=158, 44.1%) were normoglycemic (Figure 4.3).

Table 4.5: Blood glucose (RBS and HbA1c) laboratory results

Blood sugar test	Category	Frequency (n=358)	Percentage (%)
RBS (mmol/L)	Normoglycemia (3.6-7.1)	350	97.8
	Hyperglycemia (≥7.2)	8	2.2
HbA1c (%)	Normoglycemia (3.5-6.0)	159	44.4
	Hyperglycemia (≥6.1)	199	55.6
RBS and/or HbA1c	Normoglycemia (3.5-6.0)	158	44.1
	Hyperglycemia (≥6.1)	200	55.9

RBS: Random blood sugar; **HbA1c**: Glycated hemoglobin 1Ac

4.8: Patient related factors associated with hyperglycemia development

The results of bivariate analysis indicate that a statistically significant association exists between hyperglycemia development and age, sex, overweight and obesity. It was observed that the odds of developing hyperglycemia for those above 40 years was 1.7 (95% CI, 1.1-2.7, p = 0.014) times those below 40 years of age. This was the same case for female gender where the odds were 1.6 (95% CI, 1.1-2.5, p = 0.029) times that of male gender. The results also indicate that being either overweight (25.0-29.9 kg/m^2) or obese (≥30.0 kg/m^2) increases the risk of hyperglycemia development.

The odds of being overweight was 1.8 (95% CI, 1.1-2.9, p = 0.017) times, whereas that of being obese was 3.1 (95% CI, 1.7-5.6, p = <0.001) times more likely to develop hyperglycemia than those having a normal BMI respectively.

On multivariate analysis with forward stepwise selection, and limiting the entry for p-values between 0.05 to 0.10, the final and reduced model resulted to only age (aOR=1.7;CI, 1.1-2.7, p = 0.026), overweight (aOR=1.7; CI, 1.1-2.8, p = 0.026) and obesity (aOR=3.1 (CI, 1.7-5.5, p = <0.001) as the statistically significant independent patient factors associated with development of hyperglycemia in the study population. However, the risk estimates were comparable to those on bivariate analysis.

Table 4.6: Patient related factors associated with hyperglycemia development

	Bivariate analysis		Multivariate analysis	
	COR (95% CI)	**p-value**	**AOR (95% CI)**	**p-value**
Age				
18 – 40	Reference			
>40	1.7 (1.1 – 2.7)	**0.014**	1.7 (1.1 – 2.7)	**0.026**
Sex				
Male	Reference			
Female	1.6 (1.1 – 2.5)	**0.029**		
BMI				
≤24.9	Reference			
25.0-29.0	1.8 (1.1 – 2.9)	**0.017**	1.7 (1.1 – 2.8)	**0.026**
≥30.0	3.1 (1.7 – 5.6)	**<0.001**	3.1 (1.7 – 5.5)	**<0.001**
Level of physical activity				
None/Minimal	1.1 (0.7 – 1.8)	0.657		
Moderate/Active	Reference			
Smoking status				
Yes	4.0 (0.5 – 34.8)	0.206		
No	Reference			
Alcohol use status				
Yes	0.7 (0.3 – 1.6)	0.403		
No	Reference			
Comorbidity				
Yes	1.6 (0.9 – 3.1)	0.122		
No	Reference			
DTG-based ART duration of use (months)				
<12	Reference			
12 – 24	1.5 (1.0 – 2.4)	0.053		
>24	2.2 (0.6 – 7.3)	0.211		
Current regimen				
DTG/ABC/3TC	Reference			
DTG/AZT/3TC	-			
DTG/TDF/3TC	0.4 (0.04 – 4.0)	0.444		

4.9: Healthcare related factors associated with hyperglycemia development

No significant associations between healthcare related factors and the development of hyperglycemia were identified at both bivariate and multivariate logistic regression analysis (Table 4.8).

Of all the cases, one hundred and ninety-four (97%) had no documented glycemic status since DTG initiation. Six (85.7%) out of the seven patients whose glycemic status were known during DTG initiation were hyperglycemic, suggesting lack of significant association between blood sugar status established at DTG initiation or during treatment, and hyperglycemia development. While 101 (50.5%) of the cases denied receiving any form of counselling or education on hyperglycemia, a similar proportion of patients (49.5%) reported having received some form of counselling on the condition, despite being hyperglycemic. Due to subjectivity of the responses on having ever been counselled or not by a healthcare provider, it was difficult to derive any significant association with hyperglycemia development.

Table 4.7: Healthcare related factors associated with hyperglycemia development

		Bivariate Analysis		**Multivariate Analysis**	
Variable	**Category**	**cOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Number of blood sugar done	Done	Reference		Reference	
	Not done	0.2 (0.03-1.7)	0.145	0.2 (0.02 – 1.6)	0.131
Counselling	Yes	Reference		Reference	
	No	0.8 (0.5 – 1.1)	0.182	0.7 (0.5 – 1.1)	0.155

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study was a hospital based descriptive cross-sectional study where 358 patients on dolutegravir (DTG) regimens for at least 3 months were assessed to determine the prevalence of DTG associated hyperglycemia. Two hundred patients (55.9%) were hyperglycemic, the blood sugar status being determined by glycated hemoglobin and/or random blood sugar. A significant association between DTG use and hyperglycemia development was identified. Patient factors such as age (>40 years) and BMI above 25kg/m^2 were also found to be independently associated with hyperglycemia development. No associations between healthcare related factors and the development of hyperglycemia were identified.

The finding suggests that hyperglycemia is relatively prevalent among patients using DTG-based regimens at KNH. So far, there are no published studies on prevalence of DTG associated hyperglycemia except for the case and incidence reports from various studies (10,11,38,60,61). This is the first prevalence study done in Kenya, given that the drug is relatively new for HIV management in Kenya and Sub- Saharan Africa.

Factors that were found to be independently associated with development of hyperglycemia in this study population were increased age, overweight and obesity. Out of the two hundred hyperglycemic patients, seventy three percent were >40 years, compared to only twenty seven percent in the younger (18-40 years) population. Patients above 40 years of age were 1.7 times more likely to develop hyperglycemia compared to those below 40 years. This suggests that, with the growing number of people on DTG-based regimen living longer, incidence of hyperglycemia is expected to rise. This finding concurs with other reports indicating that adverse drug events from antiretroviral therapy occur more frequently in older population with HIV infection than in younger individuals(62) hence the need to closely monitor them.

Similar reports have also indicated that advancing age in most populations put patients at high risk of developing hyperglycemia due to natural physiologic changes as well as comorbidities and impaired organ functions associated with aging(62,63).

The medications used for their co-morbidities such as thiazides, β-blockers have all been found to have a role in hyperglycemia development(12,60).

Some studies concluded that aging is the most significant risk factor for hyperglycemia complications, as seen in older patients due to reduced beta cell function and impaired insulin sensitivity with consequent progressive loss of glucose regulation ability (63). Other related studies have reported a decline in glucose tolerance from the young to the old due to secondary influences of both physical activity and body fat. However, these changes are usually significant in advanced age (>60 years), even after accounting for confounding factors (63).

Contrary to these findings, another study concluded that prevalence of hyperglycemia and its complications such as DM in patients on HAART was age-independent, but detectable in patients <42 years. The main difference between our study and this particular one was that patients were mainly Ethiopian immigrants in Israel, with all obese patients being excluded from the study, unlike in our study where a number of patients had a BMI >29.9kg/m^2 (64,65).

Out of the two hundred hyperglycemic patients, 37.5% were overweight, whereas 29% were obese. Overweight patients were found to be 1.7 times more likely to develop hyperglycemia compared to those with a BMI <25kg/m^2. The same case was with obese patients whose odds of developing hyperglycemia were 3.1 times higher compared to those with normal BMI. This finding concurs with those of other several studies done in diverse populations. In one of the cohort studies, a number of patients were reported to have discontinued dolutegravir-based regimen due to abnormal weight gain, ranging between 4 to 12 kg. In that studied population, the high BMI, mainly seen in women, was also found to be associated with a number of non-HIV related events. The body fat changes experienced by these patients affected their self-perception and adherence to ART (39).

One of the findings in a prospective trial of dolutegravir monotherapy conducted on individuals stable on ART, switched to dolutegravir monotherapy revealed a 4 kg mean increase in body weight, observed after 24 weeks of follow up (40).

The mechanism of DTG induced increase in weight is unclear, but a report of a study suggests that exposure is associated with increased adipocyte differentiation, with enhanced expression of markers associated with lipid storage (44). Our finding also concurs with that of a randomized control trial in South Africa (ADVANCE study) which reported that approximately 35% of the studied population on DTG-based regimens were either clinically obese or clinically overweight.

Similar finding of association between DTG use and increased BMI was reported in another randomized trial in Cameroon (NAMSAL study), and another cohort study done in US, mainly comprising of whites (43,45).

On the contrary, the finding of a case-control study in Uganda, although comprising largely of men, reported that majority of patients who developed hyperglycemia with severe symptoms had lost weight rather than gaining. However, the definition of cases in this particular study was different from the present study, being restricted mainly to symptomatic patients and/or those on antidiabetics, that could be partly responsible for the observed weight loss (60).

The population studied was largely female dominated (62.0%) On bivariate analysis, the females had 1.6 times higher odds of developing hyperglycemia compared to men, revealing an association between the female gender and hyperglycemia development. However, on multivariate analysis, the association was not statistically significant. So far, published studies on weight gain and DTG use suggest that women and blacks on DTG, compared to NNRTs are most likely to be affected. The likely contributing factor in the observed hyperglycemic state in these women is increased BMI, usually associated with insulin insensitivity, seen in more women compared to men.

This is supported by the NAMSAL study in Cameroon which followed patients on DTG and those on EFV for 48 weeks and found a 10% increase in BMI, mainly in women taking DTG ($p<0.05$), when compared to those taking EFV.

The weight gain observed in men was insignificant. In another study, after a multivariate analysis, the main independent risk factor that led to DTG discontinuation, after an adverse event was female gender.

Another randomized control trial in South Africa also reported clinical obesity emerging more frequently in women than men, further predisposing women than men to development of hyperglycemia. (45).

The study did not reveal a statistically significant association between duration of DTG exposure and hyperglycemia development. A Ugandan study on DTG-associated hyperglycemia also established that the onset of hyperglycemia was approximately 4 months from DTG initiation (60). A similar finding was reported in another study, VIKING-3, where severe hyperglycemia was observed in 14% of patients at week 48 of follow-up (60).

However, other contrary findings were reported on other pivotal DTG studies (SPRING-2 and SINGLE) where their results suggested an association between longer duration of DTG exposure and hyperglycemia development and reported that from their study participants,<7% compared to 11% patients developed hyperglycemia after 96 weeks and 144 weeks of follow-up respectively(60).

In our study, on bivariate analysis, those who had used DTG for more than 12 months had 1.5 times higher odds of developing hyperglycemia compared to those who had used it for less than 12 months. The association was however lost in the multivariable model.

The results of this study did not reveal any significant association between presence of a comorbidity and hyperglycemia development. However, on bivariate analysis, we found that those with comorbidities, mainly cardiovascular disorders had 1.6 (95% CI, 0.9-3.1, p=0.122) times higher odds of developing hyperglycemia compared to patients without any comorbidity.

This finding concurs with results of a number of studies that have shown that insulin sensitivity and secretion can be affected by coexisting illnesses such as hypertension, usually common in older and obese patients, just like in our population. Acute illnesses have also been found to precipitate hyperglycemia through release of stress hormones (62).

HIV patients with other chronic illnesses require close attention during choice of drugs to prevent drug-induced hyperglycemia and its complications.

The medications used for treatment of the comorbidities such as β-blockers and thiazide diuretics have all been shown to impair insulin release from the pancreas (66,67) and may induce or worsen hyperglycemia. The medications should form part of the differential diagnosis to ascertain the exact cause of the observed hyperglycemia.

No statistically significant associations between healthcare related factors and developments of hyperglycemia were identified. Choice of DTG regimen, determination of blood sugar level at DTG initiation or in the course of treatment, and the nature of counselling given to patients were all found to have no association with hyperglycemia development observed in the study population.

However, from a number of reports from other related studies, it is recognized that patient education and counseling by their healthcare team usually play an important role as far as their disease, medications, side effects, nutrition and lifestyle modifications are concerned, with improved therapeutic outcomes. Studies have confirmed that a number of drug-related complications in chronic illnesses such as HIV can be reduced by regular monitoring of patients' response to medications and early recognition of adverse events. Poor understanding and lack of behavioral changes as well as inadequate intervention strategies from the entire team can result in poor treatment outcomes (50,53,68).

The study's main strength was the large sample size in addition to the fact that it was the very first DTG associated hyperglycemia prevalence study conducted in Kenya. The lack of comparison between patients on DTG regimens and those on non-DTG-based regimens to evaluate the varying risks of developing hyperglycemia was a limitation.

The fact that the glycemic status of >90% of the studied population was not documented at the initiation of DTG regimen, it was difficult to establish if DTG exposure proceeded or followed hyperglycemia and the causality may not be ascertained. This may have resulted in over-estimation of the observed association.

The exact prevalence of DTG associated hyperglycemia could not be established before carrying out the study, therefore an estimate of PI associated hyperglycemia had been used as proxy in calculation of the sample size for this study.

Because of this assumption, there was a likelihood of an under- or over-estimation of the association. A prospective cohort study involving several patients on DTG is recommended to confirm the findings.

The study design was susceptible to bias due to low response and misclassification due to recall bias. Some of the data obtained through patient reports were however confirmed from the KNH IQ-care database.

5.2 Conclusion

The findings of this study show a consistent hyperglycemic risk for patients on dolutegravir and confirmed the usefulness and safety of glucose monitoring plan for patients on DTG. Early diagnosis of DTG associated hyperglycemia is important in providing optimal effective treatment while preventing complications for patients on HAART. The study has also highlighted the importance of routine body weight monitoring for all patients on DTG.

5.3 Recommendations

5.3.1 Recommendation for Policy and Practice

1. Screening for hyperglycemia should be considered for all patients being initiated on DTG.
2. Monitoring of blood sugars for patients on DTG should be done regularly, if possible, at every visit.
3. DTG use should be withheld in all patients at risk of hyperglycemia (advanced age, overweight, obese, familial history of DM), who are virally suppressed on other regimens.
4. All patients on DTG to be sensitized on the risk of hyperglycemia development and advised appropriately on necessary measures to prevent or recognize it.

5.3.2 Recommendations for Further Research

1. A prospective cohort study involving larger populations from different ART centers to better understand the other contributing factors to abnormal glucose homeostasis in patients on DTG.
2. A comparative analysis of the DTG-regimen and the non-DTG regimen cohorts to ascertain causality.

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APPENDICES

APPENDIX I: ELIGIBILITYASSESSMENT FORM

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

a. Study Information

Title:	Prevalence of Dolutegravir Associated Hyperglycemia and its Covariates Among Persons Living with HIV on Treatment at Kenyatta National Hospital
KNH/UoN-ERC Protocol Number	**P77/02/2020**
Principal Investigator (PI)	Dr. Judith A. Odenyo

b. Participant Information

Subject identification number	
Gender	Male ☐ Female ☐

c. Inclusion/Exclusion Criteria

Inclusion Criteria (tick as appropriate)	**Yes**	**No**
1. Adult patient (> 18 years) of sound mind?		
2. On follow up at KNH CCC?		
3. Has consented to participate in the study?		
4. On DTG based regimen for not less than 3 months?		
5. No documented diagnosis of diabetes type 1 or 2, nor has history of current use of hypoglycemics		

Exclusion Criteria (tick as appropriate)	**Yes**	**No**
1. On cancer chemotherapy or hyperglycemia inducing agents?		
2. Has end stage renal disease or uncontrolled hypertension?		
3. Is expectant at the time of recruitment?		

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

d. Statement of Eligibility

This subject is (tick as appropriate)

Eligible ☐ Not eligible ☐ o participate in the study.

Signature:	**Date:**
Name:	

APPENDIX II A: CONSENT FORM

Title of the Study: Prevalence of Dolutegravir Associated Hyperglycemia and its Covariates among Persons Living with HIV on Treatment at Kenyatta National Hospital.

Institution: Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy.

Principal Investigator: Dr. Judith A. Odenyo

Supervisors: **1. Dr George A. Mugendi** **2. Dr. David G. Nyamu**

Department of Pharmaceutics and Pharmacy Practice,

University of Nairobi, P.O Box 30197 – 00400, Nairobi.

3. Dr. Andrew Okiko

Department of Pharmaceutical Services

Kenyatta National Hospital, P.O Box 20723 – 00202, Nairobi

Ethical Approval: This study has the approval of Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) Protocol number: **P77/02/2020.**

Introduction

I would like to inform you about a medical research to be conducted by the above-mentioned researchers. The importance of having this discussion is to give you detailed information on what the research involves so that you can make informed decision on whether to participate or not. Please feel free to ask any questions on what may happen to you should you agree to participate, concerning any dangers or risks to you, benefits, your rights, or anything you have not understood. After we address your concerns, you will make a decision whether to take part in the study or not. If you decide to participate, I will ask you to sign the consent form below.

You are therefore required to understand the following general principles, which apply to all participants in a medical research before we can proceed.

What is the research about?

The reason for doing this research if to determine the proportion of patients taking a new antiretroviral drug called dolutegravir (DTG), that may have developed increased levels of blood sugar since they started using it. The findings of this research will make it possible for your doctor to regularly monitor your blood sugar level to prevent development of diseases and complications associated with increased blood sugar while improving your wellbeing as you continue taking your medications.

Procedure

With your permission, I will ask you some questions on personal information, like age, other previous or existing medical conditions, social and family history, to help us find out other factors that can contribute to increased blood sugar. Physical examination will be done to determine your weight and height.

To establish the true state of your blood sugar, I will request you to proceed to the clinic laboratory for blood sample withdrawal. All the procedures will be free of charge. Delays will be minimized as much as possible during sample collection.

Any Risks involved?

This will be a low risk procedure requiring one withdrawal of venous blood under sterile conditions. Risk of infection during the procedure will be minimized by observing standard infection control measures (minimal physical contacts, use of hand gloves, surgical masks, cleaning and disinfecting the skin, proper disposal of materials used).

Benefits from the study

There will be no immediate direct benefits to you, but the findings may be used by your healthcare team to manage you better and improve your well-being. Depending on your results, if there is need for immediate clinical intervention, we will advise and appropriately refer you to a specialist for further management.

Assurance of Confidentiality

All information obtained from you will be kept in utmost confidence, and at no point will your name on clinic number be used or mentioned during data handling or in any resulting publication. Unique anonymous codes will be used instead.

Your rights as a participant:

1. Your agreement to participate is entirely voluntary.
2. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal and no injustice or loss of benefit will be meted on you.
3. Refusal to participate will not lead to any penalty, nor affect the services you are entitled to in this health facility or any other.
4. After reading the explanation given to you, please feel free to ask any questions that will enable you to understand clearly the nature and purpose of this study.
5. We will give you a copy of this form for your records.

Contacts

If you have any questions about your rights as a research participant, please get in touch with any of the following, using the contacts given;

1. Dr. Judith A. Odenyo; phone number. Email: *juodenyoa@students.uonbi.ac.ke*
2. Lead Supervisor: Dr. George A. Mugendi,
   Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi.
3. The chairperson, KNH/UoN Ethics and Research Committee, P.O Box 20723-00100, Nairobi. Telephone number,020-726300-9/020-716450 Ext. 44102.Email: *uonknh-erc@uonbi.ac.ke*
4. I now request you to sign the attached consent form.

CONSENT TO PARTICIPATE IN THE STUDY

I, the undersigned, having read and also been explained to the information in this consent form, and having fully understood the content, with all my questions and concerns addressed, do hereby volunteer to participate in this study. The risks and benefits have been explained to me and I understand that my participation is voluntary and I can withdraw from the study anytime without injustice or loss of any benefit. I also know that all efforts will be made to keep information regarding my personal identity confidential, and that all information gathered will be solely for the purpose of this study.

Name of participant…….

Date…… Signature of participant…….

Researcher statement

I confirm that I have explained the details of the research to the participant and that he/she has understood.

Name of investigator/research assistant……Date……

Signature……

APPENDIX II B: RIDHAA YA KUSHIRIKI KATIKA UTAFITI

Kichwa cha Utafiti:

Maambukizi ya uzidishaji wa sukari kupita kiasi katika damu unaotokana na utumiaji wa dawa ya Dolutegravir na sababu zinazohusika miongoni mwa wagonjwa wanaougua ugonjwa wa ukimwi katika hospitali ya Kuu ya Kiataifa ya Kenyatta.

Taasisi:

Idara ya mazoezi ya Famasia, Shule ya Famasia, Chuo Kikuu cha Nairobi.

Mtafiti Mkuu:

Dkt. Judith A. Odenyo

Watafiti Wengine pia Wasimamizi:

1. Dkt. GeorgeA. Mugendi
2. Dkt. David G. Nyamu

Wahadhiri, Idara ya mazoezi ya Famasia, Shule ya Famasia, Chuo Kikuu cha Nairobi.

S.L.P. 30197 – 00400, Nairobi.

3. Dr. Andrew Okiko

Idara ya Famasia, Hospitali Kuu ya Kitaifa ya Kenyatta, S. L. P. 20723 – 00202, Nairobi

Idhini ya Idara ya Adili:

Utafiti huu umeidhinishwa na Hospitali kuu ya Kataifa ya Kenyatta, ikishirikiana na Kamati ya Adili na Utafiti ya Nairobi. Nambari ya itafiki ikiwa…….

Utangulizi:

Ningependa kukujulisha kuhusu utafiti huu utakaofanywa na waliotajwa hapo juu. Umuhimu wa mazungumzo haya ni kukufahamisha zaidi ili uweze kufanya uamuzi wa hekima kushiriki au kutoshiriki katika utafiti huu.

Una uhuru wa kuuliza maswali yoyote kuhusu kitakachofanyika utakapokubali kushiriki, madhara yanayoweza kutokea, manufaa ya utafiti huu, haki zako kama mshiriki na maswali yoyote kuhusu lolote ambalo hulielewi. Tutakapo jibu maswali yako yote, basi utaamua kushiriki au la. Ukikubali kushiriki, nitakuuliza utie sahihi na majina yako kwa ukurasa hapo chini. Unahitaji kuelewa maelezo yafwatayo kuhusu nguzo muhimu ambazo zinalinda washiriki wote katika utafiti wa sayansi ya afya kabla tuendelee.

Utafiti huu unahusu nini?

Sababu kuu ya kufanya huu utafiti ni kuweza kutambua hali ya maambukizi ya uzidishaji wa sukari kwenye damu kutokana na utumiaji wa dawa mpya ya kuzuia ukali wa ugonjwa wa ukimwi unaoitwa Dolutegravir, tangu waanze kuitumia. Matokeo ya utafiti huu yaweza kuimarisha matokeo ya tiba unaopata kutoka kwa madaktari wako, ili kusaidia kuzuia yale magonjwa hutokana na sukari iliyozidi kupita kiasi kwenye damu, n ahata madhara yanayotokana na sukari nyingi kwenye mwili, na kuimarisha afya yako kijumla hata ikiwa unaendelea kutumia madawa zako.

Mtindo

Ukinipa ruhusa, nitakuuliza maswali yanayokuhusu binafsi, kama umri wako, magonjwa mengine ulikuwa nayo hapo awali ama unayougua kwa sasa, maisha yako ama ile ya familia yako kijumla. Kutokana na maalezo yako, tutaweza kujua kama kuna uhusiano wowote kati ya sababu unazotoa na uzidishaji wa sukari kwenye damu yako. Uzito na urefu wako pia utapimwa kwa kutumia mashine zifaavyo.

Ili kujua hali ya sukari kwenye damu yako, utahitajika kutokula kwa masaa isiyo chini ya manane (8), kuanzia saa sita usiku wa kuamkia siku ya miadi, hadi utakapotolewa damu kwenye maabara, hapa kwenye kliniki yetu. Yale uchunguzi yote yatafanywa yatakuwa bila maalipo. Tutafanya vyote twaweza ili utowaji wa damu ufanywe bila kucheleweshwa.

Hatari yoyote?

Kutakuwa na hatari kidogo ya uchungu, kutokana na utowaji wa damu wakati wa kudungwa sindano. Vifaa vyote vitakavyotumika vitakuwa vimechazwa kwa ile kiwango inatakikana ili kuzuia maambukizi yoyote yanayoweza kutokea (utumiaji wa glavu, usafisaji wa ngozi kabla kudungwa, na usahihi wa utupaji wa vifaa vyote vitavyotumika bila madhara).

Manufaa kutokana na utafiti

Hakuna manufaa wa moja kwa moja utakaopokea bali matokeo ya utafiti kwako utajadiliwa pamoja na wote wanaokuhudumia kuboresha matibabu yako na kumaarisha afya yako.

Dhibitisho la usiri:

Habari zote utakazotueleza zitalindwa kwa siri kuu. Hakutakuwepo wakati wowote ambapo jina lako au nambari ya cliniki litatumika au kutajwa wakati wa kutayarisha matokeo ya utafiti huu. Badala ya jina lako, tutalitumia nambari speshali ya kukutambua kwenye utafiti.

Haki zako kama mshirika:

1. Kushiriki kwako kwa utafiti huu ni kwa hiari.
2. Unaweza kujiondoa wakati wowote bila kushurutishwa kutoa maelezo.
3. Kutoshiriki kwako katika utafiti huu hakutaathiri huduma unazopaswa kupata kwa hospitali hii au ingineyo iwayo.

4. Una uhuru wa kuuliza swali lolote baada ya kusoma na kuelewa ujumbe huu ili upate habari kamili kuhusu utafiti wenyewe.
5. Tutakupa nakala yako ili ujiwekee kwa manufaa yako binafsi.

Nambari ya mawasiliano ya baadaye:

Ukiwa na swali lolote baadaye kuhusu haki zako kama mshiriki, tafadhali wasiliana na:

1. Dkt. Judith A. Odenyo. *Tovuti: juodenyoa@students.uonbi.ac.ke*
2. **Mhadhiri mkuu:** Dkt. George A. Mugendi, Idara ya mazoezi ya Famasia, Shule ya Famasia, Chuo Kikuu cha Nairobi.
3. **Mwenyekiti:**
   Hospitali Kuu ya Kitaifa ya Kenyatta ikishirikiana na
   Kamati ya Adili na Utafiti ya Nairobi, S.L.P. 20723 – 00100, Nairobi.
   Nambari ya simu- 020-726300-9/020-716450kiendelezi 44102. Tovuti: *uonknh-erc@uonbi.ac.ke*

Sasa, ninakualika kushiriki katika utafiti huu kwa kutia sahihi yako kwa ridhaa hii.

FOMU YA RIDHAA

Mimi, mwenye sahihi iliyo hapo chini, nikiwa nimesoma, na pia kupokea maelezo katika ridhaa hii, na mimeyaelewa kikamilifu na maswali na haja zangu kuhusu huu utafiti kuyajibiwa, nimekubali kwa hiari yangu kushiriki katika huu utafiti. Hatari na manufaa yote yanayohusiana na utafiti huu nimeelezewa na kuelewa kikamilifu, na ninafahamu ya kwamba kushiriki kwangu ni kwa hiari na nina uhuru wa kujiondoa bila dhuluma au kuathirika kwa huduma ninazopaswa kupokea kwa hospitali hii au ingine iwayo. Nimefahamu tena ya kwamba, juhudi zote zitafanywa kuweka habari zote kunihusu siri, na yatatumika tu kwa ajili ya huu utafiti.

Jina la mshiriki…….
Tarehe…… Sahihi ya mshiriki…….

Andiko la Mtafiti Mkuu

Nadhibitisha ya kwamba nimemuelezea mshiriki habari zote anapaswa kujua kuhusu utafitu hu una amepata kufahamu.

Jina la mtafiti
mkuu……Tarehe……

Sahihi ya Mtafiti mkuu……

APPENDIX III: QUESTIONNAIRE

Serial number……Date……(DD/MM/YY)

TITLE: Prevalence of Dolutegravir Associated Hyperglycemia and its Covariates among Persons Living with HIV on Treatment at Kenyatta National Hospital.

Section A: Socio-demographic data

1. Patient identification number ☐
2. Age (years) or year of birth ☐
3. Sex: (0) Male ☐ (1) Female ☐
4. Marital status:
   (0) Single ☐ (1) Married ☐ (2) Widowed ☐
   (3) Divorced ☐ (4) Separated ☐
5. Employment status:
   (0) Unemployed ☐ (1) Self-employed ☐ (2) Formal ☐ (3) Informal ☐
6. Educational level:
   (0) Informal ☐ (1) Primary ☐ (2) Secondary ☐ (3) Tertiary ☐
7. Weight (kg) ☐ Height (m) ☐ BMI (kg/m^2) ☐
8. Level of physical activity: (0) None ☐ (1) Minimal ☐
   (2) Moderate ☐ (3) Active ☐
9. Currently smokes cigarette: (0) No ☐ (1) Yes ☐
10. Currently takes alcohol (0) No ☐ (1) Yes ☐

Section B: Blood glucose laboratory results

1. Random blood glucose (mmol/L)
2. HbA1c (%)

Section C: Patient related clinical data

1. HIV diagnosis: Month Year
2. Baseline investigations: Weight(kg) Height (m) BMI (Kg/m^2)

   Viral load (copies/ml)

   CD+ count (cells/mm^3)

   Blood pressure (mmHg):

   RBS (mmol/L

   HbA1c (%)

   Co-morbidity (if any,specify)
3. Initiation of HAART: Month Year
4. Current Regimen: Date

5. Initial regimen (if any): Date stopped

6. Reason for discontinuation(tick):

   (0) Treatment failure

   (1) Adverse event If yes, specify

   (2) Treatment optimization

   (3) Other (specify)

7. Duration of DTG-based ART (months)

8. Current blood pressure (mmHg):

9. Known chronic disorder and/or patient on follow-up (specify)

   Cardiovascular

   Kidney

   Liver

   Dyslipidemia

   Other

10. Have you ever used any herbal remedy with your current regimen?

(0) No (1) Yes

Section D: Healthcare provider related factors

1. Other concurrent medications prescribed(name)

i
ii.
iii.
iv.
v.

2. Number of blood sugar measurements done and documented since initiation of DTG? (from patient data base)

3. Do you receive counseling/information on your condition (s) and medications from your healthcare team regarding:

Side effects (0) Yes (1) No

Adherence (0) Yes (1) No

Nutrition (0) Yes (1) No

Lifestyle modifications (0) Yes (1) No

APPENDIX IV: PATIENT BASELINE DATA ABSTRACTION FORM

Serial No……Date……(DD/MM/YY)

S. NO	PATIENT NO.	UNIQUE CODE	FBS/RBS (mmol/L)	Hba1C (%)	BLOOD PRESSURE (mmHg)	BMI (kg/m^2)	VIRAL LOAD (copies/ml)	CD4+ COUNT (cells/ml)

PI/Research assistant (Name)…….

Sign……Date……

APPENDIX V: KNH TECHNICAL OPERATING PROCEDURE FOR PLASMA GLUCOSE MEASUREMENT AND GLYCATED HAEMOGLOBIN ENZYMATIC ASSAY METHOD.

Kenyatta National Hospital

Hospital Road, off Ngong Road

Department of Laboratory Medicine; Biochemistry Laboratory

P.O. Box 20723

Nairobi, TEL: 020 2726300

LABORATORY TESTING PROCEDURES

a. Procedure for Finger Prick Random Blood Sugar (RBS) Testing using cera-chek 1070 glucometer

i. Welcome the client and let him/her sit comfortably.
ii. Confirm the expiry date, then remove the test strip from the vial and immediately close the cap.
iii. Insert the strip(sensor) into the insert port of the glucometer and await the blood symbol to blink on the glucometer screen.
iv. Choose the site to be punctured and disinfect using the available disinfectant.
v. Obtain a blood sample using the lancing device. Wipe off the first drop (tissue fluid).
vi. Let the glucometer sensor(strip) suck a generous homogenous sample (into the absorption hole of the strip) till the confirmation window is full of blood.
vii. After 5 seconds an accurate result display appears on the glucometer screen.
viii. Record it and sign in the request form and inform the client of the result before he/she goes back to the clinician.
ix. The result is automatically stored in the test meter memory.

b. Procedure for glycated Hemoglobin Enzymatic assay method

1) Receipt and registration of specimen, after verifying the integrity of each specimen in terms of packaging, right container, volumes; and assigning of a laboratory number at the specimen reception desk.

2) Specimen preparation and assaying by assigned laboratory staff.

Specimen preparation

i. Centrifuging/ spinning of whole blood at 2000 revolutions per minute for 5 minutes.
ii. Aliquot 25µl of the deposited red blood cells into a sample cup or Eppendorf microfuge tube, using the calibrated pipette in use.
iii. Add 500µ l of the hemolysin / denaturant or pretreatment solution to the 25 µl of the aliquoted erythrocytes.
iv. Shake the mixture vigorously in a closed Eppendorf microfuge tube or vacutainer till lysis is achieved.
v. Homogeneously mix the resultant hemolysate gently and then run the assay after
vi. minutes using the appropriate automated analyzer.

Assaying procedure

Involves two reactions.

i. Measuring the concentration of hemoglobin at an absorbance of a fixed wavelength, with simultaneous generation of fructosyl dipeptides from the N-terminal amino groups of beta chain of HbA1c, by the reaction of a protease.
ii. Reacting fructosyl peptide oxidase with the generated fructosyl dipeptides, with generation of hydrogen peroxide. This allows the 10-carboxymethylaminocarbonyl)-3,7-bis(dimethylamino) phenothiazine sodium salt to develop a color in the presence of peroxidase. The HbA1c determination is done by measuring the change in absorbance.
iii. The combined assay results for total hemoglobin and HbA1c are used to calculate and express HbA1c as a percentage.

3) Result validation, interpretation and indication for repeat testing if necessary.
4) Transcription and release of ready results; involves verification of test results and documentation using appropriate reporting tools.

Quality control procedure

1) The HbA1c analyzer will be calibrated before use. A control rehydrating reagent, a bi-level liquid stable frozen product will be used for machine calibration at a frequency dictated by CCC laboratory QC procedures and reagent/instrument manufacturer instructions. The quality control reagent and HbA1c cartridge and their expiry dates will be confirmed and kept at room temperature for a minimum of 10 minutes before use.
2) During use, the QC reagent will be stored between 2-8 ^{0}C. Once the instrument is ready for QC testing, a barcode on the control card of the appropriate QC level will be located and scanned, with the view screen displaying a prompt to proceed with loading of the cartridge. The control rehydrating reagent will be added to the cartridge within 1 minute, then blood specimen added immediately and lid of the analyzer closed. A beep will be heard at the end of the test cycle.

3) The HbA1c % QC result (range: 2.5 – 16.0%) will be displayed, indicating QC name, print date, machine serial number, test date, sample serial number, cartridge lot number and user ID.
4) If result is outside the QC range, the calibration of reagent cartridge is repeated and analysis procedure repeated. If the second result is still not within QC range, analysis procedure is repeated with freshly made QC material.

APPENDIX VI: LABORATORY RESULTS REPORT FORM

Serial Number……. Date……(DD/MM/YY)

S. NO.	UNIQUE CODE	RESULTS		REPORTED BY:	
		RBS (mmol/L)	HbA1c (%)	Name	Sign

APPENDIX VII A: DIAGNOSTIC CRITERIA FOR DIABETES AND PRE-DIABETES IN KENYA.

Test	Normo-glycemia	Intermediate hyperglycemia	Diabetes
Fasting glucose	3.5 – 6.0 mmol/L	6.1 – 6.9mmol/L	≥7.0 mmol/L
2-hour glucose following ingestion of 75g glucose load	< 7.8 mmol/L	7.8 – 11.0 mmol/L	≥11.1mmol/L
Random plasma glucose (RBS)	3.6 – 7.7mmol/L	7.8 – 11.0 mmol/L	≥11.1 mmol/L
HbA1c	5.0 – 5.6 %	≥5.7 - 6.4%	≥6.5% (48mmol/mol)

APPENDIX VII B: KENYATTA NATIONAL HOSPITAL GLYCEMIC RANGES

Test	Normo-glycemia	Hyperglycemia
Fasting glucose	3.5 – 5.6 mmol/L	≥5.7 mmol/L
2-hour glucose following ingestion of 75g glucose load	< 7.8 mmol/L	≥7.8 mmol/L
Random plasma glucose (RBS)	3.6 – 7.1 mmol/L	≥7.2 mmol/L
HbA1c	3.5 – 6.0 %	≥6.1%

APPENDIX VIII: KNH-UON ERC APPROVAL LETTER

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/212

10th July 2020

Judith Awuor Odenyo
Reg. No. H56/11023/2018
Dept.of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Judith

RESEARCH PROPOSAL – PREVALENCE OF DOLUTEGRAVIR ASSOCIATED HYPERGLYCEMIA AND ITS COVARIATES AMONG PERSONS LIVING WITH H.I.V ON TREATMENT AT KENYATTA NATIONAL HOSPITAL (P77/02/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 10th July 2020 – 9th July 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. George Mugendi, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Dr. David Nyamu, Dept.of Pharmaceutics and Pharmacy Practice, UoN
Dr. Andrew Okiko, Department of Pharmaceutical Services, KNH

APPENDIX IX A: KNH RESEARCH AND PROGRAMMES APPROVAL LETTER

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
DR. JUDITH AKUOR ODENYO
2. Email address: jvodenyo@gmail.com Tel No. 0722499345
3. Contact person (if different from PI) N/A
4. Email address: ..... Tel No. .....
5. Study Title
PREVALENCE OF DOLUTEGRAVIR ASSOCIATED HYPERGLYCEMIA AND ITS COVARIATES AMONG PERSONS LIVING WITH HIV ON TREATMENT AT KNH
6. Department where the study will be conducted KNH COMPREHENSIVE CARE CENTRE
(Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
Name: Dr. S.K. Walumbe Signature ..... Date 23/07/2020
8. Endorsed by KNH Head of Department where study will be conducted.
Name: Dr. S.K. Walumbe Signature ..... Date 23/07/2020
9. KNH UoN Ethics Research Committee approved study number P77/02/2020
(Please attach copy of ERC approval)
10. I DR. JUDITH A. ODENYO commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
Signature ..... Date 23/07/2020
11. Study Registration number (Dept/Number/Year) ..... /106/2020
(To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL
23 JUL 2020
Research Resource Centre

All studies conducted at Kenyatta National Hospital must be registered with the Department of Research and Programs and investigators must commit to share results with the hospital.

Version 2: August 2014

APPENDIX IX B: KNH COMPREHENSIVE CARE CENTER APPROVAL LETTER

KENYATTA NATIONAL HOSPITAL, P.O. BOX 20723-00202, TEL: 2726300-9:

KNH//MED/CCC/35/VOL.I 19th June, 2020

Head, Research and Programs Department,
KNH

Dear Sir,

RE: LETTER OF SUPPORT FOR DR.JUDY ODENYO

I am writing to express the willingness of the Kenyatta National Hospital HIV Care and Treatment Program towards supporting the Postgraduate research study titled " *Prevalence of Dolutegravir associated hyperglycemia and its covariates among persons living with HIV on treatment at Kenyatta National Hospital*" upon successful ethical approval by the KNH-UON ERC.

The Kenya HIV treatment Guidelines have Dolutegravir as an integral drug in both first-line and second-line regimens due to its tolerability, effectiveness and durability. To this this end, eligible adults and children have been optimized to Dolutegravir containing regimens. The study will therefore be timely in our setting to establish the prevalence of Dolutegravir associated hyperglycemia which is one of the reported adverse effects.

Kenyatta National Hospital HIV care and treatment program will therefore accord the required support towards the proposed study.

Yours sincerely,

DR. SIMON WAHOME,
HEAD OF UNIT, COMPREHENSIVE CARE CENTRE,
KENYATTA NATIONAL HOSPITAL

APPENDIX X: ORIGINALITY REPORT

Dissertation

by Judith Odenyo

PREVALENCE OF DOLUTEGRAVIR ASSOCIATED HYPERGLYCEMIA AND ITS COVARIATES AMONG PERSONS LIVING WITH HIV ON TREATMENT AT KENYATTA NATIONAL HOSPITAL

Submission date: 24-Nov-2020 06:24AM (UTC+0500)

Submission ID: 1455588670

File name: 24TH_FINAL_SIGNED_DISSERTATION_DOCUMENT.docx (989.8K)**Word count:** 18289**Character count:** 106534

ORIGINALITY REPORT

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Dr. G.A. Mugendi 24/11/2020