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SAFETY AND EFFECTIVENESS OF DOLUTEGRAVIR-BASED REGIMENS IN HIV PATIENTS AT QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI

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A Thesis submitted in partial fulfilment of the requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi

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DECLARA**TION OF ORIGINALITY**

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Title of the work: Assessment of the safety and effectiveness of Dolutegravir-based regimens in HIV patients at Queen Elizabeth Central Hospital in Malawi.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
COMREC	College of Medicine Research Committee
DTG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
EVG	Elvitegravir
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
QECH	Queen Elizabeth Central Hospital
KNH/UoN-ERC	Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
LPV	Lopinavir
MOH	Ministry of Health
NVP	Nevirapine
PI	Protease Inhibitors
RAL	Raltegravir
RBS	Random Blood Sugar
R	Ritonavir
SE	Side Effects

OPERATIONAL DEFINITIONS

Adherence: Taking medicine as per the instructions of a healthcare provider (42).

Adverse drug reaction: A noxious, unwanted, and unintended response to a medicinal product following its use at normal doses in humans (43).

Viral load: Number of HIV RNA copies in 1 milliliter of blood (42).

Viral suppression: HIV serum viral load of less than 1000 copies per milliliter (44).

ABSTRACT

Introduction: Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTI) recommended by WHO for the treatment of HIV in low-and middle-income countries. DTG is safe, potent, and tolerable with a wide barrier to resistance, unremarkable drug-drug interactions, and good pharmacokinetic profile. Apart from safety and effectiveness data from clinical trials conducted in developed countries, DTG safety and effectiveness data from resource-limited settings is scarce. There is particularly no data in Malawi since the guideline change to DTG-based ART regimen in. This study 2019 seeks to assess the safety and effectiveness of DTG-based regimens in a Malawian population.

Objective: The main objective of the study is to assess the safety and effectiveness of Dolutegravir-based regimens in HIV patients at Queen Elizabeth Central Hospital, in Malawi.

Methods: This was a descriptive retrospective cohort study which included analytical retrospective cohort methods during exploratory data analysis. It was conducted at Umodzi Family Clinic at Queen Elizabeth Central Hospital in Malawi. Sample size was calculated using the Cochran formula and a consecutive sampling technique was used. Data was extracted from participants' records and additional safety data was obtained using a structured data collection tool. Means and standard deviations were used to summarize normally distributed continuous variables while median and interquartile range for variables that were not normally distributed. Frequencies and percentages were used for the categorical variables. For continuous variables, two sample t-tests or sign rank tests were used for inferential analyses depending on data distribution. For categorical variables, proportions were compared amongst those who developed the adverse effects

and those who did not, and Pearson's Chi-test or Fishers exact test was used for inferential data analysis. To identify the influence of other variables on the outcome of interest, logistic regression was used. Multivariable regression analysis was done to adjust for potential confounders. The level of significance was set at 0.05 for all the analyses.

Results: A total of 262 participants were included in the study. Of these 163(62%) participants were females. The mean age was 42.3 years and 65% of the participants were aged between 35-65 years. Participants reported side effects such as: neuropsychiatric symptoms 18(6.87), hypersensitivity reactions 34(12.9), diarrhoea 5(1.91), back pain 21(8.02), abdominal pain11(4.20), dizziness, muscle aches 5(1.91), nausea 15(5.73), vomiting 6(2.29), weakness15(5.75), and dysuria 7(2.08). DTG based- regimens were associated with diarrhoea, nausea, vomiting and dysuria. All covariates of interest could not explain the occurrence of mild hypersensitivity reaction in participants experiencing the symptom. The median viral load significantly dropped from 40 (IQR:40-839) to 30 (IQR:30-40) in about six months of follow up in participants on DTG-based ART regimen (p= 0.000). The concurrent use of herbal medication was associated with (dizziness, back pain, abdominal pain, weakness, and dysuria) and use of concurrent medication was associated with (neuropsychiatric symptoms and back pain)

Discussion and Conclusion:

DTG-based regimen was associated with mild hypersensitivity reactions, nausea, vomiting dysuria, and diarrhoea. However, no association was observed between presence of neuropsychiatric symptoms and DTG-based regimen. Therefore, DTG-based regimen was safe and were not associated with serious adverse events. DTG-based regimen was also effective in suppressing and maintaining viral load to undetectable level.

1.0 CHAPTER ONE: INTRODUCTION

1.1. Background

HIV is one of the most important public health problems in the world. The Global HIV statistics estimated that 37.7 million people were living with HIV in 2020 (1). In the year 2020, new HIV infections accounted for 1.5 million adults and children, and approximately 27.5 million people were on anti-retroviral therapy (1). The prevalence of HIV in Malawi was estimated at 1 million in 2016 and 89% of these people were on antiretroviral treatment (2).

To combat the spread of HIV and to reduce the mortality and morbidity associated with the epidemic, the World Health Organisation (WHO) periodically reviews the treatment guidelines to accommodate newer and more effective antiretroviral drugs as they become available. The revised treatment guidelines are aimed at promoting regimens that are safer, effective, tolerable, and cost-effective. In 2016, WHO recommended the use of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) (or emtricitabine, FTC) and efavirenz (EFV) (3) as the preferred first-line antiretroviral therapy (ART) regimen for adults and adolescents. The guidelines were therefore, revised to include the Integrase Inhibitor, dolutegravir (DTG), as alternative first line treatment. Since then, many countries including Kenya, Botswana, Uganda and Brazil have adopted the DTG-based first line ART regimen (3) .The new guidelines recommend a combination of DTG, TDF and 3TC in those starting ART and those with virological load of less than 1000 copies per millilitre and are currently on first-line treatment (3). Furthermore, the guidelines recommend the DTG-based combination as a second line treatment regimen in those who failed on TDF, 3TC and EFV. A combination of AZT, 3TC and DTG was recommended in this case (4). The recommendation to use

DTG-based regimen was based on safety reports (5–7) in randomized controlled trials. DTG-based regimen were found to be more tolerable than EFV-based regimen according to systematic reviews (6). In addition, studies demonstrated a high barrier to development of resistance with the use of DTG-based regimen than EFV-based regimen (3, 7). Patients are therefore more likely to stay longer on DTG-based regimen without developing resistance and regimen failure. (4) The manufacturing process of DTG is cheaper than that of EFV thus lowering the cost of ART. The factors above, put together, ensures patient compliance to treatment and reduced risk of treatment discontinuation. The affordability of DTG provides an assurance of a sustainable ART program.

However, it is noted that the safety data for DTG-based regimen is based on clinical trial findings with sample size limitations. Such studies may not be fully representative of the general population and special groups like pregnant women and children. Usually, participants with comorbidities such as tuberculosis (TB), and taking rifampicin-based regimen; and treatment-naive or patients with pre-existing NRTI drug resistance would be excluded in clinical trials. This leads to selected information regarding the safety of the medicines. In one observation study in Botswana, neural tube defects in babies born to mothers on DTG-based regimens were reported (8). However, the incidence of neural tube defects, could not be observed in clinical trials due to exclusion of this group.

1.2. Statement of Problem

Malawi transitioned to DTG-based regimen in January 2019 after WHO recommendation. However, there is no post marketing clinical data demonstrating the safety and efficacy of DTG-based regimen in Malawi and other low-income African countries. The use of DTG-based regimen in most

African countries is therefore, based on studies done in high-income settings. This highlights the need to establish own safety and efficacy data as some unique factors in low-income settings such as genetic, socio-economic as well as geographical differences may affect the safety of DTG-based regimen.
Poor safety profile of medicines results in problems of non- adherence. This might lead to development of resistance, treatment failure, loss of public trust in the system and of course waste of these expensive medicines.

Various reports from studies have shown that DTG-based regimens cause adverse effects such as neuropsychiatric effects, hyperglycaemia, hepatotoxicity, and hypersensitivity reactions (7, 9–12). This study therefore sought to assess the safety and effectiveness of DTG-based regimen in patients taking this regimen in Malawi.

1.3. Research questions

The research questions for the study were:

- **a)** What is the prevalence of adverse drug reactions in patients taking DTG-based regimens at Umodzi Family clinic at Queen Elizabeth Central Hospital?
- **b)** What is the prevalence of adequate viral suppression in patients on DTG-based regimens at Umodzi Family clinic at Queen Elizabeth Central Hospital?

1.4. Study Objectives

1.4.1 Main objective

The main objective of the study was to assess the safety and effectiveness of DTG based regimens used in the treatment of HIV patients at Queen Elizabeth Central Hospital, Malawi.

1.4.2. Specific Objectives

The study was specifically:

a) Describing the prevalence of adverse drug reactions in patients on DTG-based regimen at Queen Elizabeth Central Hospital in Malawi.

b) Investigating the effectiveness of DTG-based regimen in suppressing virologic load in patients at QECH.

1.5. Justification Study

Since the introduction of ARVs in 1996 there has been a reduction in the rate of mortality and morbidity among HIV positive individuals (13). However, ARVs are reported to cause adverse events in individuals taking them (14). Due to poor reporting of adverse drug reactions (ADRs) in Malawi, the percentage of ADEs reported to the pharmacovigilance centre due to antiretroviral medicines is very low (average of 6 reports per months at QECH).

Malawi transitioned to DTG-based regimen in January 2019 following the WHO recommendation. The DTG-based regimen replaced old first-line regimens due to safety concerns with the old ART regimens (13). According to Malawi Clinical HIV guidelines, the DTG-based regimen promised to be more potent, more durable and cause fewer adverse-effects and interactions with other medicines (15). The aim was to phase out the Efavirenz-based regimen (TDF/3TC/EFV) as it was associated with many side effects. No studies have been done in Malawi to assess the nature and extent of both documented and unknown ADRs arising from DTG-based regimen use. A medicine that causes serious or life-threatening effects may lead to reduced quality of life, increased mortality, and morbidity and the cost of managing these effects may be high.

1.6. Significance of the study

The findings of the study would provide preliminary safety information on DTG-based ART use in HIV patient population. Once the findings are disseminated to the patients, they would be knowledgeable of the safety of the DTG-based regimen. This would guide adherence, support, and minimize ART regimen failure and reduce costs.

To prescribers and other health care professionals, the findings would prompt and advocate for monitoring of clients on DTG-based regimen for emergence of other ADRs and any potential signals. The study would be of particular importance to the Ministry of Health (MOH) especially the Department of HIV/AIDS, which monitors and reports the national ART program data. The findings might also demonstrate to donors the need for additional funding to address emerging issues such as laboratory-based monitoring of adverse effects to enable early detection of the adverse effects. This study was well set to address the aims of pharmacovigilance to improve patient and public health care delivery and safety in relation to the use medicines (49). Information on effectiveness of DTG-based regimen was also obtained in this study.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1. Introduction

WHO recommended the use of an integrase inhibitor based regimen (TDF + 3TC or FTC + DTG) as alternative first-line treatment in adults in 2016 (16). A systematic literature review (SLR) and network meta-analysis (NMA) which was conducted in 2015 demonstrated improved tolerability and efficacy with DTG and EFV (15). The evidence led to the recommendation for use of DTG and EFV as alternative first-line regimens and not as the preferred treatment. The recommendation was made based on the high cost of DTG and uncertainties around sub-populations. As a result, it was difficult to recommend it for low and middle-income countries under the public health approach (15). An extensive SLR and NMA aimed at updating the SLR and NMA was conducted in 2015 to determine the efficacy and safety of DTG and EFV relative to third agents that were in use (17,15). The findings of this extensive systematic review gave a strong conclusion about the improved efficacy and tolerability of DTG relative to EFV and evidence that strongly supported DTG-based regimen to be used as preferred first-line regimen (15). Generic fixed-dose combinations of DTG-based regimens are now available for the low and middle-income countries.

2.2 The rationale for the WHO recommendation to Use DTG-based regimen for the treatment of HIV

The World Health Organization's recommendation to use DTG-based regimens as the preferred first-line treatment was made based on evidence from SLRs and NMAs that reported DTG-based regimen to be well tolerated, highly efficacious, protective against treatment discontinuation from ADRs and of lower cost because of the formulation of generic fixed dose

combinations for low and middle-income countries. The evidence also reported DTG-based regimens to have fewer drug-drug interactions compared to EFV600mg and protease inhibitors (15-17). DTG-based regimens have a higher genetic barrier to resistance (3, 7,16, 17, 19, 20, 21, 22). DTG is active against HIV-2 infection, which is resistant to EFV (17). However, this evidence did not demonstrate if DTG is safe in special populations like pregnant women and in patients with co-infections and are taking other drugs like rifampicin-based anti-tuberculosis drugs (16, 17). Information on the use of DTG-based regimen in paediatrics and pregnant women is insufficient (18)

2.3. Pharmacology of Dolutegravir

DTG is a nitrogen-containing polycyclic compound possessing an amide functional group with two chiral centres. The presence of the two chiral centres leads to stereoisomerism (19). DTG is the newest second-generation integrase strand transfer inhibitor derived from the patent drug S/GSK1265744, which is available as long-acting injectable formulation. DTG was developed as an oral formulation (16, 18,19,20, 21). It has powerful antiviral activity and is safer (22). DTG was approved for use in the United States for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral agents like abacavir-lamivudine by WHO (12,16, 21,46). Other examples in this group are raltegravir and elvitegravir. DTG's activity is equivalent or superior to existing treatment regimens in treatment-naïve, treatment-experienced and in those with failure to raltegravir or elvitegravir (19,20). (16, 16, 20–22). INSTIs exert their action by blocking HIV DNA integrase so that it does not absorb into the host T-lymphocyte sequence, restricting viral transmission (21). This happens by compromising the function of HIV integrase-DNA complex (20).

DTG is rapidly absorbed when taken orally and achieve its maximum plasma concentration after hours of oral administration (20). Its plasma half-life is between 12 -14 hours and hence requires once-daily administration (16,20,21). However, in experienced patients and patients with resistance to integrase Inhibitors it is given twice daily (17). Metabolism of DTG is through the hepatic glucoridation by UDP-glucuronosyltransferase1A1 and minor pathway is throughcytochrome P450 (CYP)-3A4 (20, 46). Small amounts of DTG are excreted through the kidneys (17, 20) and hence, the it is not affected in renal impairment (21)

2.4. Drug-Drug Interactions between Dolutegravir and Other Medicines

DTG does not induce or inhibit cytochrome p450 enzymes as such drug-drug interactions takes place to a smaller extent (20, 46). However**,** drugs that are metabolic inducers may decrease the plasma concentrations of DTG (31).

No food-drug interactions has been reported with DTG use (23). This puts DTG at an advantage of having fewer drug-food interactions.

DTG interacts with efavirenz and etravirine and tripanavir, therefore, co-administration of Efavirenz and etravirine with DTG should be avoided because they significantly lower the levels of DTG (15, 20). However, addition of ritonavir to etravirine prevents the reduction of DTG levels, (21). DTG does not interact with rilpivirine (21) and protease inhibitors such as darunavir, lopinavir, fosamprenavir, atazanavir (20) and tenofovir (22). These drugs can safely be co-administered with DTG (21). Co-administration of DTG and tenofovir does not require any dose adjustment (24).

The frequency of DTG should be increased to twice daily in TB patients who are on rifampicin because rifampicin lowers the plasma concentration of

DTG. Replacing rifampicin with rifabutin is an alternative way to overcome this problem because this requires no dose (21).

There are fewer drug–drug interactions between DTG and antimicrobial agents. Neither oral contraceptive pills nor proton pump inhibitors interact with DTG (21).

Antacids, negatively affects the effectiveness of DTG, hence, DTG and antacids must not be co-administered but rather DTG be administered 2 hours before or 6 hours after taking antacids (20). Similarly, all product that contain polyvalent cations such as calcium, magnesium, aluminum, iron, and zinc decrease, oral sucralfate, and laxatives as these decrease DTG concentration (12, 16, 31). Alternatively, these polyvalent cations must be taken with a fatty meal because this avoids the interaction between DTG and polyvalent cations. DTG enhances gastrointestinal adverse events of Metformin (21).

DTG causes increase in serum creatinine because it inhibits the renal organic cation transporter 2 (OCT2) responsible for the secretion of creatinine. The inhibition causes a decrease in tubular secretion of creatinine, leading to non-progressive increases in serum creatinine (20).

Carbamazepine is an inducer of CYP3A and it causes significant reduction of DTG levels when the two are co-administered (25) therefore, as recommended with other CYP3A inducers, twice daily DTG at a dose of 50mg should be given when co-administering the two (25)

Dolutegravir does not require dose adjustment or additional clinical monitoring is required in people with functional UGT1A1 polymorphisms (46)

2.5 Safety of Dolutegravir

Generally, DTG is safe fewer side effects and well tolerable than other regimens (13, 15,17,21,23,29,30). A number of studies have demonstrated no deaths, serious adverse events and even no withdrawals (17,23,29). The total incidence rate of adverse events due to DTG is 90% (18) of which most mild to moderate (18,29) and diminish with time only 1% of the patients experience severe adverse events (17, 21,23).

Studies and meta-analysis and systemic reviews have reported that DTG had significantly low possibility of causing adverse events and discontinuation than all other treatment regimens (17,23,26). However, some studies have demonstrated a comparable safety profile of ADEs between DTG and ratelgravir (23).

The most commonly reported mild to moderate ADEs are diarrhea, upper respiratory tract infection, and headache nausea and dizziness, rash, nasopharyngitis, and fatigue (18,21,23,26).

In biochemistry tests, severe adverse events such as hypertriglyceridemia, lipase increase, migraine, and night sweats (31). Creatinine elevation is the most consistent abnormal parameter with DTG (18,26,29). DTG use is also associated with elevation in alanine aminotransferase (ALT), creatinine kinase urinary albumin levels and hyperlipidemia (26). Elevation in ALT can happen without concomitant bilirubin elevations (26). Mild increases in transaminase levels occurred in 5% of participants on DTG use, (20). Transaminase levels went up to 16% with hepatitis B and C co-infections (21). However, DTG is not associated with increases in cholesterol, LDL (21)

Use of DTG is associated with hypersensitivity reactions although it is uncommon, occurring in less than 1% of individuals on DTG shortly after initiating treatment (18,20).

Neuropsychiatric events such as abnormal dreams, anxiety, dizziness, and somnolence are not common with DTG (18-20, 27). However, mild insomnia is more prevalent with DTG/ABC/3TC group (18-20, 27).

In observational studies, no increased risk for adverse birth outcomes, among women initiating DTG-based ART in pregnancy have been demonstrated (32) An observational study which was conducted in Botswana found similar adverse birth outcomes in pregnant women taking DTG-based regimen and women taking EFV-based regimen (32). However, four cases of neural tube defects (41) occurred in babies born to mother exposed to DTG (30, 41) but this number is significantly low. The women who gave birth to these babies were not on any folate supplementation (41)

A systematic review assessing the safety and pharmacokinetics of DTG in HIV-positive pregnant women reported no safety signals for pregnant women treated with DTG of birth outcomes or congenital anomalies (3). According to the review, there is no evidence that DTG does not cause increased risks of stillbirths, preterm birth and congenital anomalies as compared to historical control studies of ARV-treated pregnant women. This supports largest observational study in Botswana that demonstrated no evidence for increased risk of adverse birth outcomes for women treated with DTG compared with EFV (3). However an increased risk of neural tube defects was seen with DTG use in early pregnancy (33).

2.6. Efficacy and Resistance of Dolutegravir

Meta-analyses, systemic reviews, clinical trials have demonstrated that DTG is significantly effective at reducing viral load (HIV RNA<50 copies/mL) and increasing in CD4+ cells/µ (17, 50) than other agents (e.g., ATV/r, DRV/r and EFV, LPV/r) (17, 26 50).

SPRING 2 Study, a 96-week phase 3, randomized, double-blind, active-controlled, non-inferiority study which compared raltegravir against DTG with either abacavir-lamivudine or TDF-FTC as initial treatment for adults with HIV, reported that DTG is efficacious and non-inferior. The study reported that 88% participants in the DTG group achieved an HIV-1 RNA value of less than 50 copies per ml as compared 85% participants that achieved the same value in the rategravir group (21). Those who did not achieve virologic suppression did so, because they discontinued the treatment because other reasons rather than development of resistance (20,21). SINGLE, SPRING-1(26), SAILING, FLAMINGO and VIKING studies reported similar findings whereby, DTG demonstrated a rapid and sustained virologic response (HIV-1 RNA level of less than 50 copies per millilitre) (19, 27) as compared to other regimens (19,23,26,27,28,30).

2.7. Resistance to Dolutegravir

Dolutegravir was recommended for use because of its barrier to resistance among other reasons. (18). DTG's barrier to resistance was demonstrated in T in the STARTMRK, SPRING 2 and SAILING studies where no resistance mutations to DTG developed during analysis of patients with virologic failure while on DTG-based regimen. In all these studies resistant strains were observed with raltegravir, and elvitagravir (18, 12, 21, and 23).

Similar findings were observed in the SINGLE and SPRING 2 studies where participants on DTG did not develop resistance to the drug unlike participants on efavirenz-tenofovir-emtricitabine (20, 27). Findings of SAILING study therefore, supplemented the results of the SINGLE and SPRING-2 studies (13, 15). DTG is effective in a variety of INSTI-resistant phenotypes (34).However an observational study in Kenya reported one patient in Kenya had highly resistant strains to DTG (47). However, this patient had a history of non-adherence and there were drug shortages during that period (47).

3.0. CHAPTER THREE: MATERIALS AND METHODS

3.1 Study Design

A descriptive retrospective cohort approach was used to describe the demographic characteristics of the study participants and an analytical retrospective cohort was used during data analysis to compare participants who developed the outcomes of interest and those did not. Comparison of variables such as the first viral load results with the follow-up viral load results; descriptive analytical retrospective cohort was used because information on the variables being studied such as adverse drug reactions and viral load was obtained from medical records or depended on the participants' recall through interviews. Several variables were compared at the same time., For example, age, gender, smoking, alcohol intake, concurrent medication in relation to development of different outcomes of interest with little or no additional cost. The data collection took place from 1st May 2020 to 31st July 2020.

3 .2 Study Site

The study was conducted at Umodzi Family Clinic at Queen Elizabeth Central Hospital. Queen Elizabeth Central hospital is a referral hospital situated in Blantyre District in Southwest of Malawi. Blantyre is a referral hospital for eight districts in the south-west zone which include Mulanje, Thyolo, Chiradzulu, Nsanje, Chikwawa, Mwanza, Neno and Phalombe. It has a bed capacity of 1400 hospital beds and it is the largest hospital in Malawi Blantyre is the second largest city in Malawi. It is a densely populated district in the southern region with a population of 800,264 (35). Blantyre district has HIV prevalence rate of approximately 18.2% (35) though estimates within the district vary by location and population group (11). Umodzi Family clinic is

an ART Clinic providing free ART treatment and care and it was founded in 2004. The clinic is in the centre of Blantyre and is affiliated with the Light House Trust (11).

3.3Target and study Population

The target population were all HIV patients on anti-retroviral therapy (ART) at Umodzi family clinic at QECH. The study population were all adult HIV patients on DTG-based regimen that were seen at Umodzi Family Centre at QECH. They were required to have been on DTG ART for at least six months.

3.4 Inclusion criteria

Patients were included in the study if they met the following criteria confirmed from their medical records and by inquiring from them:

a) Adults of either gender aged 18 years and above.

b) Adults confirmed to be on DTG based antiretroviral therapy for at least six months.

c) Adults who had attended ART clinic at Umodzi family clinic for at least six months before starting the DTG-based regimen to make sure the participants records were present at the clinic.

d) Had no documented neuropsychiatric manifestations, diabetes, liver problems and hypersensitivity reactions at least six months before starting the DTG-based regimen.

e) For DTG effectiveness, participants to have at least two viral load test results since the initiation of the DTG-based regimen.

f) Willing to give voluntary informed consent to participate in the study

3.4. Exclusion criteria

Participants were excluded from the study if they did not meet any of the inclusion criteria. In addition, those who initially met the criteria were excluded for the following reasons:

a) Their medical records were incomplete
b) They were pregnant at the time of the study

3.5 Sample Size Computation

The Cochran formula (45) was used to calculate the sample size. A study done in Northern Ethiopia demonstrated a prevalence of adverse drug reactions of 19% to be due to ART (36).Therefore sample size was computed as follows:

n= t2pq/d2

Where:

n = estimated sample size
t = corresponding Z score at 95% confidence interval (1.96)
P = estimated prevalence of ADRs (assumed to be 0.19) (11).
q = (1-P)
d = level of significance (0.05 at 95% confidence interval)
n= 1.96 ×1.96×0.19×0.81/0.05×0.05
0.59122224/0.0025
n = 236.5
The sample size was adjusted by 10% to cater for missing records. Therefore, the sample size was 261 participants
The total number of registered HIV positive patients at QECH central hospital is 7345. Out of this population, 869 clients are on Tenofovir/3 TC/DTG regimen.

3.6 Sampling Method and Participant Recruitment

Consecutive sampling technique was used to sample participants to be included in the study. At Umodzi family clinic, patients follow scheduled visits for refill of medications fall on difference days depending on estimated competition dates of a three-monthly refill package. The data collection period coincided with usually low clinic attendance period due to a pick of the COVID-19 pandemic at this time. As a result, all participants who visited the clinic on the days of data collection and met the inclusion criteria were included in the study. Data collection was scheduled on the dates the patients came for follow-up and medication refill. Participants were screened and recruited in the pharmacy as they came to collect their drugs. This was done to minimise interruption of the normal clinic flow. Participants on DTG-based regimen were invited to a private room that was provided by Umodzi clinic where they were informed about the study. Upon consenting for participation, they were screened for eligibility using the eligibility checklist in Appendix II1. The study details and procedures were explained to them with the aid of the informed consent form in Appendix IV. Participants who met the eligibility criteria and gave an informed consent were then recruited into the study after signing the consent form. One on one interviews were conducted the same day in a private room that offered adequate participant privacy. Recruitment of participants continued until the required sample size was reached.

3.7. Data collection Tools

A structured data collection form (Appendix V) was used to collect data from participants' manual medical records on viral load, hypersensitivity reactions, neuropsychiatric symptoms (CNS) effects; patient reported side effects, participants' demographic data, blood pressure, weight, height, BMI, social

history, medication history, previous ART regimen, and medical history and participants' chronic illnesses. Additionally, data collecting questionnaire (Appendix VI) was used to guide interviews on the same participant whose clinic records were included to supplement the collection of additional data on the hypersensitivity reactions, neuropsychiatric CNS effects and other patient reported side effects. Data from the two sources were supplementing each other in cases where the clinic records contained insufficient information. Data on other laboratory test results like liver functions and random blood sugar were not collected because they were not available in the participants' medical records as they are not routinely collected. Data collection tools were pretested for validity and feasibility and appropriate corrections were made before the actual study was done. Validity was measured by assessing the data collection form and the questionnaire if they contain the questions and areas that the study wanted to measure. Items for the data collection form and the questionnaire were formulated in line with the three specific objectives.

3.8 Data Collection

Data was collected for 3 months from 1st May 2020 to 31st July 2020.The researcher and two pharmacy technicians who had undergone 2-day training on the data collection procedures were responsible for the data collection. Data was collected from only the participants that met the inclusion criteria and had signed a consent form.

Apart from collecting data from participants' records, interviews were conducted to collect data from the same study participants whose clinic records were included in the study. Viral load results were also collected from the same participants. A one-on-one interview session was done after collecting data from the participants' records to supplement the data. Data collection was done every day at the clinic as the participants came for follow-

up or refill of their medications When the participants visit the clinic, they are provided with a file of their clinic records for a clinical consultation. The data collectors for the study approached the potential participants and invited them to a private room for a short introduction about the study when they are through with the clinic visit. When they come to the private room, the aim and procedures of the study were explained and those who gave an informed consent and met the inclusion criteria were recruited and the questionnaire administered. The questionnaire was structured to capture the side effects that the participants have encountered since they started taking DTG-based ART regimens but were not recorded in the participants' records.

3.9 Case Definition

Neuropsychiatric effects (CNS effects) were defined using the DAIDS AE Grading Table Corrected Version 2.1-July 2017 (37). According to the DAIDS AE Grading table, the CNS effects includes insomnia, headache, suicidal ideation or tendencies, depression, and psychosis. However, in this study participants experienced headache only which was graded as shown in Appendix VII. All the participants had been on DTG -based ART regimen for at least six months

Hypersensitivity reactions were defined as pruritus, the appearance of a rash on the skin and itching. These were graded into four categories as shown in Appendix VIII. According to the grading all the three were grade 1(mild reactions).

Other parameters that were collected were Body Mass Index, Blood pressure and body weight. These additional two parameters were collected as part of assessment of safety to see if DTG-based regimens are associated with increases/decrease in weight and blood pressure. Baseline and follow up body mass index (BMI) and body weight before initiation of DTG-based regimen

and 12 months after initiation of DTG-based regimen were extracted from participants' records to assess if there was any change in these measurements overtime in participants on DTG at QECH in Malawi. BMI readings are recorded during each visit to the clinic whether scheduled or unscheduled visits.

Laboratory results for random blood sugar and liver function tests (ALT) were not collected from patients' files because they were not routinely collected from participants.

Effectiveness was evaluated using the viral load test results after having been on DTG for eighteen months. Two viral load test results taken six months after the initiation of DTG-based ART regimen, and then approximately twelve months after the first viral load test were compared to evaluate whether there has been viral suppression. If the first viral load test result was already suppressed (<20-199 copies/ml) if there is maintenance of the suppressed value at the second test. Viral suppression was defined as serum HIV RNA numbers of less than 20-199 copies/ml (15) after having been on DTG -based ART for at least six months. DTG-based regimen was considered effective if the second viral load test result has a suppressed value range (less than 20-199 copies/ml). The Malawi 2018 clinical management of HIV in Children and Adults Policy updates Addendum to the 4th Edition of Malawi integrated guidelines and standard operating procedures for Clinical HIV services, stipulates that viral load testing be scheduled after 6 months on ART. Routine Viral load monitoring is scheduled approximately every 12 months from the last test, but additional viral load test be done when treatment failure is suspected.

3.9.1. Quality Assurance

All the data collection instruments used in the study were pretested on twenty patients and improved based on the feedback received. A pharmacy technician with a diploma in pharmacy was involved in the study as a research assistant to support the researcher. The Researcher trained the assistant on the use of the data collection tools before the study commenced. The researcher checked the data collected for completeness and accuracy against the source documents daily. Validity was done by ascertaining that the questions in data collection forms and questionnaire contained the variables that the study wanted to measure

3.9.2 Data Management

The reviewed data was entered an Epi Info version 7 database. Data was entered within 24 hours of collection. Information contained in the database was backed up daily onto an external storage device that was kept in a locked cabinet as well as sent to the researcher's email. Hard copies of the filled data collection forms and questionnaires were stored in a lockable cabinet.

At the end of the data collection process, data cleaning and validation process was done before exporting the data to Stata software Version 14.0 for analysis. Reliability of the questionnaire was evaluated by pre-testing them on collecting data from 10 manual records and then giving the manual records to the two pharmacy technicians to collect data from the same records and compared the results from the three data collectors were similar

3.10 Study Variables

Hypersensitivity reactions and neuropsychiatric (CNS) effects were the main outcome variables (dependent variables). Other variables were viral suppression and other patient reported side effects. Potential predictor

(independent variables) variables were classified as patient sociodemographic characteristics, which included age, gender, and alcohol intake; smoking status, medical characteristics, which will include co-morbidities and medication history that include concurrent drugs, herbal medicines, opportunistic infections.

DTG-based ART regimen was the exposure variable. Possible confounding variables include gender, comorbidities, concurrent drugs, herbal medicines, and alcohol intake,

3.11 Data Analysis

All data were subjected to descriptive statistics. Continuous variables such as age, BMI, blood pressure and viral load results were tested for normal distribution using Shapiro Wilk test. In addition to the Shapiro Wilk test, histograms were plotted to examine the distribution. Age was normally distributed ($p>0.005$); hence, it was summarised as mean and standard deviation. Continuous variables that were not normally distributed ($p<0.05$) such as BMI, viral load was summarised as median and IQR. Categorical variables such smoking status, alcohol intake, gender, presence/absence of opportunistic infection, concurrent medication, comorbidities, and herbals were summarised as frequencies and percentages.

Measures of central tendency were compared across the levels of the main outcome variables, which is those who had their viral load suppressed and versus those were not. Others are those who developed the adverse effects and those who did not develop the adverse effects, and for continuous variables; sign rank test was used for inferential analyses because the viral load was not normally distributed. For categorical variables, proportions were compared amongst those who developed the adverse effects and those who did not. Two-by-two summary statistical test for the risk factors of neuropsychiatric

symptoms, hypersensitivity reactions and other side effects reported by the participants on DTG-based ART regimens were conducted using Fishers exact test or Pearson's Chi test.

Apart from neuropsychiatric symptoms and hypersensitivity reactions, other reported side effects such as back pain, dizziness, diarrhea, muscle-aches, general body weakness, vomiting, abdominal pains, were analyzed.

Back pain was reported in 8.02% of the participants on DTG based ART regimen. Covariates such as age, gender, opportunistic infection, comorbidity, alcohol, smoking, concurrent medication, and herbal medicines were assessed to identify their association with back pain using Fisher's exact inferential test. Similar covariates were also analyzed for all the other side effects mentioned above.

All analyses were done using a Stata/IC 14.1 package. P value was set at 0.05.

3.12 Ethical Consideration

Ethical approval was attained from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) reference number KNH-ERC/A/106 as well as College of Medicine Research and Ethics Committee (COMREC) number P.02/20/2966 in Malawi (Appendix I and II). To implement the study, permission was sought from the relevant hospital management authorities at QECH central Hospital.

All participants were required to give written informed consent by signing an Informed Consent Form (Appendix) before taking part in the study.

Utmost care was taken by the researcher to ensure maximum privacy and confidentiality of the information obtained during the study. No participant's name was used instead codes were used. Electronic data were stored in a

password protected database that was only be accessible to the researcher. The data collection tools and any other materials that were used during the study were kept in a locked cabinet.

4.0. CHAPTER FOUR: RESULTS

This section describes the results in tables of the descriptive analysis (baseline characteristics of social demographic traits of participants on dolutegravir at QECH, disease history of the participants, medication that they are taking). Exploratory data analysis (comparison of the measures of central tendency across participants who developed the outcome of interest and those who did not, and inferential statistics to determine if the differences are statistically significant) and regression analysis (to control for confounding, and to identify the important predictor variables or risk factors of the outcomes). The main outcomes of this study are development of adverse effects such as neuropsychiatric symptoms, hypersensitivity reactions, dizziness, nausea, vomiting, abdominal pain, dysuria, diarrhoea, back pain, and muscle aches

4.1. Socio demographic Characteristics of study participants

A total of 262 participants were enrolled in the stud of which 163 (62%) were female. The mean age of the study participants was 42.28 years (SD 10.10). A total of 175 (about 67%) were aged between 35 and 55 years. More than 90% of the participants revealed that they had not smoked or taken alcohol since the initiation of DTG –based ART (table 4.1).

Table 4. 1: Socio- demographic characteristics of study participants (n=262)

Variable	Frequency or Distribution
Age: mean (SD)	42.28 (10.10)
Age group (years) n (%)	
= 18	1 (0.38)
>18- <30	35 (13.36)
>30-<40	85 (32.44)
>40-<50	92 (35.11)
>50-<60	40 (15.27)
>60	9 (3.44)
Gender: n (%)	
Male	99 (37.79)
Female	163 (62.21)
Duration on DTG-based regimen (months): Median (IQR)	15 (10-18)
Alcohol: n (%)	
Yes	26 (9.92)
No	236 (90.08)
Smoking: n (%)	
No	251 (95.80)
Yes	11 (4.20)

4.2. Medication history of the study participants

A total of 140 (about 53%) participants were taking TDF/3TC/EFV ART regimen before national guideline change to DTG -based 1st line ART regimen, and 118 (45%) started ART during the national transition period to DTG –based first line regimen. Most participants (over 90%) were not on herbal or hospital prescribed concurrent medication and 98.85% of the participants did not experience any opportunistic infection during the study period (Table 4.2).

Table 4. 2: Medication history of study participants (n=262)

Variable	n (%)
ART regimen:	
Before national transition to DTG	
TDF/3TC/EFV	140 (53.44)
NEW (ART NAÏVE)	118 (45.04)
TDF/3TC/NVP	2 (0.76)
ABC/3TC/EFV	2 (0.76)
After national transition to DTG	
TDF/3TC/DTG	257 (98.09)
ABC/3TC/DTG	5(1.91)
Opportunistic infection	
No opportunistic infection	259 (98.85)
Syphilis	1 (0.38)
Oral candida	1 (0.38)

Pneumonia	1 (0.38)
Comorbidities	
No comorbidity	252 (96.18)
Asthma	6 (2.29)
Peptic ulcer disease	1 (0.38)
Cancer of the cervix	1 (0.38)
Tuberculosis	1 (0.38)
Diabetes	1 (0.38)
Concurrent medication	
No concurrent medication	238 (90.84)
Depo-Provera	7 (2.67)
Salbutamol	6 (2.29)
Metformin	1 0.38)
Ibuprofen	1 (0.38)
Amitriptyline	3 (1.15)
RHZE and Pyridoxine	1 (0.38)
Pyridoxine	1 (0.38)
Ferrous sulphate	1 (0.38)
Herbal drugs	1 (0.38)
Omeprazole	1 (0.38)
Microgynon	1 (0.38)

Key: RHZE – Fixed dose Combination of Rifampicin Isoniazid Pyrazinamide Ethambutol

4.3. Prevalence of adverse drug reaction (n=262).

Majority of participants, 244 (93%) did not report any neuropsychiatric symptoms since they started DTG-based ART, while 18 (6.87%) reported experiencing headaches. Most of the participants did not report any hypersensitivity reactions (228 (87%) while 21 (8%) reported pruritis, 11 (4.2%) reported a mild rash and urticaria was rare 2 (0.76%) Apart from neuropsychiatric symptoms and hypersensitivity reactions, participants reported other side effects such as dizziness, weakness, abdominal pain, diarrhea, nausea, vomiting, muscle aches, back pain, joint pains, and dysuria. Dizziness was reported in 18 (6.87%), weakness in 15 (5.75%), abdominal pain in 11 (4.2%), diarrhea in 5 (1.91), nausea in 15 (5.73%) vomiting in 6 (2.3%), muscle aches in 5 (1.9%), back pain in 21 (8.02%) and dysuria in 7 (2.08%) of the participants (Table 4.3).

Table 4. 3: Prevalence of adverse effects in the study participants (n=262)

Variable	N (%)
Neuropsychiatric effects	
No	244(93.13)
Yes	18 (6.87)
Hypersensitivity reaction	
No reaction	228(87.02)
Mild rash	11 (4.20)
Urticaria	4 (0.76)
Pruritis	21 (8.02)
Dizziness	
No	244 (93.13)
Yes	18 (6.87)
Weakness	

	No	244 (94.25)
	Yes	15 (5.75)
Abdominal pain		
	No	251 (95.80)
	Yes	11 (4.20)
Diarrhea		
	No	257 (98.80)
	Yes	5 (1.91)
Nausea		
	No	247 (94.27)
	Yes	15 (5.73)
Vomiting		
	No	256 (97.71)
	Yes	6 (2.29)
Muscle aches		
	No	257 (98.90)
	Yes	5 (1.91)
Back pain		
	No	241 (91.98)
	Yes	21 (8.02)
Dysuria		
	No	254 (97.32)
	Yes	7 (2.08)

4.4. Viral load suppression and change in Body Mass Index and Blood pressure in the study participants (n=262).

The median viral load of participants significantly dropped from 40 copies/ml (40-839) to 30copies/ml (30-40) $P < 0.001$ (table 4.4). First viral load for the participants was taken 6 months after the initiation of DTG-based ART and second sample of viral load was taken approximately twelve months from the first viral load sample

Baseline and follow up body mass index (BMI) and body weight before initiation of DTG-based regimen were also extracted from participants' records to assess if there was any change in these measurements overtime in participants on DTG at QECH in Malawi

Overall, the median BMI significantly increased from 22.62 (IQR 20.55-25.65) to 23.93 (IQR 22.55-26.70) P=0.000. The mean systolic blood pressure (BP) significantly increased from baseline of 119.59 (13.64) to 120 (114-127) P=0.0299, while diastolic BP change was not statistically significant P=0.065 (Table 4.4)

Table 4. 4: Viral load suppression and change in Body Mass Index and Blood pressure in the study participants (n=262).

Variable	median (IQR)	P-value	Inferential Test
Viral load		0.001	Rank sum sign
Viral load at 6 months after DTG initiation	40 (40-839)		
Viral load at approximately 12 Month after DTG initiation	30 (30-40)		
BMI: Median (IQR)		0.000	Rank sum sign
Baseline BMI Before DTG- based regimen	22.62 (20.55 - 25.65)		
BMI at 12 months after DTG- based regimen	23.97 (21.55-26.70)		
Blood Pressure Mean (SD)			Paired t-test
Systolic BP (baseline) Mean (SD)	119.59(13.64)	0.0299	
Systolic Bp (follow-up at 12 month) Median (IQR)	120 (114-127)		

Diastolic BP (baseline): mean (SD) Diastolic BP (follow-up at 12 moths): mean (SD)	78.56(9.88) 80 (77-87)	0.0651	

Exploratory Data analysis

4.5 Relationship between of neuropsychiatric symptoms and DTG-based regimen

Concurrent use of herbal drugs was significantly associated with neuropsychiatric symptoms (P < 0.001); while age (p=0.824); gender (p=0.207); alcohol (p=0.105); smoking (p=0.185); co morbidities (p=1.000); opportunistic infection (p=0.193); concurrent medication (p=0.202); ART regimen that the participants were on before national transition to DTG-based regimen (p= 0.316) and after transition (p=0.159), were not associated with neuropsychiatric symptoms. The median duration of taking DTG-based regimens for all the participants included in the study was 15 months (IQR 10-18). However, data were not collected on the exact time the participants started experiencing the symptoms after the initiation of DTG –based regimen. (Table 4.5)

Table 4. 5: Relationship between neuropsychiatric symptoms and DTG-based regimens (n=262)

Variable	No Neuropsychiatric Symptom	Neuropsychiatric Symptom	Total	P-Value	Inferential test
ART regimen				0.316	
(After national transition to DTG)					
TDF/3TC/DTG	239	18	257	0.159	
ABC/3TC/DTG	4	1	5		Fisher's exact
(Before national transition to DTG)					
TDF/3TC/EFV					
NAÏVE					
TDF/3TC/NVP	132	8	140		Fisher's exact
ABC/3TC/EFV	108	10	118		
	2	0	2		
	11	2	13		
Herbal medicine					Fisher's exact
No herbal medicine				0.000	
Ginger	230	9	239		
Aloe vera	3	0	3		
Unknown	2	0	2		
Moringa	8	4	12		
Kigeria pinata	3	2	5		
	1	0	1		

4.6. Relationship between hypersensitivity reactions and DTG-based regimens

Age (p=0.119); gender (p=0.308); alcohol (p=0.444); smoking (p=0.570); opportunistic infection (p=1.000); concurrent medication (p=0.193); ART regimen that the participants were on before national transition to DTG-based regimen (p= 0.692) and after transition (P=0.496); and concurrent use of

herbal medicines (p=0.767) were not associated with hypersensitivity reaction (Table 4.6).

Table 4. 6: Relationship between hypersensitivity reactions and DTG-based regimens (n = 262)

Variable	No Hypersensitivity reaction	Hypersensitivity reaction	Total	P Value	Inferential Test
Gender				0.308	Pearson's chi
Male	88	11	99		
female	140	23	163		
Smoking				0.570	Fisher's exact
No	218	33	251		
Yes	10	1	11		
Alcohol				0.444	Fisher's exact
No	206	30	236		
Yes	22	4	26		

4.7. Relationship between Back pains reactions and covariates

Concurrent medication (p=0.002), herbal medicine (0.012) and opportunistic infection (p=0.018) had a statistically significant association with back pains. Age (p=0.346); gender (p=0.976); alcohol (p=0.358); smoking (p=0.609); co morbidity (p=0.291; regimen before and after national transition (p=0.544 and p=0.656 respectively) were not associated with back pains (Table 4.7).

Table 4. 7.: Relationship between back pain and DTG-based regimens (n=262)

Variable	No backpain	Back pain	Total	Inferential Test	P- value
Concurrent Medication				Fisher's exact	0.002
No Concurrent Medication	223	15	238		
Depo povera	5	2	7		
Salbutamol	6	0	6		
Metformin	1	0	1		
Ibuprofen	0	1	1		
Amitriptylline	2	1	3		
Rhze & pyridoxine	1	1	1		
Pyridoxine	1	0	1		
Ferrous sulphate	1	0	1		

Herbals	1	0	1		
Omeprazole	1	0	1		
Microgynon	0	1	1		
Opportunistic infection				Fisher's exact	0.018
No Opportunistic Infection	240	19	259		
Syphilis	0	1	1		
Oral candida	1	0	1		
Pneumonia	0	1	1		
Herbal Medicines				Fisher's exact	0.012
No herbal medicine	221	18	239		
Ginger	2	1	3		
Aloe veva	0	2	2		
unknown	0	1	2		
Moringa	5	0	5		
Kigeria pinata	1	0	1		

4.8. Relationship between dizziness and covariates.

(Table 4.8) describes risk factors of experiencing dizziness in participants on DTG-based regimen. A two-by two table with Fisher's exact inferential test, showed a statistically significant association between presence of co morbidities and dizziness ($p<0.001$); and concurrent medication and dizziness ($p=0.002$), while age ($p=0.759$); gender ($p=0.942$); alcohol ($p=0.142$); smoking ($p=0.450$); herbal medication ($p=0.317$)**;** opportunistic infections ($p=1.000$); ART regimen that the participant was taking before national transition to DTG-based regimen ($p= 0.2000$); and after transition ($P=0.301$ were not associated with dizziness in participants on DTG based ART regimen (Table 4.8).

Table 4. 8.: Relationship between of dizziness and covariates (n=262).

Variable	No Dizziness	Dizziness	Total	P-Value

Co morbidities				
No co morbidity	237	15	252	P < 0.001
Asthma	5	1	6	
PUD	0	1	0	
Ca cervix	1	0	1	
TB	1	0	1	
Diabètes	0	1	1	
Concurrent medication				0.002
No Concurrent Medication	226		238	
Depo povera	6	12	7	
Salbutamol	5	1	6	
Metformin	0	1	1	
Ibuprofen	0	1	1	
Amitriptylline	1	1	1	
RHZE & pyridoxine	2	0	3	
Pyridoxine	1	1	1	
Ferrous sulphate	1	0	1	
Herbals	1	0	1	
Omeprazole	0	0	1	
Microgynon	1	1	1	
		0		

4.9. Relationship between the covariates and abdominal pain, vomiting, nausea, diarrhoea, weakness, muscle aches and dysuria (n=262).

A similar analysis (as in i and ii above) was conducted to assess risk factors for abdominal pain, vomiting, nausea, diarrhea, weakness, muscle aches and dysuria in participants on DTG-based regimen. A similar set of covariates such as age, gender, co morbidities, opportunistic infections, concurrent medication, alcohol, smoking, herbal medication, ART regimen the participant was taking before national transition to DTG-based regimen, and after transition.

4.9.1. Abdominal pain

Only gender and concurrent use of herbal medication had a statistically significant association with abdominal pain (p=0.005 and p=0.009 respectively).

4.9.2. Vomiting

None of the covariates demonstrated significant association with the symptom: Age (p=0.280), gender (p=0.817), co morbidities (p=0.999), opportunistic infections (p=1.000), concurrent medication (p=1.000), alcohol (p=0.411), smoking (p=0.604), herbal medication (p=0.938), ART regimen the participant was taking before national transition to DTG-based regimen (p=0.987), and after transition (p=0.730).

4.9.3. Nausea

None of the covariates demonstrated significant association on with the symptom: Age (p=0.845), gender (p=0.115), co morbidities (p=1.000), opportunistic infections (p=1.000), concurrent medication (p=0.128), alcohol

(p=0.549), smoking (p=0.484), herbal medication (p=1.000), ART regimen the participant was taking before national transition to DTG-based regimen (p=0.547), and after transition (p=0.743).

4.9.4. Diarrhea

None of the covariates demonstrated significant association with the symptom: Age (p=0.771), gender (p=0.374), co morbidities (p=1.000), opportunistic infections (p=1.000), concurrent medication (p=0.058), alcohol (p=0.590), smoking (p=0.806), herbal medication (p=1.000), ART regimen the participant was taking before national transition to DTG-based regimen (p=0.688), and after transition (p=0.907).

4.9.5. Weakness

Only concurrent use of herbal medication demonstrated a statistically significant association with the symptom while the rest did not: Age (p=0.411), gender (p=0.272), co morbidities (p=0.245), opportunistic infections (p=0.163), concurrent medication (p=0.286), alcohol (p=0.547), smoking (p=0.515), herbal medication (p=1.000), ART regimen the participant was taking before national transition to DTG-based regimen (p=0.835), and after transition (p=0.258).

4.9.6. Muscle aches

ART regimen the participant was taking before national transition to DTG-based regimen (p=0.047) showed a statistically significant association with the symptom while the rest of the covariates did not: Age (p=1.000), gender (p=0.626), co morbidities (p=1.000), opportunistic infections (p=0.163), concurrent medication (p=0.173), alcohol (p=0.590), smoking (p=0.806), herbal medication (p=0.143), and after transition (p=0.093).

4.9.7. Dysuria

Concurrent medication (p=0.041) was the only covariate which showed a statistically significant association with dysuria while the rest did not: Age (p=0.712), gender (p=0.075), co morbidities (p=0.112), opportunistic infections (p=1.000), alcohol (p=0.525), smoking (p=0.263), herbal medication (p=1.000), ART regimen the participant was taking before national transition to DTG-based regimen (p=0.514), and after transition (p=0.128).

4.10. Regression analysis

Regression Models for predictors on outcomes such as: neuropsychiatric symptoms, hypersensitivity reaction, dizziness, weakness, muscle aches, abdominal pain, and dysuria.

4.10.1. Predictors of neuropsychiatric symptoms

In the univariate and multivariate model, concurrent use of herbal medicine predicted occurrence of neuropsychiatric symptoms in participants on DTG based ART regimen (adj OR: 2.237 p=0.000 P < 0.001). Although alcohol was 3 times more likely and opportunistic infections 2.6 times more likely to be associated with neuropsychiatric symptoms in the adjusted model, this was not statistically significant (p=0.217 and p=0.142 respectively) (Table 4.10.1)

Table 4.10. 1: Univariate and Multivariate logistic regression of predictors of neuropsychiatric symptoms

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Previous regimen	1.833	(0.860, 3.905)	0.116	1.623	(0.556, 4.738)	0.375
Smoking	3.059	(0.611, 15.292)	0.173	0.708	(0.649, 7.726)	0.771
Alcohol	2.679	(0.818, 8.777)	0.104	3.033	(0.520, 17.678)	0.217

Opportunistic infections	3.027	(0.997, 9.664)	0.050	2.603	(0.728, 9.319)	0.142
Herbal medicine	2.242	(1.610, 3.122)	0.000	2.237	(1.558, 3.213)	0.000

4.10.2. Predictors of dizziness symptoms

Co morbidities, concurrent medication, previous ART regimen (ART regimen before national guideline change to DGT based ART regimen) were run in a univariate and multivariate model to determine risk of dizziness among participants on DTG based ART regimen. The adjusted model showed that, co morbidities, concurrent medication, and previous ART regimen did not predict dizziness (adj OR: 1.788, p=0.085; 1.166, p-0.203; 1.931, p=0.113 respectively) (Table 4.10.2).

Table 4.10. 2: Univariate and multivariate analysis of predictors for experiencing dizziness.

	Univariate			**Multivariate**		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Co morbidities	2.071	(1.166, 3.678)	0.013	1.788	(0.924, 3.463)	0.085
Concurrent medication	1.295	(1.070, 1.568)	0.008	1.166	(0.920, 1.477)	0.203
Previous ART regimen	1.739	(0.798, 3.786)	0.164	1.930	(0.856, 4.350)	0.113

4.10.3. Predictors of weakness symptoms

Herbal medication, and opportunistic infections were run in a univariate and multivariate model to determine risk of weakness among participants on DTG based ART regimen. The adjusted model showed that, herbal medication has a statistically significant association with weakness (OR 1.574 p=0.020) compared to opportunistic infections (OR 3.162, p=0.088) (Table 4.10.3).

Table 4.10. 3: Univariate and multivariate analysis of predictors for experiencing weakness.

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Herbal medication	1.651	(1.149, 2.371)	0.007	1.574	(1.075, 2.302)	0.020
Opportunistic Infections	3.381	(1.072, 10.664)	0.038	3.162	(0.843, 11.862)	0.088

4.10.4. Predictors of muscle aches

A univariate and multivariate model was run to determine if concurrent medication, current ART regimen, previous ART regimen and herbal medication predicted the occurrence of muscle aches among participants on DGT-based ART regimen.

Current ART regimen was 15.65 times more likely to be associated with muscle aches, but this was not statistically significant (p=0.103) and therefore not a significant predictor of muscle aches in the model. Concurrent medication (OR: 1.095, p=0.695), previous ART regimen (OR: 1.158, p=0.842), and herbal medication (OR: 0.710, p=0.607) did not also predict muscle aches in participants on DTG based ART regimen (Table 4.10.4).

Table 4.10. 4: Univariate and multivariate analysis of predictors of muscle aches

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Current ART Regimen	15.813	(1.430,174.935)	0.024	15.647	(0.754, 426.318)	0.103
Previous ART regimen	1.089	(0.262, 4.532)	0.907	1.158	(0.273, 4.908)	0.842
Herbal medication	0.916	(0.295, 2.849)	0.880	0.710	(0.192, 2.625)	0.607

4.10.5: Predictors of back pains

A continued univariate and multivariate regression modelling was performed to determine if concurrent medication, herbal medication and opportunistic infections could predicted the occurrence of back pains among participants on DGT based ART regimen, concurrent medication (OR: 1.321, p=0.004) and opportunistic infections (OR: 4.795, p=0.019) were statistically significant predictors of back pain in the model while herbal medication (OR: 0.832, p=0.582) p=0.695), did not predict back pain in participants on DTG based ART regimen (Table 4.10.5).

Table 4.10.5: Univariate and multivariate analysis of predictors for experiencing Back pain.

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Concurrent medication	1.300	(1.08, 1.560)	0.006	1.321	(1.092, 1.597)	0.004
Herbal Medication	0.970	(0.575, 1.636)	0.908	0.832	(0.432,1.603)	0.582

Opportunistic infection	4.208	(1.123, 15.767)	0.033	4.795	(1.287, 17.865)	0.019

4.10.6: Predictors of abdominal pains

In a further univariate and multivariate regression model was to determine if concurrent medication and herbal medication predicted the occurrence abdominal pains among participants on DGT based ART regimen, both concurrent medication (OR: 1.287, p=0.047) and herbal medication (OR: 1.600, p=0.029) demonstrated statistically significant prediction for the occurrence of abdominal pains in participants on DTG based ART using the model (Table 4.10.6)

Table 4.10. 5: Univariate and multivariate analysis of predictors for experiencing abdominal pain.

	Univariate			**Multivariate**		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Concurrent Medication	1.262	(1.011, 1.573)	0.039	1.287	(1.003, 1.576)	0.047
Herbal Medicine	1.601	(1.061, 2.416)	0.025	1.600	(1.051, 2437)	0.029

4.10.7: Predictors of dysuria

A final univariate and multivariate regression modelling were performed to determine if gender, co morbidities, concurrent medication, and previous ART regimen predicted the occurrence, dysuria among participants on DGT based ART regimen presenting this symptom. None of: Gender (OR: 0.236, p=0.105), co morbidities (OR: 1.257, p=0.566) and concurrent medication (OR: 1.286, p=0.149) predict dysuria in participants on DTG based ART in the model (Table 4.10.7).

Table 4.10. 6: Univariate and multivariate analysis of predictors for experiencing dysuria.

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Gender	0.235	(0.045, 1.235)	0.087	0.236	(0.041, 1.349)	0.105
Co morbidities	1.967	(1.048, 3.690)	0.035	1.257	(0.575, 2.747)	0.566
Concurrent Medication	1.279	(0.996, 1.642)	0.054	1.286	(0.914, 1.809)	0.149

5.0. CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1. DISCUSSION

This study was conducted with the aim of assessing the safety and effectiveness of Dolutegravir in HIV-infected patients at QECH in Malawi. In the study, 262 eligible participants were included. Most of the participants were female (62%). This very well reflects adult HIV clinic attendance trend in Malawi hospitals (61). Centre for Disease Control suggests that there is a higher proportion of women than men who are HIV infected due the anatomical/biological make-up of women which contributes to them contracting HIV more than men (61). The mean age of participants is 42.2 years and most 92 (35.11%) of the participants were in the middle-age group

(40-50 years). This population is noted as a high risk because of high sexual activity and early marriages (62).

Among the participants included in the study, 140 (53%) were previously on TDF/3TC/EFV, 2 (0.76 %) were on ABC/3TC/EFV and another 2 (0.76%) were on TDF/3TC/NVP ART regimens before policy change to switch to DTG based ART regimen as first-line regimen for the treatment of HIV infection in adults in Malawi. A total of 118 (about 45%) were initiated on DTG based ART regimen during the transition phase. The period is marked by increased ART enrolment rate due to a test and treats policy that was implemented during the same period. The test and treat policy replaced treatment of HIV by WHO clinical disease stage or CD4 count. Once a person tests HIV, positive ART is started immediately without waiting for occurrence of HIV disease symptom or decline of CD4 count to defined threshold (65).

A total of 251 (95%) of participants declined smoking and taking alcohol during the period under study. Only 10% of the participants disclosed that they were on herbal medicines. This may partly be because the management of HIV in Malawi involves prescription of conventional medicine and hence herbal medicines are not approved for use by doctors (67). This would potentially affect disclosure of use of herbal medicines although in most situations, HIV positive patients use herbal medicines to self-treat side effects of ART and / or opportunistic infections (67).

Opportunistic infections among participants on DTG based ART regimen were rare (2%). This might be due to the test and treat policy in Malawi (65). Early ART initiation in the era of test and treat in Malawi allows inclusion of asymptomatic HIV positive individuals on ART. Early access to HIV

treatment, care and support leads to better treatment response hence preventing the development of opportunistic infections (50, 51).

5.1.1. Prevalence of adverse drug reactions

Majority (93.13%) of participants did not have neuropsychiatric symptoms. This finding is contrary to that from a randomized controlled trial that assessed the adverse events of rategravir and dolutegravir, neuropsychiatric event was the most common reported adverse event among participants on dolutegravir (6.87%) (58). Common neuropsychiatric symptoms in these controlled studies included insomnia, headache, suicidal thoughts (23,27,29). Another study revealed that 14% of participants who were started on dolutegravir, discontinued because of neuropsychiatric symptoms (59). The rate was said to be higher than what was observed during clinical trials. In this study however, the only reported neuropsychiatric symptom by the participants was headache occurring in 6.9% of participants. Being a retrospective study, possibility of recall bias might have affected the participants to recall what other side effects they might have experienced. Data from records was also not reliable as some information was missing from the records. Headache is a non-specific symptom that can occur due to so many other factors including medicines and HIV. In ART, headaches usually occur early in the treatment initiation phase and eventually go away over time (53). In clinical trials, prevalence of headache due to DTG was low (1-2%) as compared to real-life studies (69). Proportions as high as 33% have been reported in other studies (54). Several studies have also reported headache in participants taking DTG-based regimens (52, 53, and 60). In this study, the occurrence of headache was not associated with gender, smoking, alcohol, co morbidity, opportunistic infections, concurrent medicine, previous and current ART regimen. However, concomitant use of herbal medicine was associated

with occurrence of headache (p= 0.000). Out of seventeen participants who reported that they were on herbal medicines, six of them experienced a headache. Of the six people who experienced a headache, four participants who did not reveal the type of herbal medicine they were on, experienced the headaches, while 2 of the participants who experienced headaches revealed that they were on Moringa olerifera. Participants who revealed being on ginger, kigeria piñata and aloe vera did not experience headaches. In a multivariate model, the use of herbal medicine only predicted occurrence of neuropsychiatric symptoms (OR=2.237, p=0.000).

Hypersensitivity reaction was another important outcome experienced by participants on DTG-based regimen at Queen Elizabeth Central Hospital. Hypersensitivity reactions to medicines are common among HIV patients and it occurs at very much high rate among this population as compared to the general population (70). Reports from studies have also demonstrated that hypersensitivity reactions occur with all antiretroviral agents (both newer and older) and drugs to treat opportunistic infections (70). These reactions have a delayed onset. Several studies have reported pruritis, skin rash and itching as common hypersensitivity reaction to DTG based ART regimen (52). In this study majority of the participants (87.02%) did not experience any hypersensitivity reaction. The most common hypersensitivity reaction that the participants experienced was pruritis (8.02%) followed by skin rash (4.2%). Urticaria was rare (0.76%). There was no association in the occurrence of hypersensitivity reaction among participants on DTG based ART regimen with age (p=0.119), gender (p= 0.308), smoking (p= 0.570), alcohol (p=0.444), co morbidities (p=0.757), opportunistic infections (p=1.000), concurrent medication (p=0.838), previous ART regimen before national transition to DTG (p=0.692) ART regimen after national transition (p=0.496) and herbal medicine (0.767). Since all the covariates did not demonstrate any

association with the occurrence of the hypersensitivity reaction, there is a possibility that, the DTG-based ART regimens are responsible for the occurrence of hypersensitivity reactions.

Apart from neuropsychiatric symptoms and hypersensitivity reactions, data on other side effects reported by the participants was also collected. Among the 262 participants, 18(6.9) reported experiencing dizziness since they started the regimen. The dizziness started occurring the same day of starting DTG-based regimen and in most participants; it was short term which went off after some weeks of continuing treatment. Majority 244(93.13) of the participants did not experience dizziness. Age group, gender, alcohol use, ART regimen before and after national transition to DTG-based regimen and being on herbal medicine were not associated with the occurrence of dizziness ($p>0.05$). Exploratory data analysis showed that having a comorbidity and taking concurrent medication were associated with occurrence of dizziness ($p=0.000$ and 0.002 respectively). Regression analysis model revealed same finding that co morbidities, concurrent medication, and previous ART regimen predicted dizziness (adj OR: 1.788, $p=0.085$; 1.166, p-0.203; 1.931, $p=0.113$) although the p-values were insignificant. This finding is different from what was observed in other studies where participants reported dizziness with DTG (59, 60). Dizziness due to DTG- based regimens has also been reported in similar studies and non-inferiority trials in proportions of 6% (70). Multivariate logistic regression revealed that ART regimen that the participants were taking before the national policy change to DTG-based regimens had an association with the occurrence of dizziness although the p- value was not significant (OR 1.930, $p=0.113$). The ART regimen was 1.930 times more likely to be associated with the occurrence of dizziness.

Generalized body weakness occurred in 15(5.5%) of the participants. All the variables were not associated with occurrence of generalized body weakness (p>0.05) but being on herbal medicine was associated with the occurrence of generalized body weakness. However multivariate logistic regression revealed the existence of an association between generalized body weakness and being on herbal medicine (OR 1,574, p=0.002) and having an opportunistic infection (OR 3.162, p=0.088).

Some participants 11(4.2) experienced abdominal pain. No significant association was observed between the occurrence of abdominal pain and having a co morbidity, smoking, taking alcohol, being on concurrent medicine, or the age group. A significant association was observed between the occurrence of abdominal pain and gender as well as being on herbal medicine (p=0.005 and 0.009 respectively). Females experienced abdominal pain more than males. After multivariate regression, an association was observed that being on concurrent medication was associated with the occurrence of abdominal pain (OR 1.287, p= 0.047) and similarly, taking herbal medicine (OR 1.600, p= 0.029).

Diarrhea was rare occurring in 5(1.91) of the participants on DTG at QECH. Other studies reported higher proportion of participants presenting with diarrhea on DTG based ART regimen. In a clinical study assessing the efficacy and safety of DTG, diarrhea was reported in 12.9% of the participants (52) similarly SAILING and FLAMINGO studies reported 18% and 10% respectively in participants receiving DTG-based regimen (23, 53, and 60). Being a descriptive study, the low proportion of diarrhea in our study can be explained by missed diarrhea reports and/or recall bias. However, the results indicate that occurrence of diarrhea was not associated with age, gender, smoking, concurrent medicine, and co morbidity; and a multivariate

regression model supports that these covariates did not predict occurrence of diarrhea. This then points to DTG based ART regimen as a potential risk for diarrhea.

About 15(5.73) of participants on DTG-based ART regimen at QECH reported nausea while taking DTG-based regimen. Alcohol, smoking, co morbidity, concurrent medication, herbal medicine, gender, and age group were not associated with the symptom. In some randomized control studies assessing the efficacy and safety of DTG, nausea was reported by significant proportions of 17% and 18.2% of the study participants (23, 55, and 56, 57). Despite the limitations attributable to the cross-section study design which accounts for the low proportion of nausea cases, the results indicate that DTG based ART regimen was associated with nausea and are therefore, in keeping with the findings of the randomized trials above. A similar finding was also noted with vomiting symptom where 6(2.3) of the participants reported experiencing vomiting. This was not associated with gender, age, smoking, alcohol, co morbidity, concurrent medication, herbal medicine, and opportunistic infection or other covariates of interest. This also suggests that DTG based ART regimen was a potential risk for vomiting in participants on this regimen.

Having adjusted for confounders, dysuria experienced by 7(2.1) of the participants could only be explained by DTG based ART regimen as a potential factor. A final univariate and multivariate regression modeling was performed to determine if gender, co morbidities, concurrent medication, and previous ART regimen predicted the occurrence, dysuria among participants on DGT based ART regimen presenting this symptom. None of: Gender (OR: 0.236, p=0.105), co morbidities (OR: 1.257, p=0.566), concurrent medication

(OR: 1.286, p=0.149), and previous ART regimen (OR: 0.517, p=0.432) predict dysuria in participants on DTG based ART in the model

Back pain occurring in 21(8.02) of the study population could be explained by being on concurrent medicines and having an opportunistic infection. It is possible that participants took concurrent medication because they experienced back pain. In this study, opportunistic infections were very rare and therefore less likely to be a reason for use of concurrent medication among participants on DTG based ART regimen.

Although muscle aches were experienced by a small proportion of participants 5(1.91), a previous ART regimen which the participant was taking before transition to DTG-based ART regimen contributed to this symptom (p=0.047). Majority of participants (53%) were on TDF/3TC/EFV before being on DTG based ART regimen suggesting TDF/3TC/EFV to be a potential culprit for the symptom. Current ART regimen was 15.65 times more likely to be associated with muscle aches, but this was not statistically significant (p=0.103) and therefore not a significant predictor of muscle aches in the model. Concurrent medication (OR: 1.095, p=0.695), previous ART regimen (OR: 1.158, p=0.842), and herbal medication (OR: 0.710, p=0.607) did not also predict muscle aches in participants on DTG based ART regimen. Therefore, DTG was a potential factor for occurrence of muscle aches in the participants.

During interviews, it was noted that participants also experienced polyphagia, heart palpitation, breast enlargement, hot flushes, increased libido or decreased libido, arthritis, numbness, joint pains, ankle pain, ringing in ears, chest pain, hot legs, blurred vision, memory loss, sweating and loss of appetite. However, these symptoms were rare in the study population.

Participants on DTG based ART regimen gained weight. This was noted to be statistically significant, and that gender and smoking played a significant role in BMI distribution. These findings are like those of a study which reported significant increase in BMI in participants on INSTIs (53). Weight gain with DTG use was also reported in randomized control studies (71, 72). These trials demonstrated weight gain from 2.4kgs to 3.9kg at exactly 96 weeks of study. Average BMI readings were collected from the date the DTG regimens were initiated. On average, the participants visited the clinic 4 times, and on each visit, a BMI reading was recorded though data was missing in some participants.

Data on blood pressure was also collected from participant's records. Significant increase in systolic blood pressure were noted after 6 months of starting DTG regimens (p=0.030), while there was no significant changes diastolic pressure (p=0.651). While the systolic blood pressure change was statistically significant it had no clinical significance.

Although some of the side effects witnessed after DTG-based regimens initiation could not be exclusively attributed to DTG, we are certain that this can be done because the concurrent backbones such as 3TC, TDF, ABC were used even before DTG initiation.

5.1.2. Effectiveness

The median viral load dropped from 40 (839-40) to 30 (30-40) HIV RNA<50 copies/mL. This viral load suppression was noted to be statistically significant (p=0.000). This reveals that the viral load continued to be suppressed or maintained to undetectable levels (< 20- 199 copies/ml) in participants on DTG-based regimen at QECH in Malawi. This finding mirrors that of a study that was done by the Ministry of Health of Malawi. However, viral load data

was only available in 92 participant's records out of the 262. There was no baseline viral load taken just before the participants started DTG based ART regimen in all the records of participants studied. Routine viral load test was done six months after the initiation of the DTG regimen and then at approximately twelve months from the first viral load test.

5.1.3. Strengths of the study

This study has large sample size enough to enable description of the side effects that the participants encountered during their treatment. Data for the study was obtained from participants through interviews and review of their medical records. The dual source of data adds merit to validity of the data collected. The study describes symptoms reported by participants as experienced while they are on DTG based ART regimen. The study also reinforced the WHO recommendation of using DTG-based regimens

5.1.4. Limitations of the study

Some limitations in this study can be acknowledged. The use of participants records which were primarily not meant for study purposes resulted in missing and/incomplete data such as missing records on viral load, blood pressure and important laboratory data to detect DTG toxicity. In addition, there was limited observation time on DTG-based ART regimen which only enabled data capture of short term DTG related side effects. A longer observation period would have captured comprehensive data on DTG related side effects. Furthermore, the use of interviews requiring recall on retrospective events were likely to lead to participant recall bias. Although a dual data source was used, missed and/or incomplete data on participant records would lead to recall challenges. Some patients who had been on DTG-based regimens found it difficult to recall some adverse events they had experienced especially if the events were just for a short time. Due to time constraints, a consecutive

sampling technique was employed to realize the sample size at the time when clinic attendance had significantly dropped due to COVID-19 pandemic. A random sampling technique could have been preferred under ideal circumstances for more representative results. Additionally, this study was only able to include participants who were in care at the time of the study. There might be selection bias of participants with major adverse events defaulting ART care and hence not captured in this study and those with minor or no adverse events being retained in care. At the time of the study, HIV pregnant women were not treated with DTG-based ART regimen due to un-established safety data for DTG use in this group of patients. Therefore, data for DTG-based ART regimen in pregnant women was not available.

5.1.5. Delimitations of the study

The study did not analyse the adverse events that the ART treatment-naïve experienced. Furthermore, the study did not include the duration or time points when the adverse effects occurred. It would be interesting to understand the timing of the adverse effects among the participants on DTG-based ART regimen. The study included participants who had been on DTG-based regimens for at least 6 months as such adverse effects that might have occurred soon after initiation of the DTG-based ART regimen might have been missed.

5.2. CONCLUSION

DTG was effective in suppressing viral load in the observed period although it was associated with mild hypersensitivity reactions (rash, itching and pruritis), dysuria, diarrhea, and nausea. DTG was not associated with neuropsychiatric symptoms. This makes DTG-based regimens safe medication to be used as first and second-line treatment in HIV positive patients. The use of herbal medication was an important factor of side effects participants on DTG based ART regimen reported.

5.3. RECOMMENDATIONS

1. Further studies are needed to better understand DTG effectiveness and adverse events profiles in the longer term in Malawi. The studies should include the time points at which participants experience the outcomes.
2. Routine and consistent monitoring and documentation of viral load is needed to address a major gap in understanding effectiveness of ART regimens in Malawi. In addition, routine monitoring of blood pressure, blood glucose and other basic and targeted laboratory test would help detect and assess ART side effects and toxicity.
3. Further studies are recommended to assess the safety and the effects of use of concurrent herbal medication

5.4. DISSEMINATION PLAN

The results of this study will be presented in a Master of Pharmacoepidemiology and Pharmacovigilance thesis. Study findings will be shared with the University of Nairobi Research Ethics Committee, College of

Medicine Research Ethics Committee (COMREC) in Malawi, Ministry of Health HIV unit officials in Malawi, Queen Elizabeth Central Hospital Management committee and Umodzi Family Clinic team and to the public especially the Malawi national HIV program during research dissemination forums. Results will also be published in peer reviewed journals for wider international dissemination.

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APPENDICES

Appendix I: KNH-UoN Research and Ethics Committee certificate of approval

UNIVERSITY OF NAIROBI
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KENYATTA NATIONAL HOSPITAL
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Tel: 7256062
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Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/105

20th March 2020

Christina Joshua
Reg. No. U57/11947/2018
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Christina

RESEARCH PROPOSAL – SAFETY AND EFFECTIVENESS OF DOLUTEGRAVIR IN HIV PATIENTS AT QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI (P965/12/2019)

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 20th March 2020 – 19th March 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.

Protect to discover

Appendix II: College of Medicine Research and Ethics committee certificate of approval

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.02/20/2966 - Safety and Effectiveness of Dolutegravir In HIV Patients at Queen Elizabeth Central Hospital in Malawi by Christina Joshua Mwinjiwa

On 06-May-20

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

06-May-20

Prof. E. Umar -Chairperson (COMREC)

Date

Approved by College of Medicine
06-May-2020
(COMREC)
Research and Ethics Committee

Appendix III: Participant Eligibility Criteria Checklist

All Participants enrolled must meet eligibility criteria based on the inclusion/exclusion criteria in the Study proposal section 3.4.1 and 3.4.2

I. Study Information

Protocol Title:	**Assessment of the safety and Effectiveness of Dolutegravir-based regimens in HIV patients at Queen Elizabeth Central Hospital**
Principal Investigator:	

II. Subject Information:

Participant Code Number:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria	**Yes**	**No**
Participant ≥ 18 years of Age	☐	☐
Participant on DTG- based regimen	☐	☐
Participant on Regimen≥ 6 months	☐	☐

Participant not Diabetic for at least 6 months before DTG regimen	☐	☐
Participants had no Neuropsychiatric effects before DTG	☐	☐
Participant had no liver problems before DTG- regimen	☐	☐
Participant had no rash/ pruritus before DTG regimen	☐	☐
Participant had no hypertension before DTG-regimen	☐	☐
Participant attending clinic at Umodzi family clinic	☐	☐
Participant has given informed consent	☐	☐
Exclusion Criteria		
Participant less than 18 years of age	☐	☐
Participant on DTG- regimen less than six months	☐	☐
Participant has neuropsychiatric effects 6 months before DTG	☐	☐
participant had hypersensitivity reaction 6 months before DTG	☐	☐
Participant was diabetic before DTG regimen	☐	☐
Participant is had liver problem before the DTG regimen	☐	☐
Participant had Hypertension before DTG regimen	☐	☐
Participant attending clinic at Umodzi family clinic	☐	☐
Participant has not given an informed consent	☐	☐

*****All Participant files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to laboratory test results, radiology test results.

IV. Statement of Eligibility

This subject is ☐ **Eligible** ☐ **Ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

Appendix IV (a): Participant Information and Consent Form (English version)

For Enrolment in the Study

TITTLE OF THE STUDY: **ASSESSMENT OF THE SAFETY AND EFFECTIVENESS OF DOLUTEGRAVIR BASED-REGIMEN IN HIV PATIENTS AT QUEEN ELIZABETH CENTRAL HOSPITAL IN MALAWI.**

Principal Investigator and Affiliation……

Introduction

I would like to tell you about this study being conducted by the above researcher. The purpose of this consent form is to give you the information you will need to help you decide whether to participate in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risk and benefits, your rights as a volunteer, and anything about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to take part in the study or not. This process is called "Informed consent". Once you understand and agree to be in the study, you will be requested to sign your name in this form. You should understand the general principles, which apply to all participants in medical research.

1) Your decision to participate in the study is voluntary.

2) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal. 3) Refusal to participate in the study will not affect the services you are entitled to at this hospital or any other hospital. A copy of this form will be given to you for your records.

May I continue? Yes ☐ ☐ No

This study has approval by Kenyatta National Hospital- University of Nairobi Ethics and Research Committee Protocol no P965/12/2019 and College of Medicine Research and Ethics Committee Protocol No. P.02/20/2966

Purpose of Study

World Health Organization recommended the use of dolutegravir-based regimen for the treatment of HIV. This is because DTG is safer, has a high barrier to resistance and has a low cost. The world Health Organization's recommendation to use dolutegravir was based on safety and efficacy studies from clinical trials and other studies done elsewhere. Malawi Transitioned to the use of DTG in January 2019. Currently there is no study that has been done in Malawi to assess the safety and efficacy of Dolutegravir. This study therefore seeks to assess the safety of dolutegravir in Malawi. The findings of the study will help healthcare professionals in the proper management of patients to improve their quality of life. To get this information, information on safety will be collected from patients' records as well as from patient interviews. Patients who are eligible and give informed patient will be recruited in the study. For us to get this information about the safety of this regimen, we will be asking you questions about your medication. We will be asking you about any experience you have been having since you started this regimen.

There will be approximately three hundred participants in this study. We are asking for your consent to participate in this study.

Procedure of the Study

If you agree to participate in this study, this is what will happen:

a) We will check your records for eligibility criteria, laboratory results, and adverse effects that you have encountered since you started DTG- based regimen

b) If you are eligible, we will read the purpose of the study to you and ask you if you agree to join the study.

c) If you accept to join, we access your records and a trained interviewer, in a private area where you will feel comfortable answering questions, will interview you. After the interview, we will ask your telephone number where we can contact you when necessary. If you agree to provide us your phone number, it will only be used by people working for this study and will never be shared to others.

d) We will not collect any blood sample from you or give you any medications.

Informed Consent

Your permission to join this study is voluntary. You do not need to give reasons if you do not want to be included. If you decide not to join the research study, you will continue to be able to come to this clinic for your usual treatment or any other medical problems in the future without any penalty.

Your Right as a Participant

You may stop participating in the research study at any time. Being part of this study is completely your decision. You can continue to come to Umodzi Family clinic for your usual treatment or any other medical problem in the future no matter whether you participated in the study.

Harm, risks, discomforts

One of the potential risks in this study is loss of privacy but we will keep everything you tell us as confidential as possible. We will use a code number to identify you and all our paper records will be kept a lockable cabinet.

Answering questions during the interview may be uncomfortable for you. If there are any questions that you do not want to answer, you can do so. You have the right to refuse the interview, or any questions asked during the interview.

Benefits of the Study

There are no direct benefits in participating in this study. However, the information you will provide will help us better understand if dolutegravir is safe for the population of Malawi. In addition, if there are any harm, to what extent does it cause the harm and what to do in the event that the patients experience adverse events during the course of their treatment.

Cost or Compensation

You will be compensated for transport and time at a flat rate of K1000 (300ksh) for participation in the research study.

Confidentiality

The information we get in this study will be used only for research purposes and will not be shared with anyone who is not involved with the research study or with your medical care. Our Supervisors might look at our records to be sure we are conducting the research properly. They will not record your name or any other identifying information When we share the results of this research study with others in Malawi and other countries, we will not use you, your name, or any other details that might identify you or them. Records from this study will be kept in a locked cabinet.

Further Information

Information regarding your rights as a participant can be obtained from:

Institutional Review Board (College of Medicine Research and Ethics Committee)

The secretariat
College of Medicine Research and Ethics Committee, University of Malawi
Box 360, Blantyre 3, Chichiri
Blantyre, Malawi
Tel. 01871911

The Secretariat/Chairperson

Kenyatta National Hospital-University of Nairobi Research and Ethics Committee (KNH-UoN-ERC)

P.O. Box 20173 00202, Nairobi

Tel: 2726300 ext 44102

Email : uonknh_erc@uonbi.ac.ke

If you have further questions, or concerns about participating in this study or to report any injuries or harm that you feel may be due to your participation in this research study, please contact:

Christina Joshua Mwinjiwa
University of Nairobi, School of Pharmacy
Department of Pharmacology and Pharmacognosy
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Dr Baxter Kachingwe
Head of Pharmacy department
College of Medicine,
P/Bag 360,

Chichiri Blantyre 3

Consent

a) I have had the purpose of this research study discussed with me and I have had my questions answered by the study staff.

b) In a language I understand, I have read or someone has read to me all of the above information including the benefits of the study.

c) I have been told it is up to me if I want to participate and that I can withdraw permission at any time without consequences.

d) If I withdraw permission, I will not lose any legal rights. I understand that I will receive a copy of this signed consent form. I hereby give my voluntary consent to participate in this research study.

Statement of consent (must be an adult age 18 or older (signature or thumbprint required)

I have read above, or it has been read to me, and I agree to take part:

Signature: _____Date: _____

Thumb print:

Participant's name: _____

For persons who cannot sign or read

The above consent was read, opportunity was given for questions and all questions were answered. All individuals who placed fingerprints above agreed to take part in this study.

Signature: _____ Date: _____

Witness's name: _____

Declaration of the person administering the consent

I agree that the procedures, the objectives, the benefits and risks associated with this study have been explained as indicated above.

Consent obtained by: _____

Name of the study staff member obtaining the consent/ assent

Signature: _____ Date: _____

Appendix IV (b): Participant Information and Consent Form (Chichewa version) For Enrolment in the Study

TITLE OF THE STUDY: **ASSESSMENT OF THE SAFETY AND EFFECTIVENESS OF DOLUTEGRAVIR BASED REGIMEN IN HIV PATIENTS AT QUEEN ELIZABETH CENTRAL HOSPITAL IN MALAWI.**

Principle Investigator and Affiliation……

Chiyambi

Ndifuna ndikulongosolereni za kafukufukuyuamene akupangidwa ndi Cristina yemwe ndi Student ku University of Nairobi ku Kenya koma kwawo ndi konkuno ku Malawi. Cholinga cha fomu ya chilolezoyi ndi kukulongosolerani zones zimene mukuyenera kudziwa zokhudza kafukufukuyu kuti zikuthandizeni kupanga chiganizo choti mutenge nawo mukafukufukuyu. Mukhale omasuka kufunsa mafunso aliwonse okhudza cholinga cha kafukufuku, chomwe chingachitike ngati mutasankha kutenga nawo mbali mu kafukufuku, ubwino ndi kuyipa zomwe zingathe kuchitika, ufulu wanu ngati odzipereka mu kafukuyu komamso china chili chonse chokhudza kafukufukuyu komanso pena paliponse pamene musakumvetsetsa. Tikakuyankhani mafunso anu onse ndipo inu mwakhutitsidwa ndi mayankhowo, muli ndi ufulu osankha kutenga nawo mbali mu kafukufukuyu kapena kukana kutenga mbali. Ndondomeko yomwe ndalongosolayi imatchedwa kuti "Kupereka Chirolezo mwachisankho". Ngati mwamvetsetsa cholinga cha kafukufuku ndipo mwavomera kutenga mbali kutenga nawo mbali, mudzafunsidwa kulemba kusayina dzina lanu pa fomu ya chirolezoyi. Mukuyeera kumvetsetsa ndondomeko zokhazikika zomwe zimakhudza munthu wina aliyense amene akutenga nawo mbali pa kafukufuku aliyense

zomwe ndi izi: 1) Chisankho chotenga nawo mbali mu kafufuku ndi kufuna kwanu. 2) Mukhonza kusiya kutenga nawo mbali mu kafukufuku nthawi ina iliyonse imene mwaganiza kutero popanda kupereka chifukwa/zifukwa zimene mwasiyira kutenga mbali. 3) Kukana kutenga mbali mukafukufuku sikungapangitse kusintha kwina kuli konse kwa chithandizo chimene inu mukuyenera kulandira kuchipatala kumene kukupangidwa kafukufuku ngakhale ku chipatala kwina. Mudzapatsidwa kope ya fomuyi kuti nanu mukhale nayo ngati umboni wanu

Ndingathe kupitiliza? Eya ☐ ☐ Ayi

Chilolezo chopanga kafukufukuyu chinapatsidwa kuchokera ku Kenyatta National Hospital- University of Nairobi Ethics and Research Committee Protocol no P985/12/2019and College Of Medicine Research and Ethics Committee Protocol No.p.02/20/296

Cholinga Cha Kafukufuku

Bungwe loona za umoyo padziko lonse lapansi la World Health Organization analimbikitsa kuti tidzigwiritsa ntchito mankhwala okhala ndi dolutegravir (DTG) ngati thandizo loyambirira loti lidziperekedwa kwa anthu amene apezeka ndi kachilombo ka HIV. Langizoli linaperekedwa chifukwa choti ma kafukufuku anaonetsa kuti DTG alibe mavuto ambiri kwa anthu amene amamwa, sikwenikweni kukhala ndi resistance, salimbana ndi mankwala ena amene anthu amatha kumwera pamodzi ndi mankhwalawa komamso ali ndi mtengo osaboola mthumba a. Makafukufuku amenewa anapeza izi anachitikira kumayiko ena monga mayiko azungu amene timatha kusiyana mu zinthu zina monga nyengo, genetic komanso chakudya. Kuno ku Malawi mankhwala awa okhala ndi DTG tinayamba kugwiritsa ntchito mwezi wa January chaka cha 2019 motsatira langizo la bungwe la world Health

Organization.Padakali pano palibe kafukufuku amane anachitikapo mmalawi owunika kuti DTG akugwira ntchito bwanji komanso nanga anthu amene akumwa akukumana ndi mavuto anji. Choncho, tinaona kuti nkofunikira kupanga kafukufuku ameneyu kuti tione ngati pali mavuto amene akudza kamba ka mankhwalawa komanso ngati akugwira bwino ncthito pochepetsa chiwerengero cha ma virus mmagazi. Zotsatira za kafukufukuyi, zidzathaniza ma dokotala kuti athe kuthandiza odwala moyenerera kuti akathe kuchepetsa ululu umene odwala amakumana nawo. Kuti tipeze uti tidziwe zambiri za mavuto a mankhwalawa mmene akugwirira ntchito, tidzapempha kuona nawo mabuku a odwala kuchipatala komanso kuwafunsa mafunso odwalawo. Odwala okhawo amene ali oyenera ndi amene adzafunsidwa kutenga nawo mbali mu kafukufukuyu. Odwalawa adzafunsidwa mafunso kuchokera pa fomu ya mafunso imene tili nayo. Mafunsowa ndi okhudza mankhwalawa a DTG omwe odwala ofunsidwawo akumwa padakali pano.

Tikuyembekezera kufunsa anthu okwan mazana atatu kuti tipeze zambiri zokhudza mankwala amenewa. Munthu mmodzi azidzatenga mphindi zokwana makumi awiri mongoyerekeza

Machitidwe a Kafukufuku

a) Ngati muvomera kutenga nawo mbali mu kafukufukuyu, izi ndi zomwe zidzachitike:

b) Tidzapempha kuti tione nawo ma buku anu a kuchipatala kapena mbiri yanu kuti tione ngat muli oyenera kutenga nawo mbali

c) Ngati muli oyenera, tidzakuwererngerani cholinga cha kafukufukuyi ndipo tidzakufunsani ngati muli ovomera kutenga nawo mbali

d) Ngati mwavomera kutenga nawo mbali, tidzapempha kuti musayine form yopereka chilolezo mosakakamizidwa

e) Mukasayina, tidzapempha kuti tione nawo zotsatira za ku laboratory mma bukumo komanso mavuto amene mwakhala mukukumana nawo chiyambureni kumwa mankhwala amenewa a DTG.

f) A kadaulo ophuntsidwa bwino, adzakutengerani pa malo abwino malo a chinsinsi kuti akufunseni mafunso, ndipo mudzapatsidwa mwayi ofunsa mafunso pamene musanamvetsetse bwino. Nthawi yofunsana mafunso ikadzatha tidzapempha ngati mungatigawireko nambala yanu ya foni kuti ngati pali chinthu chimene tinayiwala kapena chomwe tikufuna kumvetsetsa bwino kuchokera kai nu tidzathe kulumikizana nanu. Tikukutsimikizirani kuti nambala yanu ya foni idzagwiritsidwa ndi anthu okhawo amene akukhudzudwa ndi kafukufukuyu, sidzagawidwa kwa ena ayi.

g) Mu kafukufukuyi simudzakhala kutenga magazi kaena kupatsidwa mankhwala ayi

Chilolezo Chotenga Nawo Mbali

Chilolezo chotenga nawo mbali pa kafukufukuyu ndi chisankho/ kufuna chanu. Simukuyenera kupereka chifukwa chilichonse ngati simukufuna kutenga nawo mbali mu kafukufukuyu.. Ngati musankha kusatenga nawo

mbali mu kafukufukuyu, mudzapitiriza kubwera kuchipatala kudzalandira thandizo lanu monga mwa nthawi zones popanda chilango china chili chonse.

Ufulu Wanu Ngati Otenga Nawo Mbali

Muli ndi ufuu osiya kutenga nawo mbali mukafukufuku nthawi ina ili yonse. Kutenga mbali mu kafukufuku ndi chisankho chanu. Mudzapitiriza kubwera kuno ku umodzi Family Clinic kudzalandira chithandizo chanu monga mwa masiku onse komanso thandizo la vuto lina lili lonse limene mungakhale nalo mtsogolo mosatengera kuti mwatenga nawo mbali mu kafukufukuyu kapena ayi.

Kodi Pali Mavuto, Chiopsezo Zanji Mukatenga Nawo Mbali Mu Kafukufukuyu?

Chiopsezo chimodzi chimene mungate kukumana nacho pamene mwatenga mbali mu kafukufukuyu ndi kuytayika kwa chinsinsi chokhudza infomeshoni yanu koma tikukutsimikizirani kuti tidzasunga china chili chonse chimene mwatiuza komanso chomwe tatenga mma buku anu mwachinsinsi chozama. Tidzagwiritsa ntchito nambaa ya chinsinsi mmalo mwa dzina lanu. Ma pepala onse amene tidzagwiritse ntchito tidzawatsekera mu kabati yoti wina aliyense sangatsegule. Nthawi zina kuyankha mafunso ena kukhonza kukhala kokuvutani. Ngati pali funso lina loti simukufuna kuyankha, musapanikizike, mukhonza kunena kuti simukwanitsa kuyankha. Muli ndi ufulukukana kuyankha mafunso or mafunso ena ofunsidwa nkati mwa kuyankhulana kwathu.

Phindu La Kafukufukuyu

Palibe phindu lachindunji lomwe lizapezeke chifukwa chakutenga nawo mbali pakafukufukuyu. Komabe, zambiri zimene inu mudzapereke zidzathandiza kudziwa zina mwa zimene odwala amene ali pa mankhwala amenewa a DTG akukumana nazo ku Malawi kuno zimene zidzathandize kuti nafenso tikhale ndi zambiri ya mankwala amenewa kusiyana ndi kudalira zambiri yochokera mayiko ena. Ngati anthu akukumana ndi mavuto chifukwa cha mankhwala amenewa, ndi mavuto a akulu bwanji nga achipatala kapena a za umoyo angapangepo chani pofuna kuchepetsa mavutowa ndi kuthandiza odwala athu kuti adzikhala ndi moyo wabwino panthawi imene akumwa mankhwalawa.

Mtengo Kapena Kubwezera

Palibe malipiro ena ali onse amene adzaperekedwa chifukwa cha kutenga nawo mbali pa kafukufuku.

Chinsinsi

Zambiri zimene mutatiuze mu kafukufukuyu zidzagwirutsidwa ntchito mukafukufuku yekhayu ndipo sitidzauza wina aliyense kuti zachokera kwa inu. Otiyangani'ra akhonza kufuna kuona zimene mwatiuza ndi cholinga chofuna kuona ngatitikupanga kafukufuku moyenera. Pamene akupanga izi sadzatenga dzina lanu or china chili chonse chohudza inu. Ngati pangadzafunike kugawa zambiri zimene tapeza kuchoka mu kafukufuku ameneyu mmalawi muno komanso ku mayiko ena, sitidzagwiritsa ntchito inu, dzina lanu kapena tsatanetsatane amene angathe kupangitsa kuti zikadziwike kuti zachikera kwa inu ayi, Zolembera zones zokhudza kafukufuku ameneyu zidzasungidwa bwino lomwe mma kabato otseka bwino ndi ma kiyi amene munthu wamba sangathe kuwapeza.

Kufuna Kudziwa Zambiri

Zambiri za ufulu wathu ngati otenga nawo mbali mungazipeze pa:

Institutional Review Board (College of Medicine Research and Ethics Committee)

A kalembera

College of Medicine Research and Ethics Committee, University of Malawi
Box 360, Blantyre 3, Chichiri
Blantyre, Malawi
Tel. 01871911

A Kalembera/ Wa pa Mpando

University of Nairobi Research and Ethics Committee

P.O. Box

Nairobi

Tel: 2726300

Email : uonknh_erc@uonbi.ac.ke

Ngati muli ndi mafunso ena kapena nkhawa zokhudza kutenga nawo mbili pa kafukufukuyu, kapena mukufuna kupanga lipoti za kuvulala kapena

kuvulazidwa kumene mukuganiza kwanu mukuona ngati kwadza chifukwa cha kutenga nawo mbali pa kafukufukuyu, chonde apezeni anthu awa kapena ayimbireni foni anthu awa :

Christina Joshua Mwinjiwa
University of Nairobi, School of Pharmacy
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College of Medicine,
P/Bag 360,
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Kuvomereza

a) Ndamva cholinga cha kafukufuku, andiongosolera ndipo ndafunsa mafunso omwe ndinali nawo ndipo ogwira ntchitoyi andiyankha mafunso onse bwinobwino ndipo ndakhutira.

b) Muchiyankhulo chomveka bwino, ndawerenga kapena munthu wandiwerengera zones zambiri zimene zili m'mwambamo kuphatikiza phindu la kafukufukuyu.

c) Andiuza kuti zili kwa ine kusankha kutenga nawo mbali pa kafukufukuyu komanso ndili ndi ufulu osiya kutenga mbai nthawi ina iliyonse popanda kulandira chilango cha mtundu wina uli onse.

d) Ngati ndasankha kusiya kutenga nawo mbali, ufulu wanga udzapitirirabe monga kale. Ndamvetsetsa kuti ndilandira kope ya fomuyi yosayina. Apa

ndikuvomera mwakufuna kwanga kuti nditenga nawo mbali pa kafukufuku ameneyu.

Mawu ovomereza (akhale munthu wamkulu wa zaka 18 kapena kuposerapor)

(signature or thumbprint required):

Ndawerenga kapena andiwerengera zonse zili mumtundamo ndipo ndavomereza kutenga nawo mbali mu kafukufuku ameneyu:

Signature: _____Date: _____

Thumb print:

Participant's name: _____

Kwa amene sangawerenge

Andiwerengera kuvomera ndipo nnapatsidwa mwayi ofunsa mafunso ndipo ndayankhidwa mafunso anga onse mokhutira.

Anthu onse amene adinda chala chawo avomereza kutenga nawo mbali.

Signature: _____Date: _____

Witness's name: ___

Kulengeza kwa munthu amene akupereka kuvomera

Ndikuvomereza kuti njira, cholinga, phindu komanso zoopsa zogwirizana ndi kafukufukuyu zalongosoledwa monga mu mtundamo.

Kuvomera kwaperekedwa ndi obtained by: _____Name of the study staff member obtaining the consent/ assent

Signature: _____Date: _____

Assessment of the safety and effectiveness of Dolutegravir in HIV patients at Queen Elizabeth Central Hospital in Malawi

DATA COLLECTION FORM

PART A: PATIENT BIODATA

Participant Unique Number..... Sex.....

Date of birth..... Age (years).....

Weight at treatment initiation..... Current Weight…….

BMI..... Height (cm).....

Initial Blood pressure ..... Current Blood Pressure……

PART B: SOCIAL HISTORY

Smokes Cigarette…… ☐ Yes ☐ NO Takes alcohol: ☐ Yes ☐ NO

Current Smoker/past smoker

If yes no. of cigarettes per day..... If yes no. of bottles per day.....

Medication History

Current regimen: ☐ TDF/3TC/DTG Date Started……

☐ AZT/3TC/DTG Date Started……..

Previous Regimen If on ART before …….. Date Switched……

Reason for change (if on second line therapy)

☐ Virologic treatment failure

☐ Clinical treatment failure

☐ Adverse drug reaction (Specify).....

☐ Other (Specify).....

☐ Unspecified

Other medication/herbal preparations being taken	**Date started**	**Reasons for use**

Drug allergies

☐ Yes (Specify).....

☐ No

Food allergies

☐ Yes (Specify).....

☐ No

PART C: LAB RESULTS

Test	Value	Date
Viral load (copies/ml)		
Random blood sugar (mmol/L)		
LIVER FUNCTION TEST Alanine Aminotransferase (ALT) AST ALP		
CD4 (cells/mm3		
UREA		
CREATININE		
HAEMATOLOGY RBC MCV HB		
PANCREASE Serum Amylase Serum Lipase		
Sugar Levels		
LIPID PROFILE Cholesterol Triglycerides		

PART D: MEDICAL HISTORY

Active Tuberculosis

☐ Yes
☐ No

Any History of Mental Illness

☐ Yes

☐ No

Hepatitis A

☐ Yes

☐ No

Hepatitis B

☐ Yes

☐ No

Hepatitis C

☐ Yes

☐ NO

Diabetes

☐ Yes

☐ No

Cryptococcal Meningitis

☐ Yes

☐ No

Other Illnesses……

……

……

……

WHO HIV Staging at initiation of therapy

☐ Stage I
☐ Stage II
☐ Stage III
☐ Stage IV

Chronic illness/Adverse drug reaction	**Date diagnosed**

Appendix VI(a): Data Collection Questionnaire (English Version)

Assessment of the safety and effectiveness of Dolutegravir in HIV patients at Queen Elizabeth Central Hospital in Malawi

Data Collection Questionnaire

PATIENT INTERVIEW

Patient Unique Number: .....Date of interview.....

Sex: ☐ Male ☐ Female Date of birth..... Age (years).....

For questions with options, please tick ONE appropriate answer unless specified otherwise

1. a) What drug are you currently on? TDF/3TC/DTG / AZT/ 3TC/ DTG

b) How long have you been on your current regimen ……...

c) What time do you normally take your medicine? ……..

d) How many tablets do you take daily?.....

e) Do you take your medicine before or after meals?

☐ Before meals

☐ After Meals

f) Taking drugs can be a real bother. Do you sometimes forget taking your drugs

☐ Never

☐ Once in a while

☐ Sometimes

☐ Usually

g) Has your medicine ever harmed you in any way?

☐ Yes

☐ No

If answer to 1(g) is yes. Answer question 1(h- m). If No proceed to question 2

h) How did the medicine harm you? **.....**

……
……

i) For how long had you taken your medicine when the harm occurred ……...

.....
.....

j) What action was taken?.....

.....
..

k) Were you on any other drugs at the time?

☐ Yes ☐ No

l) If yes in (k) above, Can you remember the drugs which you were taking?.....

m) What were the drugs in (l) for?.....

2. Do you have any allergies?

☐ Yes (specify).....

☐ No

3. For the following questions, circle the letter with the most appropriate response based on the scale below.

A – No difficulty

B – Mild difficulty

C – Moderate difficulty

D – Severe difficulty

a) Do you get any difficulty falling asleep A B C D

b) Do you get any difficulty staying asleep? A B C D

c) Do you get any difficulty waking up early? A B C D

4. a) Have you ever been diagnosed with a mental illness?

☐ Yes ☐ No

If answer to 4 (a) is No then jump to question 5.

b) If yes in (a), which one?

☐ Depression ☐ Mania Psychosis

☐ Don't know ☐ other

c) When was the diagnosis made?.....

d) What were the symptoms?.....

.....

.

e) What action was taken?

☐ No action ☐ Hospitalization

☐ Medication ☐ Other (Specify

For question 4 (f) use the scale given to circle the most appropriate answer

A - No or minimal interference with usual social & functional activities

B - Greater than minimal interference with usual social & functional activities

C - Inability to perform usual social & functional activities

D - Inability to perform basic self-care functions

f) To what extent did the illness affect your day-to-day activities? A B C D

g) Did you harm or threaten to harm yourself or others?

☐ Yes ☐ No

5. a) Have you ever had headaches after taking your medication?

☐ Yes ☐ No

If answer to 5(a) is No then jump to question 6.

b) Have you ever been hospitalised for the headaches?

☐ Yes ☐ No

For question-5 (c) use the scale given to circle the most appropriate answer

A - No or minimal interference with usual social & functional activities

B - Greater than minimal interference with usual social & functional activities

C - Inability to perform usual social & functional activities

D - Inability to perform basic self-care functions

c) To what extent did the headaches affect your day-to-day activities? A B C D

6. a) Do you suffer from any other illness?

☐ Yes ☐ No

b) If yes in 5 (a) above, which one (s)?.....

.....

..

1 Apart from antiretroviral drugs and cotrimoxazole ae you on any other medication?

☐ Yes ☐ No

b) If yes clarify……

…..

8. Do you take any of the following? (More than one answer is acceptable)

☐ Alcohol ☐ Cigarette

☐ Herbal medication ☐ Other (Specify).....

9. a) Have you ever felt body itching after taking your medication?

☐ Yes ☐ No

For question 9 (b) use the scale given to circle the most appropriate answer

A - No or minimal interference with usual social & functional activities

B - Greater than minimal interference with usual social & functional activities

C - Inability to perform usual social & functional activities

b) If yes in (a) to what extent did the itchiness affect your da- to-day activities?

A B C

10. a) Have you ever had a skin reaction because of your medication?

☐ Yes ☐ No

b) If yes in (a), what type of reaction was it?

☐ Rash in one part of the body

☐ Rash all over the body

☐ Rash all over the body and vesicles

☐Other (Specify).....

.....

..

c) Were you hospitalised because of the reaction?

☐ Yes ☐ No

11. a) Have you ever found yourself thinking about death a lot?

☐ Yes ☐ No

b) Have you ever thought of taking your own life?

☐ Yes ☐ No

c) Have you ever been hospitalized because of thinking or planning to take your own life?

☐Yes ☐ No

12. How long ago did you have your last meal today?

☐ Less than 1 hour ago ☐ Between 1-2 hours ago ☐ More than 2 hours ago

13. Since you started treatment with DTG, have you ever experience the following:

GENERAL

Fatigue ☐ yes ☐ No ☐ Tiredness ☐ Yes ☐ No

Weakness ☐ Yes ☐ No ☐ Dizziness ☐ Yes ☐ No

Headache ☐ Yes ☐ No ☐ Falling Down ☐ Yes ☐ No

GASTROINTESTINAL

Abdominal Pains ☐ Yes ☐ No

Diarrhoea ☐ Yes ☐ No

Nausea ☐ Yes ☐ No

Vomiting ☐ Yes ☐ No

MSKULOSKELETAL

Muscle aches ☐ Yes ☐ No

Muscle spasms ☐ Yes ☐ No

Back Pains ☐ Yes ☐ No

Joint aches ☐ Yes ☐ No

REPRODUCTIVE SYSTEM

Reduced libido ☐ Yes ☐ No

Inability to achieve erection (men) ☐ Yes ☐ NO

Disturbed menstrual cycle ☐ Yes ☐ No

LIVER

Yellow eyes ☐ Yes ☐ NO

URINARY SYSTEM

Painful Urination ☐ Yes ☐ No

Any Changes in

Weight ☐ Yes ☐ No

Any other problem……
…
……
……
……

Has any Opportunistic Infection? ☐Yes ☐No

Has the patient ever discontinued Therapy ☐ Yes ☐ No

Appendix VI (b): Data Collection Questionnaire (Chichewa Version)

Assessment of the safety and effectiveness of Dolutegravir in HIV patients at Queen Elizabeth Central Hospital in Malawi

Nambala ya chinsinsi ya odwala:..... Tsiku lofunsidwa mafunso.....

Sex: ☐Mamuna ☐ Mkazi Tsiku lobadwa..... Zaka .....

Pa mafunso amene ali ndi mayankho oposa awiri. Chonde sankhani yankho limodzi lokha pokhapokha mutauzidwa kuti muyankhe angapo

1.a) Kodi pano mukumwa mankhwla awa a TDF/3TC/DTG ☐ Eya ☐ Ayi

b) Mwakhala mukumwa mankwala amenewa kwa nthawi yotalika bwanji?.....

c) Mumamwa mankwala anu nthawi yanji? ……..

d) Mumamwa ma pilisi angati patsiku?.....

e) Mankhwala anu mumamwa mutadya kapena musanadye?

☐ Ndisanadye

☐ Nditadya

f) Nthawi zina mankhwala amatopetsa kumwa. Kodi inu mumapezeka mutayiwala kumwa mankhwala anu nthawi zina?

☐ Sindinayiwalepo

☐ Ndimayiwala mwa apo ndi apo

☐Nthawi zina

☐Ndimayiwala pafupipafupi

g) Munayamba mwakumanapo ndi vuto chifuwa cha mankhwala amene mukumwawa?

☐Eya

☐Ayi

Ngati yankho ndi Eya pafunso lamwambalo yankhani mafunso otsatirawa (h mpaka m). Ngati yankho lanu ndi Ayi pitani ku funso nambala 2

h)Vuto limene munakumana nalo kamba ka mankhwala linali lotani?

.....

.....

.....

.....

i) Munali mutamwa mankhwalawa kwa nthawi yayitali bwanji pamene mumakumana ndi vutolo? ……....

.....

.....

j) Munapanga chani mutakumana ndi vutolo?.....

.....

..

k) Pa nthawi yomwe mumakumana ndi vutolo mumamwanso mankhwala ena kupatula mankhwala awa?

☐ Eya ☐Ayi

l) Ngati ynkho lanu lili Eya pa funso lam'mwambalo kodi mungathe kukumbukira kuti munkamwanso mankhwala anji?.....

……

.....

m) Nanga mankhwalawo anali a matenda anji ?.....

2. Chilipo chilichonse chimene thupi lanu limadana nacho?

☐ Eya (Longosolani kuti ndi chani).....

☐ Ayi

3.Pa mafunso otatirawa yankhani funso limodzi pozunguliza lemba limene likugwirizana ndi yankho lanu.

A – Sindikhala ndi Vuto

B – Ndimavutika pang'ono penipeni

C – Ndimavutika pang'ono

D – Ndimavutika kwambiri zedi

a) kodi mumavutika kupeza tulo?	A	B	C	D
b) Mumapeza vuto kupitiriza tulo?	A	B	C	D
c) Mumakhala ndi vuto kudzuka mwansanga?	A	B	C	D

4. a) Munayamba mwadwalapo matenda a misala?

☐ Eya

☐Ayi

Ngati yankho lanu mu funso 4(a) nd Ayi pitani pa funso 5.

b) Ngati yankho lanu la funso4 (a) ndi Eya, ndi matenda ati mwa awa ali munsiwa?

☐ Depression ☐ Mania Psychosis

☐Sindikudziwa dzina lake ☐ Ena

c) Matenda amenewa munadwala liti?.....

d) Kodi nanga zizindikiro zake zinali ziti?.....

.....

.

e) Nanga ndi thandizo lanji limene munalandira?

☐ Sindinalandire thandizo ☐ Kugonekedwa mchipatala

☐ Mankhwala ☐ Zina (Longosolani)

Funso 4 (f) Gwiritsani ntchito muyezo(scale) ili munsiyi pozunguliza lemba limene likugwirizana ndi yankho lanu

A – sanasokoneze kapena anasokoneza mocheperako ntchito ndi makhalidwe achizolowezi

B – anasokoneza Kwakulu kuposa mochepereako ntchito ndi makhalidwe a chizolowezi

C – Kulephera kuchita ntchito zachizolowezi

D – kulephera kuchita ntchito ncthito ngakhale zodzisamalira wekha

f) Kodi matendawa anakhudza bwanji ntchito zanu za tsiku ndi tsiku? A B C D

g) Kodi munadzipweteka inu nokha kapena kubweretsa chiopsezo kwa ena?

☐Eya ☐ Ayi

5. a) Munayamba mwamvapo kupweteka mutu mukamwa mankwalawa?

☐ Eya ☐Ayi

Ngati yankho lanu pa funso 5(a) ndi Ayi yankhani funso 6.

b) Munayamba mwagonekedwapo chifukwa chakudwala mutu kobwera chifukwa cha mankhwalawa?

☐Eya ☐ Ayi

Gwiritsani ntchito muyeso(scale) ili munsiyi kuti muyankhe funso 5 (c). Zunguliza Lemba imene pali yankho lanu loyenera

1 sanasokoneze kapena anasokoneza mocheperako ntchito ndi makhalidwe achizolowezi

B – anasokoneza Kwakulu kuposa mochepereako ntchito ndi makhalidwe a chizolowezi

C – Kulephera kuchita ntchito zachizolowezi

D – kulephera kuchita ntchito ncthito ngakhale zodzisamalira wekha

1 Vuto la matenda a mutu limeneli linakhudza ntchito zanu za tsiku ndi tsiku mpaka pati?

A B C D

6. a) Kodi mumadwalanso matenda ena kupatulapo awa?

□Eya □ Ayi

b) Ngati yankho lanu ndi Eya m funso 5 (a) lili m'mwambamo ndi matenda anji amene mumadwala?.....

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..

7. Kupatulapo ma ARV kapena Bactirimu mumamwanso mankwala anji?.....

.....

.....

.....

.....

8. Kodi mumachitako zinthu izi? (Mukhonza kupereka mayankho angapo pa funsoli)

□Mowa/ kachaso □ kusuta fodya

□ mankhwala achiuda □ zina (Longosolani).....

9. a)Munayambapo mwamva kuyabwa mutamwa mankhwalawa anuwa?

□Eya □ Ayi

Pafunso 9 (b) Gwiritsani ntchito scale ili unsiyi kuti muyankhe funso 9(b).

Zungulizani lemba limene likugwirizana ndi yankho lanu

1. sanasokoneze kapena anasokoneza mocheperako ntchito ndi makhalidwe achizolowezi

B – anasokoneza Kwakulu kuposa mochepereako ntchito ndi makhalidwe a chizolowezi

C – Kulephera kuchita ntchito zachizolowezi

D – kulephera kuchita ntchito ncthito ngakhale zodzisamalira wekha

b) Ngati yankho lanu ndi Eya mu (a) Vuto limeneli linakhudza bwanji ntchito zanu za tsiku ndi tsiku?

A B C D

10. a)Munayamba mwakhalapo ndi matendaa pa khungu chifukwa cha mankhwalawa?

□ Eya □ Ayi

b) Ngati yankho lanu ndi Eya pa funso 10(a) Kodi anali matenda anji/owoneka bwanji?

□ Zilonda/Rash mbali imodzi ya thupi

□ Zilonda/Rash thupi lonse

□ Zilonda/Rash thupi lonse kuphatikizanso ma bowo a thupi

□ Zina (longosolani).....

.....

..

c) Kodi munagonekedwa mu chipatala chifukwa cha zilonda/ rash imeneyo?

□ Eya □ Ayi

11. a) Kodi munayamba mwakhalapo ndi maganizo omwalira?

□Eya □ Ayi

b) Munayamba mwaganizapo zochotsa moyo wanu?

□Eya □ ayi

c) Nanga munayambapo mwagonekedwa mu chipatala chifukwa chokhala ndi maganizo ofuna kuchotsa moyo wanu?

□ Eya □ Ayi

12. Kodi padutsa nthawi yayitali bwanji chidyereni chakudya chanu chalero?

□ osapitilira ola limodzi □ pakati pa ola limodzi kapena awiri □ kupitilira maola awiri

13. Chiyambireni kumwa mankhwala amenewa a DTG, munayamba mwamvapo izi:

GENERAL

Kutopa	☐ Eya	☐ Ayi	Tiredness	☐ Eya	☐ Ayi
Kufooka	☐ Eya	☐ Ayi	Dizziness	☐ Eya	☐ Ayi
Mutu	☐ Eya	☐ Ayi	kugwa pansi	☐ Eya	☐ Ayi

Gastrointestinal

Kupweteka m'mimba	☐ Eya	☐ Ayi
Kutsegula m'mimba	☐ Eya	☐ Ayi
Kumva nseru	☐ Eya	☐ Ayi
Kusanza	☐ Eya	☐ Ayi

MUSKULOSKELETAL

Kupweteka kwa minofu	☐ Eya	☐ Ayi

Kuphindika minofu ☐ Eya ☐ Ayi

Kupweteka kumbuyo ☐ Eya ☐ Ayi

Kupweteka ma joint ☐ Eya ☐ Ayi

REPRODUCTIVE SYSTEM

Reduced libido ☐ Yes ☐ No

Inability to achieve erection (men) ☐ Yes ☐ NO

Kusokonekera msambo ☐ Eya ☐ Ayi

LIVER

Maso a chikasu ☐ Eya ☐ Ayi

URINARY SYSTEM

Kupweteka pokodza ☐ Eya ☐ Ayi

Pali kusintha kwina kulikonse kwa kulemera kwa thupi lanu

☐ Eya ☐ Ayi

Pali vuto lina limene mwakumana nalo kuposa amene tachulawa?

……

……

……

……

Has any Opportunistic Infection? ☐Eya ☐ ayi

Munayamba mwasiyapo kumwa mankhwalawa? ☐ Eya ☐ Ayi

Appendix VII: Grading of Neuropsychiatric Side Effects (41)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	N/A
Psychiatric Disorders(inclu	Symptoms with	Symptoms with	Symptoms with	Threatens harm to self or others

des anxiety, depression, mania, and psychosis)Specify disorder	intervention not indicated OR Behaviour causing no or minimal interference with usual social & functional activities	intervention indicated OR Behaviour causing greater than minimal interference with usual social & functional activities	hospitalization indicated OR Behaviour causing inability to perform usual social & functional activities	OR Acute psychosis OR Behaviour causing inability to perform basic self-care function
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalisation indicated	Suicide attempted

Appendix VIII: Grading of Hypersensitivity Reactions (41)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLYLIFE-THREATENING
Rash *Specify type if applicable*	Localised Rash	Diffuse rash OR Target lesions	Diffuse rash AND	Extensive or generalized bullous lesions OR

			Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Pruritus	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	N/A

Appendix IX: Grading of Hepatotoxicity and Hyperglycaemia (41)

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	0 to < 10.0 x ULN	10.0 x ULN
Glucose(mg/dL; mmol/L) Fasting, High	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Non-fasting, High	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75