SAFETY, TOLERABILITY AND ADHERENCE OF DTG-BASED REGIMEN AMONG ADULT HIV PATIENTS ATTENDING KENYATTA NATIONAL HOSPITAL

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A Dissertation submitted in the Institute of Tropical and Infectious Diseases, University of Nairobi in partial fulfillment of the requirements for the award of the Degree of Master of Science Tropical and Infectious Diseases of the University of Nairobi

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DECLARATION

This research dissertation is my original work and has not been presented in any institution for the award of a degree or any other award.

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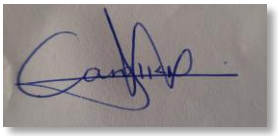
Sign…  … Date…25TH OCTOBER 2020……

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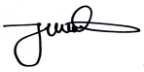
   Signature..  …… Date …25th October, 2020……

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DEDICATION

This dissertation is dedicated to all HIV heroes: persons living with HIV, scientists and healthcare providers directly and indirectly involved in the management of HIV. To all; there is hope.

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I thank God for favouring me with life, good health and peace; and the opportunity to further my studies.

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Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

3TC	Lamuvidine
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
CCC	Comprehensive Care Centre
CDC	Center for Disease Control and Prevention
CYP450	Cytochrome P450
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
KNH	Kenyatta National Hospital
KNH/UoN-ERC	Kenyatta National Hospital/University of Nairobi Ethics &Research Committee
MOH	Ministry of Health

NASCOP	National AIDS and STIs Control Programme
PIs	Protease inhibitors
RAL	Raltegravir
RBS	Random Blood Sugar
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UGT	Uridine diphosphate glucurunosyl transferase
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Adherence: The extent to which a patient's behavior corresponds with agreed recommendations from a healthcare provider without being compelled to.

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

ART optimization: The use of HIV treatment that is potent, safer and more affordable

Compliance: The extent to which the patient's behavior matches the health care provider's recommendations

Effectiveness: HIV serum viral load of less than 50 copies per milliliter (viral suppression)

HIV drug resistance: Mutation and continued replication of the virus in the presence of antiretroviral drugs

Side Effect: Unintended effects of the drug, which can be harmful or adverse effects

Tolerability: Degree to which overt adverse effects of a drug can be tolerated by a patient

Viral load: Number of HIV RNA copies in 1 milliliter of blood

ABSTRACT

Background

Integrase Strand Transfer Inhibitors (ISTIs) are the latest drugs to be introduced for management of Human Immunodeficiency Virus (HIV). A fixed dose combination antiretroviral therapy (ART) regimen containing Dolutegravir (DTG), a second-generation ISTI, has been rolled out as a first line treatment regimen for adult HIV patients in low- and middle-income countries. There is limited post market surveillance safety data on DTG-based ART regimens and a myriad of side effects and adverse effects have been reported. The aim of this study was to assess the safety, tolerability and adherence of DTG-based regimens among adult HIV patients at Kenyatta National Hospital.

Methods

The study was a descriptive cross sectional conducted at Kenyatta National Hospital. A total of 219 eligible HIV patients on DTG-based regimens were recruited and interviewed after signing informed consent forms. Data on socio-demographics, clinical, experience of adverse side effects and measures of tolerability and adherence was obtained using a pre-designed questionnaire. Data analysis was done using IBM SPSS Statistics version 21. Categorical and numerical variables were presented in frequency, distributions and measures of central tendency. To test for associations, bivariate and multivariate analysis was done using chi-square.

Results

A total of 219 adults HIV patients participated in the study. There were more (58%) male participants than female (42%) and their mean age was 47.6 years. Prevalence of DTG-based ART patients among adult HIV patients attending Kenyatta National Hospital Comprehensive Care Center was 24.7% (95% Confidence Interval: 10.9, 30.92; $p< 0.001$). The most frequent drug effects were insomnia (24.1%), headaches (19.0%) and skin hypersensitive reactions (13.9%). 87.3% of these drug effects were mild and resolved without any intervention. 2(0.9%) patients with severe skin reactions were switched from

DTG-based regimen. There were no deaths reported related to a DTG-based regimen adverse drug reaction. Adherence to DTG-based ART regimen was high (>80%) and 9.6% of the patients reported to be intolerant to the DTG-based regimen because of adverse drug reactions.

Conclusion

This study established that the DTG-based regimen was associated with mostly mild adverse drug reactions. Skin reactions were the least tolerated and resulted in DTG-based regimen switch. Generally, the DTG-based regimen had an acceptable safety profile and was tolerated by adult HIV patients attending KNH CCC.

CHAPTER ONE: INTRODUCTION

1.1 Background

Human Immunodeficiency Virus (HIV) is among the most common causes of death worldwide. In 2017, an estimated 37 million people globally were living with HIV (UNAIDS, 2018a). Eastern and Southern Africa account for 45% and 53% of the world's HIV infection and people living with HIV globally respectively (UNAIDS, 2018a). In Kenya, incidence of HIV among adults aged 15-49 has declined to 0.19% (2017) from 0.35% (2010) possibly due to scale up of various prevention and treatment programs (National AIDS Control Council, 2018). To date, there is no known cure for HIV, therefore management of HIV infection with antiretroviral therapy (ART), usually with three or more medications, is the mainstay and has proved to be a success (Jiang *et al.*, 2016; Anstett *et al.*, 2017).

Current ART drugs used in management of HIV-1 infection are of high potency, acceptable resistance profile and tolerability. Integrase Strand Inhibitors (INSI) are the newest ART drug class to be approved for HIV management (Wong *et al.*, 1998; Yadav *et al.*, 2018). Dolutegravir (DTG) is a second generation INSI and works by blocking the enzyme integrase required to integrate viral and host CD4 cell DNA leading to viral replication. DTG was USA FDA-approved as a first line drug for HIV management in 2013 and is effective in suppressing the HIV virus, it is well tolerated and has a low resistance profile (Kandel and Walmsley, 2015; Yadav *et al.*, 2018).

United States President's Emergency Plan for AIDS Relief (USA-PEPFAR), main donor partners, recommend rapid adoption of DTG drug projecting and by 2025 an estimated 15 million people will be on DTG-based regimen replacing the Efavirenz (EFV) based regimen (WHO, 2017; Hill *et al.*, 2018).

According to the World Health Organization (WHO), at least 60 Low and Middle Income Countries (LMICs) have adopted and integrated DTG in their national HIV treatment

guidelines with Kenya, Botswana, Uganda and Brazil already using the drug in a combined therapy (Wainberg, Han and Mesplède, 2016); (UNAIDS, 2018b). In October 2017, Kenya rolled out DTG as first line combination regimen composed of Tenofovir disoproxil fumerate, Lamuvidine and Dolutegravir (TDF+3TC+DTG) for HIV-1 for adult men and women on effective contraception or past the child bearing age (NASCOP, 2018).

1.2 Problem statement

The lack of a definitive cure for HIV and consequently its lifelong management with ARVs, has contributed to decreased mortality and morbidity in HIV patients. However, prolonged use of ARVs poses new challenges of drug related toxicities and intolerance, both of which directly contribute to reduced adherence and hence decreased viral suppression and increased ART resistance (Universitario and Leonor, 2016). This has led to the development and advocacy of novel antiretroviral drugs with minimal or no adverse effects. In addition, there is need for continuous monitoring for adverse effects and toxicities among HIV patients.

In regard to DTG based ART based regimens; transition to these regimens in low- and middle-income countries has been hindered by mainly limited follow up safety studies in these regions. DTG, like all other drugs is not devoid of adverse effects. Clinical trials studies (SPRING-1, SPRING-2, SINGLE and FLAMINGO) reported nausea, diarrhea, hypoglycemia, Central Nervous System side effects and headache as the most common side effects among ART naive patients on DTG-containing regimens. Safety data from post market pharmacovigilance in high resource countries showed the already recorded adverse effects from clinical trials like gastrointestinal effects, hypersensitivity reactions, hepatotoxicity and Immune Reconstitution Inflammatory Syndrome (IRIS). Other reported adverse effects included Central Nervous System (CNS) effects such as insomnia, headache, suicidal ideation and tendencies, depression, abnormal dreams and dizziness (AMPATH, 2017)

A 2016 cohort study in The Netherlands, Amsterdam, followed 556 adult HIV patients on DTG containing ART regimens for 225 days. DTG was stopped or substituted in 85(18.4%)

of the patients due to intolerance of adverse effects; mainly gastrointestinal disturbances, sleep disturbance, insomnia and neuropsychological disturbances (De Boer *et al.*, 2016). So far, data from low- and middle-income countries is limited. A country-wide active pharmacovigilance study in Brazil conducted in 2017 among 79,742 adult HIV patients receiving DTG-based ART regimens revealed that 1615 (2.24%) patients reported to have persistent gastrointestinal and CNS adverse effects. However, 88.4% of these Brazilian HIV patients reported that the adverse effects were not serious and lead to neither hospitalization or disability (Batista *et al.*, 2019a). On the other hand, a South Indian follow up study among 554 HIV patients on DTG based-ART regimens conducted between April 2017 and May 2018 did not report any adverse effects or abnormal kidney and liver function tests in those patients (Kumarasamy *et al.*, 2018).

In Africa, apart from the Tsepamo birth surveillance study in Botswana among HIV women on DTG –based regimen, there has been no concluded safety data .This creates a need for pregnancy safety surveillance and enhanced monitoring for unexpected or long-term drug-associated adverse effects as the use of DTG is scaled up. This is in line with the WHO recommendation that, in addition to routine toxicity monitoring, countries consider implementing a combination of active toxicity surveillance approaches to address the specific needs of HIV treatment and prevention programs while transitioning to new ARV drugs (WHO, 2018; Kandel and Walmsley, 2015b); (Chawla *et al.*, 2018).

1.3 Justification

Clinical trial results showed that dolutegravir was generally well tolerated with few side effects; however, several post-market surveillance studies have revealed a myriad of side effects and adverse effects associated with DTG-based regimens. More importantly, studies about the side effects of DTG are limited, especially in Africa and there is need for more studies, especially now that DTG-based regimen has been adopted as a first line treatment regimen in several African countries including Kenya (WHO, 2016). In addition, clinical trial information on drug toxicities and adverse side effects is usually inconclusive because of the limited study population. Therefore, these drug-related toxicities do not always show up right

away and may only become apparent after people have been on medications for some time.

This study therefore aimed at assessing and profiling the side effects, tolerability and adherence to the newly rolled out DTG-based regimens among HIV patients attending KNH Comprehensive Care Centre, and consequently be used as a source of information on safety and tolerability of DTG-based regimens in the Kenyan population. In addition, this information was useful to reconfirm the recommendation to use DTG-containing regimens as the preferred option for first-line and second-line antiretroviral treatment (ART) across all populations.

1.4 Objectives

1.4.1 Main objective

The main objective of this study is to assess the side effects, tolerability and adherence of DTG-based regimens among adult HIV patients attending the Kenyatta National Hospital Comprehensive Care Clinic.

1.4.2 Specific objectives

The specific objectives of the study were:

1. To assess and profile side effects reported by adult HIV patients on TDF/3TC/DTG regimen attending KNH CCC in the months of November/December 2019.
2. To determine the viral load suppression changes among adult HIV patients on TDF/3TC/DTG regimen attending KNH CCC.
3. To establish the adherence of adult HIV patients to the TDF/3TC/DTG regimen at KNH CCC.
4. To measure the rate of discontinuation from TDF/3TC/DTG among adult HIV patients attending KNH CCC.

1.5 Conceptual Framework

Predictor Variables Outcome Variables

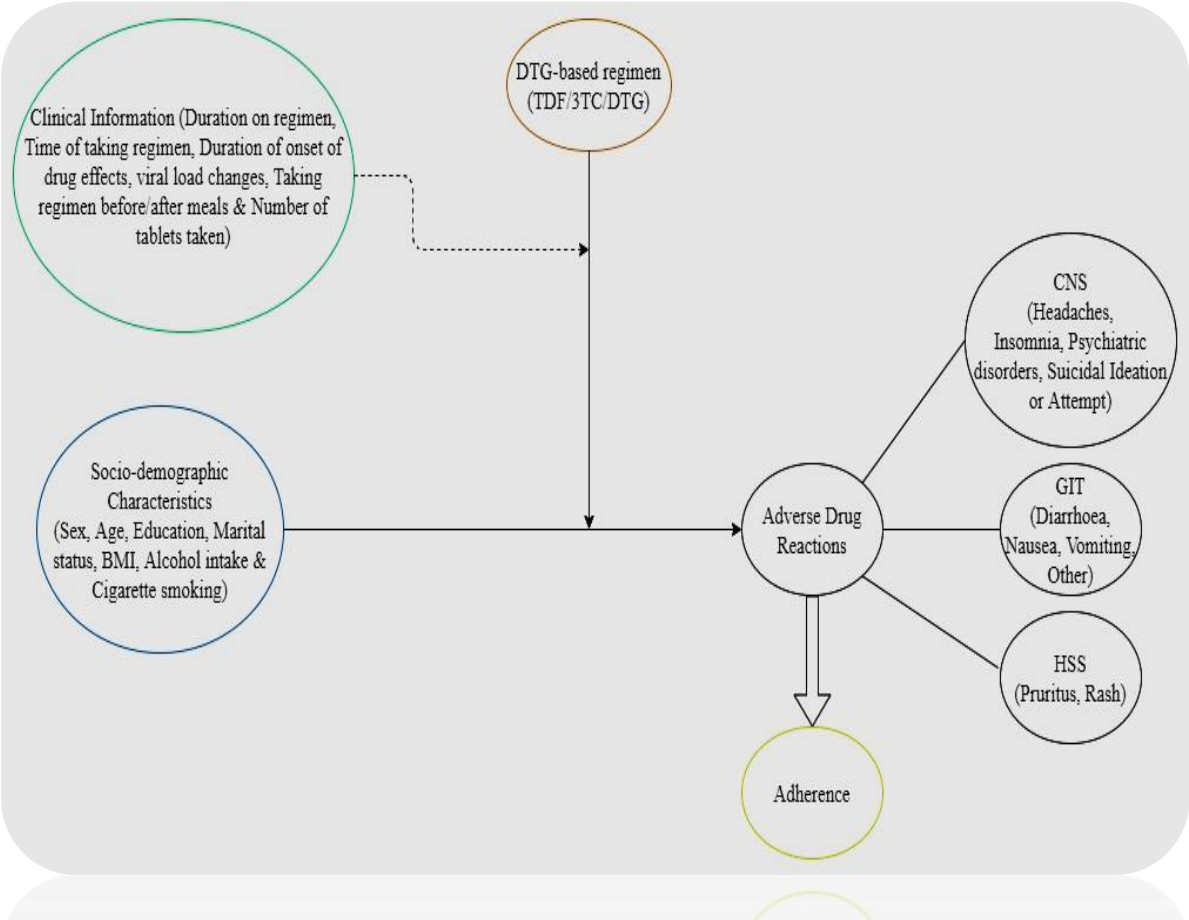

Figure 1: Conceptual framework

The main outcome for this study was reported adverse drug effects, tolerability and adherence among adult HIV patients on the DTG-based ART regimen. The independent variables were patients' socio-demographic characteristics and clinical information related to the ARV regimen intake. Tolerability and adherence to the ARV regimen are potentially affected by occurrence and severity of adverse drug reactions.

Data from clinical trial studies reported central nervous system, gastrointestinal and

hypersensitivity skin reactions as the most reported adverse drug reaction among patients on DTG-based ART regimens. Literature suggests that both sociodemographic (age, sex, BMI, alcohol/cigarette use) and clinical factors (Polypharmacy, time of drug, comorbidities) predispose one to adverse drug reactions.

CHAPTER TWO: LITERATURE REVIEW

2.1 Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) belongs to the family of Retroviridae and the genus of Lentiviruses. HIV is classified into the types 1 and 2 (HIV-1, HIV-2) on the basis of genetic characteristics and differences in the viral antigens (Blut and Blood, 2016). In Africa, HIV-1 is the more prevalent of the two types and in Eastern and Southern Africa recording over 45% of the global HIV burden (Lau and Muula, 2015).

Phylogenetic analysis of HIV-1 resulted into classification of HIV-1 into three groups, M, N and O, with group M being the predominant circulating group. It has been divided further into subtypes or clades, with subtypes A1, A2, A3, A4, B, C, D, F1, F2, G, H, J, and K being currently recognized (Taylor *et al.*, 2008). Geographic distribution of the HIV-1 subtypes is unique to regions or countries, but also a region can have several circulating strains within a specific period. The HIV-1 clades have shown to influence response to antiretroviral drugs, resistance and disease progression among infected individuals. The most prevalent clade in Kenya is HIV-1 group M subtype A (Taylor *et al.*, 2008).

For the last three decades, HIV has been a pandemic with an estimated 37 million people living with HIV-1 globally with approximately 1 million deaths annually. An estimated 1.5 million people in Kenya are living with HIV with 28,000 AIDS related deaths recorded in 2017 (NASCOP, 2018). Sub Saharan Africa continues to bear the greatest burden of HIV-1 infections; some countries are reporting a prevalence decline, for example Kenya, Burkina Faso, Zambia and Zimbabwe (Kharsany and Karim, 2016). This may be attributed to change in sexual behavior and uptake of antiretroviral drugs.

HIV-1 evade the immune system by targeting CD4+ T cells, dendritic cells, macrophages and monocytes found in the brain, liver, lung, lymph nodes, bone marrow and spleen. The HIV-1 life cycle is complex (figure 1) and its duration and outcome is dependent on target cell type and cell activation (AIDSinfo, 2005; Murray, Kelleher and Cooper, 2011). HIV-1

life cycle consists of the following stages; viral attachment, binding and fusion, reverse transcription, uncoating and nuclear entry, integration, transcription, translation, budding and maturation (AIDSinfo, 2005).

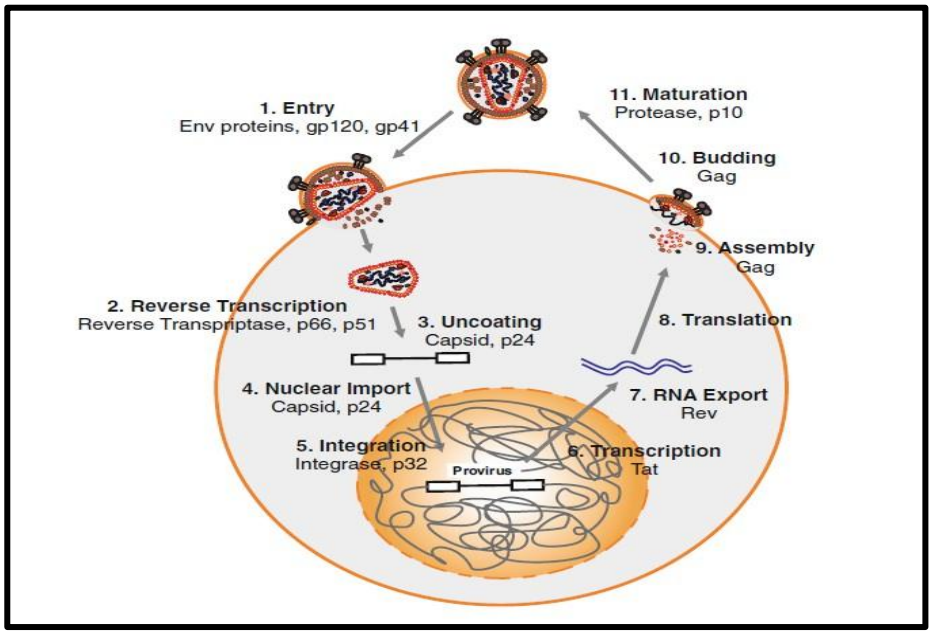

Figure 2: Life cycle of HIV

(Adapted from (AIDSinfo, 2005))

2.2 Antiretroviral Drugs

There is no known cure yet of HIV since its discovery in 1980's. Management of HIV is achieved using combination of antiretroviral drugs: Highly Active Antiretroviral Therapy (HAART) (Wainberg and Han, 2015). Primary goal of HAART is to achieve full and long-term suppression of HIV- RNA plasma viral load by inhibiting and suppressing viral replication. A reduction in HIV viral load allows the rejuvenation of the host's immune system and ability to mount a strong response to contain the HIV virus. This eventually prevents the emergence of resistance and AIDS-related morbidity and mortality (UNAIDS, 2018a).

Since the approval of the first drug, Azidothymidine for HIV-1 management, antiretroviral therapy (ART) has come a long way, from monotherapy regimen to combination therapies. Use of HAART has proved to be more efficacious in HIV-1 viral suppression, and more importantly reduced development of resistance compared to previously used mono and dual therapies (Duarte *et al.*, 2015).

ARV drugs target different life cycle steps of HIV 1 which include reverse transcriptase inhibitors both non-nucleoside and nucleoside analogues, protease and entry inhibitors which include fusion inhibitors, and CCR5 antagonists.

The most commonly recommended first-line HAART regimen typically includes two nucleoside reverse transcriptase inhibitors (NRTIs), or a NRTI and a nucleotide reverse transcriptase inhibitor (NtRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI) (UNAIDS, 2018a).

Since 2016, WHO has recommended adoption of new alternative ARV drug options in HIV treatment regimens: dolutegravir (Integrase strand transfer inhibitor) or Efavirenz 400 mg (EFV400) for first-line therapy and Darunavir/ritonavir (DRV/r) and Raltegravir (RAL) for second- and third-line therapy (WHO, 2017b). This approach is expected to lead to a full treatment response, namely sustained undetectable viral load and consequent CD4 cell count recovery leading to a remission of the disease, in the vast majority of patients (UNAIDS, 2018b). However, incomplete response to therapy can occur, and the reasons for treatment failure are varied, with incomplete adherence being often a key determinant (WHO, 2016; UNAIDS, 2018b).

2.2.1 Safety of Antiretroviral Drugs

Pharmacovigilance, also known as drug safety, is defined by WHO as science and activities associated with the detection, assessment, understanding and prevention of adverse, side effects or any other related medical problem in patients taking drugs (MOH and PPB, 2012). It involves assessing the benefit verses risks of medicines and making appropriate decisions as regards the use of drugs. Depending on the severity of the unwanted effect of drugs, they

can either be mere side effects, adverse effects or life threatening adverse drug reactions (Pharmacy and Poisons Board, 2009).

Side effects are any unintended effects of the drug, and these can be harmful or adverse effects (Karaman, 2015). These effects can be referred as adverse drug reactions (ADR) occurring at clinical therapeutic doses, or at over dosages causing toxic effects. All drugs have side effects, but the extent of their impact and severity varies from mild (such as mild itching or mild headache) to severe (such as severe rash, damage to vital organs (primarily the liver and kidneys), and possibly even death) (Ritter *et al.*, 1999).

Like all other drugs, antiretroviral drugs can cause unwanted or unintended effects, which may be toxic. Incidence, patterns and severity of adverse reactions due to ARV medicines may differ markedly owing to local environmental and genetic influences. These influences may compromise the effectiveness of HAART programs and lead to toxicity, intolerance, drug interactions, loss to follow-up and drug resistance amongst diverse populations (Mehta *et al.*, 2017). Some ARV drugs, for example Stavudine, have been implicated with serious side effects (lipodystrophy) that have warranted withdrawal from the market. Other ARV drugs currently in use with known side effects include Zidovudine (bone marrow suppression), Nevirapine and Abacavir (skin reactions) (Nomathemba *et al.*, 2012). Potential cumulative toxicity therefore remains a concern in HIV patients on ART. Pharmacovigilance is important, especially among in HIV patients on ART and information from these surveillance monitoring activities can help reduce drug induced or associated toxicities and adverse events.

Table 1: Antiretroviral therapy-related adverse effects

Antiretroviral drug	Adverse drug reactions	Common drug reactions (>5%)
Nucleoside analog reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumerate (TDF)	Tubular injury, decrease in eGFR Osteopenia Exacerbation of hepatitis B if the drug is withdrawn	-
Abacavir (ABC)	Hypersensitivity reactions Myocardial infarction	-
Emtricitabine (FTC)	Exacerbation of hepatitis B if the drug is withdrawn	-
Lamivudine (3TC)	Exacerbation of hepatitis B if the drug is withdrawn	-
Non-nucleoside analog reverse transcriptase inhibitors (NNRTI)		
Nevirapine (NVP)	Rash, DIHS, Stevens-Johnson syndrome Hepatotoxicity	Elevated transaminases Rash
Etravirine (ETV)	Rash	Nausea
Efavirenz (EFV)	Rash, Stevens-Johnson syndrome, Hepatotoxicity Teratogenicity	Dizziness, Insomnia Vivid dreams (> 50%) ,Headache, Gynecomastia
Protease inhibitors (PI)		
Darunavir (DRV/r)	Stevens-Johnson syndrome Erythema multiform Hepatotoxicity	Rash, Nausea, Diarrhea
Atazanavir (ATZ)	First-degree AV block, Nephrolithiasis	Hyperbilirubinemia

Lopinavir (LPV)	Myocardial infarction	Hypertriglyceridemia, Asthenia, Nausea, diarrhea
Integrase inhibitors (INSTI)		
Raltegravir (RGV)	-	Headache, Increased creatine phosphokinase
Dolutegravir (DGV)	-	Headache, Sleep disturbance, Insomnia Depression Diarrhea

DIHS: drug-induced hypersensitivity syndrome; eGFR: estimated glomerular filtration rate

2.2.2 Effects of Adverse Drug Reactions on Treatment

The greatest impact of Adverse Drug Reactions (ADRs) on HIV therapy is on adherence to medication (Cardoso *et al.*, 2014). Adherence to medication refers to the extent to which one takes medicine as per the instructions of a healthcare provider. ADR lowers the levels of adherence to medication which may in turn lead to poor treatment outcomes and the development of drug resistance (Ritter *et al.*, 1999).

Many theories have been explored as to how ADRs affect adherence. Visible adverse drug reactions regardless of severity may lead to low self-esteem and self-stigmatization of patients thereby affecting adherence. The psychological suffering brought about by ADRs has also been reported in some studies as a possible reason for non-adherence (Cardoso *et al.*, 2014; Ritter *et al.*, 1999).

2.2.3 Drug-related risk factors for Adverse Drug Reactions

Polypharmacy (concurrent use of multiple medications) is a common drug-related cause of ADRs especially among the elderly. The risk of ADRs and harmful effects to the patients increases with the number of drugs due to drug-drug interactions or drug-disease interactions. Among the elderly, polypharmacy represents a significant morbidity (Shah and Hajjar, 2012).

2.3.4 Social risk factors for Adverse Drug Reactions

Alcohol has an effect on drug metabolism that leads to development of ADR. Chronic alcoholism causes liver cirrhosis and hepatitis that leads to impaired metabolism of drugs. Alcoholism also lead to enzyme activation that causes toxicity through acceleration of drug metabolism (Alomar, 2014).

Cigarette smoking induces liver enzymes CYP1A1, CYP1A2 and CYP2E1 (P450 iso-enzymes) leading to increased drug metabolism that decrease the drug pharmacological action. Abrupt cessation of smoking leads to a reduction in the activities of these enzymes thereby reducing the clearance of drugs metabolised by the enzymes and increasing the risk of ADRs (Rabiu, Simbak and Haque, 2014; Alomar, 2014).

2.3.5 Disease-related risk factors for Adverse Drug Reactions

Certain disease conditions predispose one to ADRs especially those that affect organs heavily involved in the metabolism and elimination of drugs (Rabiu, Simbak and Haque, 2014). Impaired renal function secondary to renal diseases inevitably interferes with the clearance of drugs excreted via the kidneys leading to accumulation. Similarly, hepatic disorders such as hepatitis and cirrhosis increase the risk of liver toxicity from the NNRTIs and the PIs (Rabiu, Simbak and Haque, 2014; Alomar, 2014).

2.3.6 Patient-related risk factors for Adverse Drug Reactions

The elderly and children are at higher risk of ADR development due to reduced capacity to metabolise and eliminate drugs. In early and late stage of life, a myriad of changes both physiologically and anatomically alter the pharmacokinetics of drugs (Angamo *et al.*, 2017).

Elderly persons have reduced liver and kidney function, reduced total body water and increased total body fat which may lead to accumulation of drugs to toxic levels (Wasti *et al.*, 2012). Moreover, elderly persons are likely to have many age-related health problems that require many prescription and non-prescription drugs thereby increasing their risk of ADRs (Weldegebreal, Mitiku and Teklemariam, 2016). Young patients are especially

susceptible to toxic effects of most drugs because of their under-developed drug metabolism and excretion organs like the liver and the kidney. For this reason, extra care is required for paediatric dosing and formulation of medicines (Ritter *et al.*, 1999). Gender plays a key role with women being at a higher risk of developing ADRs compared to men due to differences in their anatomy, physiology and health seeking behavior. Changes that occur during pregnancy such as an increased extra-vascular fluid volume, increased total blood volume, increased renal blood flow and glomerular filtration rate, reduced serum protein and gastric motility alter the distribution and elimination of drugs (Angamo *et al.*, 2017).

In addition, obesity may also influence the distribution and elimination of drugs especially those that are fat soluble. These drugs may accumulate in fat tissue and are released slowly over time leading to prolonged exposure to the drug and possibly toxicity (Nomathemba *et al.*, 2012).

Generally, patients with a previous history of an allergic reaction to a particular drug have an increased risk of developing an ADR to the same drug or to similar drugs. The variation of genes for drug metabolising enzymes, receptors and transporters across races and between people also determines susceptibility to ADRs. Polymorphism in cytochrome P-450 enzymes results in poor, extensive and ultra- rapid metabolisers. Poor metabolisers have a higher risk of toxicities and ADRs (Rabiu, Simbak and Haque, 2014).

2.3 Dolutegravir

Dolutegravir (DTG) is a second generation Integrase Strand Transfer Inhibitor (INSTIs) which limit viral reproduction by preventing the incorporation of HIV DNA into the host T-lymphocyte genome by blocking the viral enzyme integrase (Kandel and Walmsley, 2015b; WHO, 2016). Other drugs in this class include Raltegravir and Elvitegravir.

Dolutegravir has been associated with improved tolerability, higher antiretroviral efficacy,

lower rates of treatment discontinuation, a higher genetic barrier to resistance and fewer drug interactions than other ARV drugs (UNAIDS, 2018b). In 2016 WHO recommended adoption of DTG-based regimens as new alternative first-line options for HIV treatment. The fixed dose combination regimen containing DTG in the Kenyan setting is the Tenofovir, Lamuvidine and Dolutegravir (TDF+3TC+DTG) which was rolled out in 2017 as one of the preferred first line HIV-1 treatment options for adults and adolescents aged 15 years and above (NASCOP, 2018).

Dolutegravir is an antiretroviral agent which inhibits integrase enzyme. Viruses replicate by reverse transcription, catalyzed by reverse transcriptase, also called RNA-directed DNA polymerase. Once replication has occurred, integrase catalyse the combination of the genetic material of the virus into the host CD4 T cells (Milanga and Lotti, 2018). DTG targets HIV-1 integrase enzyme. This enzyme has three domains: the N terminal domain with a His2Cys2 motif that chelates zinc, the central domain which has the catalytic DDE motif for enzymatic activity, and the C-terminal domain with an SH3-like fold that serves to bind DNA. By binding to the active site of the enzyme in the central domain, the drug blocks the vital strand transfer step of viral DNA integration into the host genome (Benarous *et al.*, 2009; Deanda *et al.*, 2013).

DTG in current clinical use is formulated as a 50mg orally administered tablet. The drug is absorbed rapidly upon oral administration and peak levels of the drug in plasma are achieved 2-3 hours after administration. Absorption takes place along the gastrointestinal tract, with maximum absorption in the liver. When administered steadily and in the same dose, the steady state of the drug is achieved after five days, and a mean half-life of about 12 hours confers DTG the advantage of a once daily administration without requiring pharmacological boosting (Taha, Das and Das, 2015; Min *et al.*, 2011). Food increases the extent of absorption of dolutegravir; especially low, moderate and high-fat foods increase it by 33%, 41%, and 66% respectively (Taha, Das and Das, 2015). Dolutegravir has a high affinity for plasma proteins, thus is transported in high concentration in blood and is well distributed in other body fluids and tissues like the cerebrospinal fluid, vaginal tissue,

colorectal tissue cervico-vaginal fluid and seminal fluid (Cottrell, Hadzic and Kashuba, 2014).

Dolutegravir is primarily metabolized by glucuronidation by UDP-glucuronosyltransferase 1A1 (UGT1A1), and is only a minor substrate for CYP3A4 and it neither induces nor inhibits CYP isozymes, hence dolutegravir has a modest drug interaction profile (Cottrell, Hadzic and Kashuba, 2014). Urinary excretion is minimal, therefore reduced renal function does not significantly alter the pharmacokinetics of DTG (Kandel and Walmsley, 2015). However, DTG inhibits the renal transporter, organic cation transporter (OCT) 2, causing a reduced tubular secretion of creatinine and this may cause non-progressive increases in serum creatinine. These serum creatinine increase have not been associated with decreased glomerular filtration rate or progressive renal impairment (Cottrell, Hadzic and Kashuba, 2014).

Dolutegravir, like most drugs, interacts with other drugs when concomitantly administered. It interferes with the mechanism of action of some drugs, either increasing or reducing their plasma concentration (Cottrell, Hadzic and Kashuba, 2014). For instance, it slows down excretion of creatinine, thereby increasing the plasma concentration of drugs that are eliminated via renal transporters organic cation transporter 2 (OCT2) such as Dofetilide and metformin. The drug also slows down the metabolism of Tenofovir, Para-amino hippurate and other drugs that require these transporters (Castellino *et al.*, 2013). Since DTG is metabolized by UGT1A1 and CYP3A, when co-administered with drugs that utilize these same enzymes, its metabolism may be slowed due to competitive inhibition (Cottrell, Hadzic and Kashuba, 2014). This explains why anticonvulsants like carbamazepine, phenytoin and phenobarbitone significantly reduce plasma levels of dolutegravir. Drugs that induce the two enzymes or stimulate the plasma protein transporters increase dolutegravir clearance from the system. Examples of drugs which significantly increase the elimination rate of dolutegravir include the NNRTIs Nevirapine, Efavirenz and Etravirine and co-administration with DTG is not recommended. DTG is also susceptible to chelation by divalent an trivalent metal cations

contained in mineral supplements and antacids containing cations such as Magnesium, Zinc, Iron, Calcium and Aluminum (Yuan and Wessler, 2011; Song *et al.*, 2014).

2.3.1 Safety and Tolerability of DTG-based regimen

According to clinical trial studies, DTG- based regimens have shown to have a good safety profile compared to most antiretroviral combination regimens; nevertheless, some side effects were reported. Four clinical trials (SPRING-1, SPRING-2, SINGLE and FLAMINGO) reported nausea, diarrhea, hypoglycemia, Central Nervous System side effects and headache as the most common side effects among the ART naive patients, with Grade 3 and 4 adverse events constituting less than 1% (Taha, Das and Das, 2015). Insomnia occurred at a higher rate with DTG than EFV containing regimens in the SINGLE study compared with the SPRING-1 study, which showed a higher occurrence of insomnia with EFV containing regimens (Castellino *et al.*, 2013; Taha, Das and Das, 2015). Elevated creatine was also noted, but this elevation has no effect on the glomerular filtration rate (GFR), because DTG inhibits the renal transporter OCT-2, the same transporter that causes renal secretion of creatinine at the proximal tubules (Castellino *et al.*, 2013; Song *et al.*, 2014). Clinical trials studies have also shown DTG-based regimens to be generally well tolerated compared to Efavirenz containing regimens, with patients on DTG-containing regimens being almost four-times less likely to discontinue their original regimen because of adverse events or to die than those in the EFV arms (Rutherford and Horvath, 2016). The SINGLE study reported the risk of serious adverse events to be similar between EFV and DTG-based regimens (Taha, Das and Das, 2015).

Post market surveillance studies have continued to support the good safety profile and tolerability of DTG-containing regimens. Nevertheless, safety of DTG-based regimens during pregnancy has been one of the most urgent questions in global health since data from the Tsepamo study in Botswana suggested that the use of DTG in early pregnancy may be linked to neural tube defects (NTDs), serious birth defects of the brain and spine (WHO,

2018). However, at the 10th IAS conference(International AIDS Society on HIV Science-IAS 2019),updated results from the Tsepamo study in Botswana and surveillance studies in Brazil revealed that the risk in the prevalence of NTDs among women taking DTG was less than originally signaled. These results helped to re-affirm the WHO recommendation of DTG-based regimens as still the preferred the option for first-line and second-line antiretroviral treatment (ART) across all populations. However, WHO emphasized the need for ongoing monitoring of the risk of NTDs and the importance of supporting women's autonomy in decision making and informed choice (10th IAS conference, Mexico July 2019).

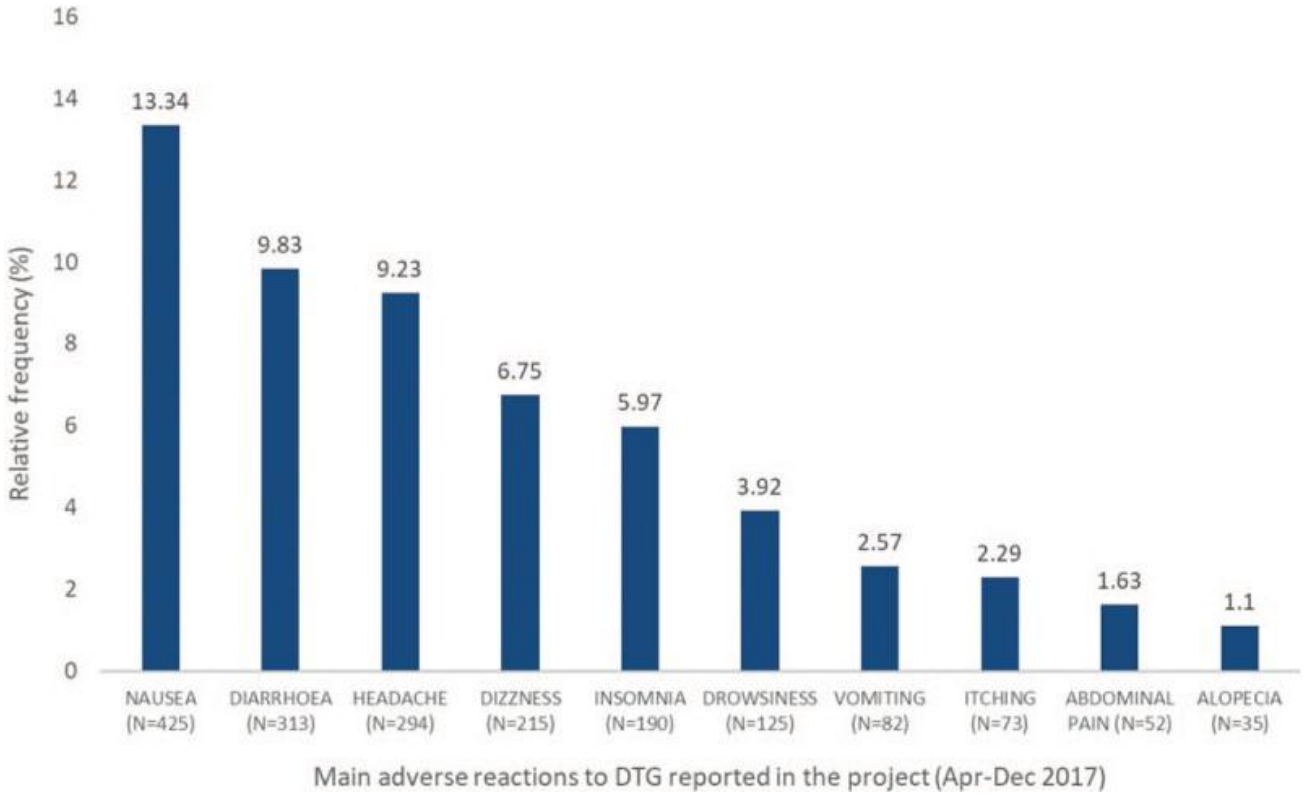

Figure 3: Main adverse reactions reported during a Brazilian DTG pharmacovigilance project and their relative frequency (%)

2.3.2 Effectiveness of DTG- based regimen

DTG-containing regimens were associated with a greater proportion of patients being virologically suppressed up to 144 weeks after initiation of therapy (Rutherford and Horvath, 2016). According to several ART randomized control trials effectiveness of DTG has been demonstrated in naïve (SINGLE, SPRING and FLAMINGO), and treatment experienced patients (STRIIVING) with DTG recording superiority among the naïve patients to Efavirenz and ritonavir boosted Darunavir and non-inferior to Raltegravir based integrase inhibitor (WHO, 2018). Superiority in effectiveness of DTG has also been reported compared to protease inhibitor and non-nucleoside reverse transcriptase inhibitor (Mondi *et al.*, 2019).

2.4 Rationale

Globally, ARVs have been proven to be lifesaving with an estimated 400,000 AIDS related deaths prevented since 2004 (NASCOP, 2018). However, the drugs have a significant safety issue. According to Pharmacy and Poisons Board (Kenya), 74% of Adverse Drug Reaction (ADRs) reported were ARV related (MOH and PPB, 2012).

The DTG-based first line treatment was rolled-out in Kenya in late 2017 without prior studies in the Kenyan setting. Kenyatta National Hospital Comprehensive Care Clinic was one of the pilot sites for the new Tenofovir/Lamuvidine/Dolutegravir first line treatment regimen for HIV type 1 management. There have been no studies reported on the side effects, tolerability and effectiveness of DTG-based regimens since its rollout in Kenya. Pharmacy and Poisons Board's (Kenya) passive pharmacovigilance data on DTG-based regimen drugs effects has revealed weight gain, deregulations of blood sugars (especially in diabetics on metformin), insomnia, rash and gastrointestinal disturbances as the most reported drug effects. Currently there is no study done in Kenya to assess the nature and extent of both documented and unknown ADRs arising from the use of DTG. ADRs may lead to patient discomfort, morbidity and mortality. They also have a negative influence on adherence which may in turn lead to drug resistance and treatment failure (Cardoso *et al.*,

2014).

Therefore, this study aimed to assess the side effects profile, tolerability and adherence of DTG-based regimens among HIV patients attending Kenyatta National Hospital Comprehensive Care Clinic.

The information obtained in this study will be used to shed light on the types and extent of side effects experienced by HIV patients at KNH CCC and give insight on the tolerability and adherence of the newly introduced DTG-based regimen .The findings may also be useful to policy makers, healthcare workers and other stakeholders in HIV management/treatment programs in providing a basis for evidence based decision making as regards rapid upscale of DTG use at KNH and in the country.

2.5 Research questions

1. What are the side effects reported by adult HIV patients on DTG-based regimens at KNH CCC?
2. What is the tolerability of DTG-based regimens among adult HIV patients at KNH CCC?
3. What is the level of adherence in adult HIV patients to DTG-based regimens at KNH CCC?

CHAPTER THREE: METHODOLOGY

3.1 Study design

This study was a descriptive cross-sectional and medical records review study. This study design was chosen because a cross-sectional study is more suitable to measure the prevalence of behavior or disease. It is also comparatively simple, inexpensive and enables quick data collection within the given time frame.

3.2 Study site

The study was conducted at the Comprehensive Care Centre (CCC) at Kenyatta National Hospital located in Nairobi County, Kenya. Kenyatta National Hospital is the main Teaching Hospital for the College of Health Sciences, University of Nairobi. KNH Comprehensive Care Centre offers a holistic approach to managing persons infected with HIV by providing socioeconomic support and VCT services. A multidisciplinary team of healthcare workers which consists of doctors, nurses, nutritionists, pharmacist, physiotherapist, laboratory technicians, public health officers and occupational therapists is responsible for the success of the KNH CCC. KNH CCC handles approximately 10,000 HIV out-patients drawn from all over the country. Currently, more than 4,000 adult HIV patients are on TDF/3TC/DTG regimen (DHIS). Patients attend clinics on appointments, and there is a strong support system for reaching out to defaulters and non-adherent patients.

3.3 Study population

Adult HIV patients attending the KNH CCC and have been on the TDF/3TC/DTG.

3.3.1 Inclusion criteria

- Adult HIV patients on TDF/3TC/DTG regimen.
- Adult HIV patients previously on TDF/3TC/DTG regimen but were switched to other regimens.

3.3.2 Exclusion criteria

- HIV patients aged less than 18 years
- HIV patients on other ART regimens and have never been on TDF/3TC/DTG regimen.
- HIV patients who have only one or no viral load information.
- Known neuropsychiatric patients.

3.4 Sample size

Cochran's formulae (Israel, 2002) was used to determine the sample size. A conservative prevalence of 50% was used because prevalence information on side effects, viral load suppression and tolerability among HIV patients on TDF/3TC/DTG attending KNH CCC is unknown. Approximately 4000 HIV patients were on the TDF/3TC/DTG combined regimen as at September 2019 (*KHIS Aggregate*, 2019).

Notations:

n – sample size

α – level of significance

$Z_{\alpha/2}$ – value of a 2-sided confidence interval obtained from a standard normal distribution (1.96)

p – estimated proportion/prevalence of side effects occurring in adult HIV patients on TDF/3TC/DTG at KNH

q – $1-p$

L – margin of error

Therefore, the single proportion sample size is calculated as:

$$n = \frac{Z^2_{\alpha/_2} pq}{L^2}$$

Using 95% level of confidence and a precision of + or – 5%, the sample size was arrived at 384 HIV patients on TDF/3TC/DTG, as per calculation below:

$$n = \frac{Z^2_{\alpha/2} pq}{L^2}$$

$$n = \frac{(1.96)^2(0.5)(1-0.5)}{(0.05)^2}$$

$$n = \frac{(1.96)^2(0.5)(0.5)}{(0.05)^2}$$

$$n = \frac{3.8416 * 0.25}{0.0025}$$

$$n = \frac{0.9604}{0.0025}$$

$$n = 384.16$$

The calculated sample size was therefore approximately 384. Further sampling was done using the finite population correction for proportions, from the known population of 4000 HIV patients on the TDF/3TC/DTG combined regimen.

Notations:

n' – adjusted sample size

n – original sample size estimate from an infinite population

N – known size of population

$$n' = \frac{1}{\frac{1}{n} + \frac{1}{N}}$$

$$n' = \frac{1}{\frac{1}{384} + \frac{1}{4000}}$$

$$n' = \frac{1}{\frac{137}{48000}}$$

$$n' = \frac{48000}{137}$$

$$n' = 350.36$$

The sample size should therefore be 350 adult HIV patients on TDF/3TC/DTG. However due to low enrolment rate and insufficient time to achieve the desired sample size, a sample size of 219 respondents was realized (response rate of 63%), which was still acceptable according to (Fincham, 2008) hence also representative of the population on the DTG-based regimen

3.5 Sampling technique

Systematic random sampling method was used in this study.

The skip/sampling interval (*k*) for this study has been calculated to be 11 as follows:

k=N/n

Where N- is the number of adult HIV patients on TDF/3TC/DTG attending KNH CCC

n- is the calculated sample size (350).

The sampling frame was derived from a list of pre-booked eligible adult HIV patients on TDF/3TC/DTG attending KNH CCC clinic, obtained from a pre-visit to the study site's

records department a day prior to the data collection day. Each patient was then assigned a random number and every 11th patient number was selected for recruitment into the study. A secondary random list was generated to fill up patients who failed to turn up for clinic or for some reason could not participate in the study.

3.6 Variables

Independent variables included socio-demographic factors (age, gender, level of education, marital status, weight, height, alcohol intake and cigarette smoking) and clinical information factors (duration on DTG regimen, duration to onset of drug effects, viral load, number of tablets taken a day, time of taking the DTG regimen, whether the regimen is taken before or after meals)

Dependent variables were the reported adverse drug effects, adherence levels and tolerability among adult HIV patients on TDF/3TC/DTG.

3.7 Data Collection Procedures

Eligible adult HIV patients on TDF/3TC/DTG with the selected random patient numbers were identified and approached as they waited to be attended to. The principle investigator then took them through all the details pertaining the study. Afterwards they were asked to sign an informed consent form to be enrolled into the study.

A trained health care provider and the principle investigator collected data from patients through interviews and by medical records reviews. The information was recorded in a structured questionnaire as the data collection tool (Appendix 4) adapted from HIV i-Base: HIV treatment information for healthcare professionals and HIV-positive people (*HIV i-Base: Guide to side effects and complications*, 2016)

The target number of patients to be interviewed per clinic day was 20. Therefore data collection was carried for a period of not more than 20 working days.

Objective 1: To assess and profile side effects reported by adult HIV patients on

TDF/3TC/DTG treatment regimen attending KNH CCC in the months of November/December 2019.

Patient Entry interviews

Data on patient reported ADRs and side effects, with emphasis on hypersensitivity reactions, CNS side effects, gastrointestinal side effects, and weight changes was collected from patients through interviews using a structured questionnaire as the data collection tool (Appendix 4).

The side effects and adverse effects were graded using the United States Division of AIDS grading system (*HIV i-Base: Guide to side effects and complications*, 2016) (Appendix 3).

Objective 2: To determine the viral load suppression trend among adult HIV patients on TDF/3TC/DTG treatment regimen attending KNH CCC.

Medical Records reviews

Viral load test results were extracted from patients' records and emphasis made to obtain at least two viral load test results: before initiation of treatment and at 3, 6, or 12 months (whichever was available) after initiation of TDF/3TC/DTG treatment therapy. This information was also captured in the data collection form (Appendix 4) and used to establish viral load change among patients.

Objective 3: To establish tolerability and adherence of adult HIV patients to the TDF/3TC/DTG regimen at KNH CCC.

Enrolled patients were also assessed for adherence through direct interviews. Adherence was assessed by frequency of attendance of clinical appointments, percentage of days covered by dispensed medicines (from pill counts) and self-reported adherence to all instructions provided by health care provider. This information was captured in the data collection form (Appendix 4) at the adherence assessment section, adapted from the International Network for the Rational Use of Drugs Initiative on Adherence to

Antiretroviral (INRUD-IAA) (Chalker *et al.*, 2010)

Objective 4: To measure the rate of discontinuation from TDF/3TC/DTG regimen among adult HIV patients attending KNH CCC.

Finally adult HIV patients who were previously on TDF/3TC/DTG regimen but were discontinued or switched to other regimens due to severe or adverse side effects during the study were identified and the reasons for discontinuation recorded.

3.8 Ethical consideration

Before the commencement of the study, approval was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC-P716/08/2019). To implement the study, authorization was obtained from KNH administration. All participants signed an Informed Consent Form (Appendix 1) before taking part in the study. The informed consent process was conducted to each patient by the researcher in privacy in a consultation room at the KNH CCC. The process involved giving all the details regarding the study as contained in the informed consent information document and answering any questions that may arise. Patient names, file and clinic number were excluded. The questionnaires were coded to maintain confidentiality. Only patients who accepted to sign the informed consent form were enrolled in the study and data extracted from them through interviews and medical records review and data recorded anonymously through use of coded patient numbers. There were no incentives to any eligible participants but patients may have benefitted from being referred for further management if they suffered from any adverse reaction or effect.

3.9 Data management

Questionnaires that were filled by study participants were stored in a cabinet under lock and key. Generated data was keyed and saved in Microsoft Excel sheet of a password-controlled laptop for security and privacy purposes. Data was analyzed using IBM SPSS Statistics

version 21.

All data was used for analysis. To handle missing data, mean imputation was used for continuous variables while mode imputation was used for categorical variables. To avoid biased data, imputation was only performed on variables with <=20%missingness.

The general considerations for categorical data are displaying frequencies and percentages. For continuous variables, descriptive statistics were performed and included: n (number of respondents), mean, standard deviation (SD), median, minimum and maximum values.

In bivariate analysis, chi-square was done for categorical variables to test for associations. All statistical tests were performed at 95% confidence level. Fishers exact p-values were used in the tests for association and exact confidence intervals were used. Exact p-values and exact confidence intervals were used because they are stable, and also because of presence of expected counts that were <5. Data was also presented and summarized in tables and graphs.

3.10 Study results dissemination plan

The results from the study will be presented in the University of Nairobi Institute of Tropical and Infectious Diseases. It will also be shared with KNH medicine and therapeutics committee, published in a peer-reviewed journal and presented at the KNH continuous medical education forums.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter presents data analysis, presentation, and interpretation of findings based on the collected data.

4.2 Socio-Demographics of Respondents

On socio-demographic information, the study collected data from 219 patients. The information sought included their gender, age group, education, marital status, and cigarette smoking, and alcohol intake.

Table 2 presets the findings obtained from the categorical variables.

Table 2: Socio-demographic Information of Respondents: Categorical variables

Variable	Category	Frequency (n)	Percent (%)
Gender	Male	127	58
	Female	92	42
Age Group (Years)	18-34 (young adults)	26	11.9
	35-49 (middle-age adults)	97	44.3
	>=50 (elderly)	96	43.8
BMI Group	Underweight	0	0
	Normal/Healthy	29	26.1
	Overweight	34	30.6
	Obese	48	43.3
Education	Primary	55	25.1
	Secondary	105	47.9
	Tertiary	56	25.6
	Informal	3	1.4
Marital Status	Married	159	72.6
	Not Married	40	18.3
	Divorced	8	3.7
	Other	12	5.5
Cigarette Smoking	Yes	6	2.7
	No	213	97.3
Alcohol Intake	Yes	33	15.1
	No	186	84.9

N=219: Percentages are based on the total number of patients; BMI: Underweight (<18.5), Normal/Healthy (>=18.5 to <25), Overweight (>=25 to <30), Obese (>=30);

Summaries of continuous variables are presented in Table 3.

Table 3: Socio-demographic Information of Respondents: Continuous variables

Variable	N	Mean	SD	Min	Median	Max
Age (Years)	219	47.6	10.7	17	48	76
Height (cm)	111	164.7	8.6	150	165	178
Weight (kg)	219	73.8	15.6	43	72	165
BMI (kg/m^2)	111	27.1	4.9	19	27.3	36

Based on the findings, the study established that majority, 127 (58%) of the respondents were male. The mean age of the respondents was 47.6 years (SD 10.7) and their mean weight was 73.8 kilograms (SD 15.6). Data on height was available in 111 of the respondents; consequently, BMI was calculated for the 111 respondents. Most of the respondents were overweight with a mean BMI of 27.1 (SD 4.9).

Majority (72.6%) of the respondents reported to be married and almost half of the participants (47.9%) reported to have attained secondary level of education. Generally, the number of smokers and alcohol consumers was low with only 6 (2.7%) and 33 (15.1%) respectively. Responses on level of education, marital status and use of alcohol and cigarettes were useful to the researcher to determine whether they predisposed respondents to adverse drug reactions/effects and adherence of DTG-based regimens among adult HIV patients attending the Kenyatta National Hospital Comprehensive Care Clinic.

4.3 Clinical Information of Study Patients

Patients' clinical information at initiation and continuation periods of the DTG-based regimen is summarized in Table 4 below.

Table 4: Clinical Information of Study Patients

Variable	Statistic	Value	
Duration on TDF/3TC/DTG Regimen (Months)	N	219	
	Mean	10.4	
	SD	9.5	
	Min	1	
	Median	8	
	Max	60	
	Category	**Frequency**	**Percent**
Duration on TDF/3TC/DTG Regimen	<6 months	53	24.2
	6-12 months	130	59.4
	>12 months	36	16.4
Time of taking TDF/3TC/DTG Regimen	Morning	125	57.1
	Evening	94	42.9
ART regimen taken Before or After Meals	Before	57	26.0
	After	162	74.0
Other tablets/drugs taken per Day	1	162	74.0
	2	7	3.2
	>=3	50	22.8
Other Regimen After TDF/3TC/DTG	Other 1st line ART regimen	2	0
	2nd line ART regimen	0	0
Last Evaluable Viral Load Assessment (Viral copies per milliliter of blood)	<50	70	32
	50-200	5	2.3
	200-400	2	0.9
	Missing	142	64.8

N=219: Percentages are based on total number of patients.

From the findings presented in Table 4, the average duration on DTG-based regimen by respondents was 10.4 months with a standard deviation (SD) of 9.5 months. Slightly more than half of the respondents were on the DTG regimen for 6-12 months (59.4%) while 24.2% were on the regimen for less than 6 months. Only 16.4% of the respondents were on the regimen for more than a year. This is an indication that most (183) of the respondents (83.6% cumulatively) had not been on the DTG-based regimen for more than a year.

During the conduction of this study, only 2 patients were switched from TLD/3TC/DTG regimen to another first line regimen because of intolerance of adverse drug effects while on the DTG-based regimen. No patient was switched to other 2nd line ART regime; suggesting there was no treatment failure encountered during the course of the study.

Regarding other tablets/drugs the patients took in a day, most patients 162 (74%) responded to be on one other tablet a day. 125 (57.1%) patients reported to be taking their DTG-based ART regimen in the morning and 94 (42.9%) of them in the evening. Finally, 162 (74%) patients responded to taken their ART regimen after meals and 57 (26.0%) before meals.

4.3.1 Clinical Information of Patient Reported Adverse ARVs Effects

The study collected information on the prevalence and outcome of adverse drug effects among 219 adult HIV patients attending KNH CCC between November 18th and December 4th 2019 as summarized in table 5 below.

Table 5: Patient reported experience of DTG-based regimen Effects

Variable	Characteristic	Frequency	Percent
Harmed by ARV regimen N=219	Yes	54	24.7
	No	165	75.3
Central Nervous System	Headache	15	19.0
	Insomnia	19	24.1
	Psychiatric disorders	6	7.6
	Suicidal ideation/attempt	9	11.4
Gastrointestinal	Nausea	8	10.1
	Diarrhea	8	10.1
	Vomiting	2	2.5
	Other	1	1.3
Hypersensitivity/ Skin reactions	Pruritus	9	11.4
	Rash	2	2.5
Outcome of drug effect	Resolved	43	54.4
	Required further management	20	25.3
	Regimen switch	2	25.3
	Persistent	14	17.7
	Death	0	0

N=219: Percentages are based on the total number of patients

N= 79: Total frequency of reported DTG-based ART drug effects

The total frequency of reported adverse drug effects/ reactions by adult HIV patients on the TDF/3TC/DTG regimen at KNH CCC was 79. The most frequent ADR was Insomnia with 19 (24.1%) entries, followed by headaches with 15 (19.0%) and skin reactions with 11 (13.9%). The least frequent drug effect was vomiting with 2(2.5%).

Harmed by ARVs

The pie chart below represents the number of patients who reported to be harmed by the TDF/3TC/DTG regimen.

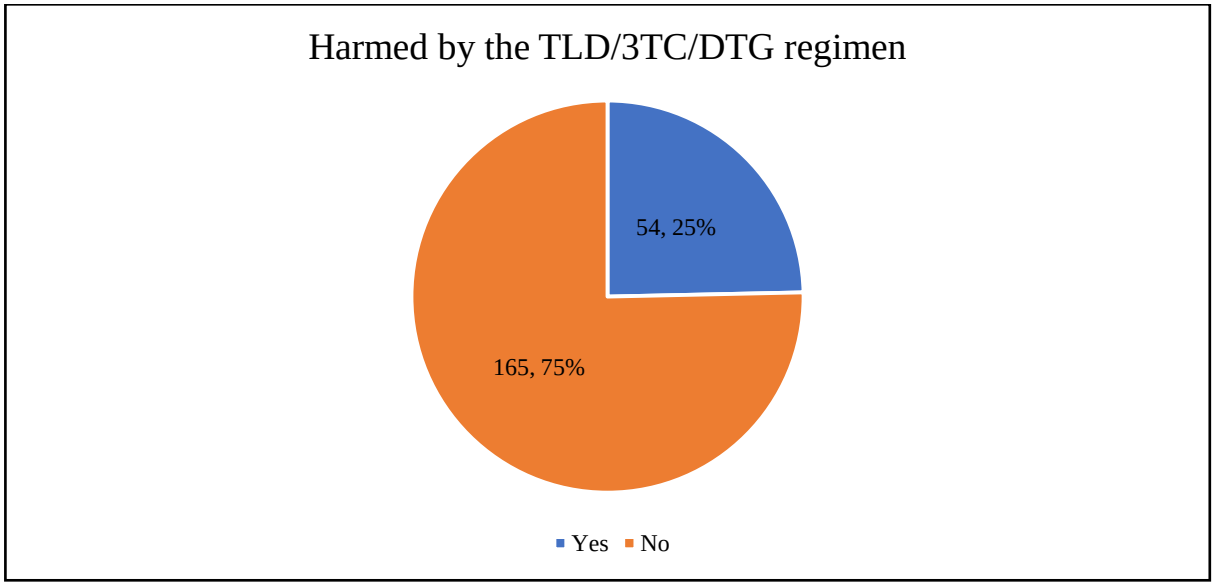

Figure 4: Patients reporting to be harmed by TDF/3TC/DTG regimen

Table 6: Ever harmed by ARV by Gender

Variable	Characteristic	Overall n	Male n (%)	Female n (%)
Harmed by ARV regimen	Yes	54	26 (48.1)	28 (51.9)
	No	165	101 (61.2)	64 (38.8)

Percentages are based on the overall (n).

From the pie chart above, 54 patients (24.7%) reported to have experienced side effects or adverse drug effects at some point whilst on the DTG-based regimen. Out of those who reported to have experienced adverse drug effects, there were 26 (48.1%) men and 28 (51.9%) females.

Outcome of DTG-based regimen adverse/side effects

More than half (54.4 %) of the reported drug effects were mild and resolved within a few days or weeks and 20% of the ADRs required the respondents to seek medical attention from their primary caregiver. During the study, 2 patients with 2 cases of severe skin reactions were switched from DTG-based ART regimen. No patient was hospitalized or died from the adverse drug effects. However 14 (17.7%) cases of drug reactions were reported to be persistent. These were 4 cases headaches and 10 cases of psychiatric disorders (depression and suicidal ideation).

Prevalence of pre-specified drug effects

Table 7: Frequency of reported DTG-based ART drug effects

Body system affected by drug effect	Frequency	Percentage (%)
Overall	79	100
Central nervous system	49	62
Gastrointestinal	19	24
Skin hypersensitivity reactions	11	14

N=79: Percentages are based on the frequency of reported drug effects.

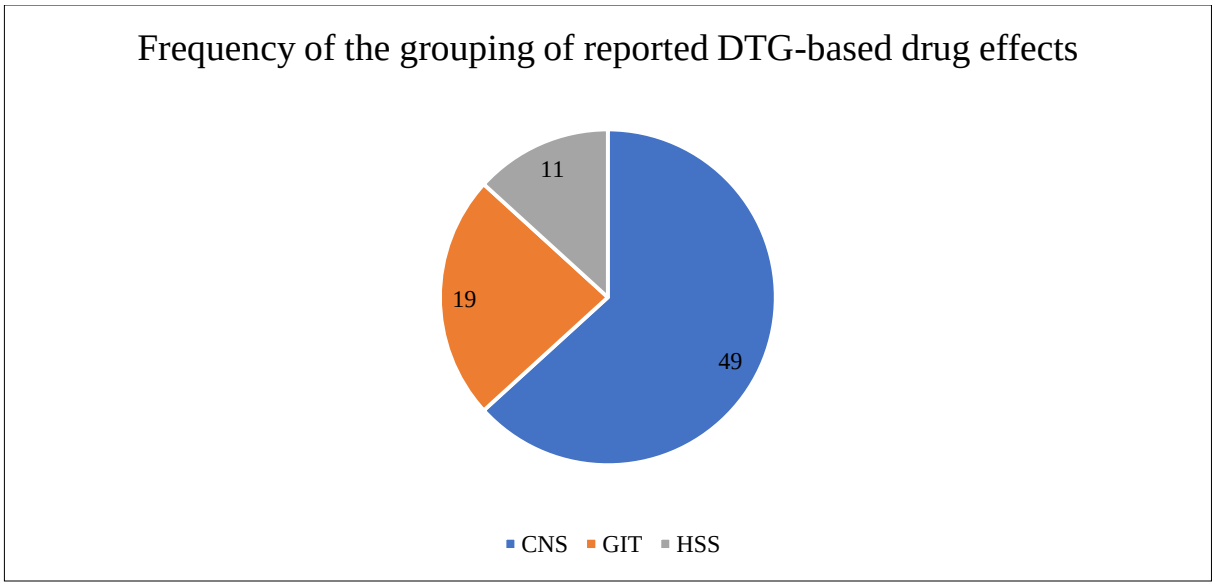

Figure 5: Pie-chart illustrating frequency of reported DTG-based ART drug effects

CNS – Central Nervous System; GIT – Gastro-Intestinal Infections; HSS – Hypersensitivity Skin Reactions.

From the table 7 and pie-chart above, of all 54 patients who reported 79 DTG-based regimen drug effects, the most frequent were central nervous system effects with 49 cases (62.0%), followed by gastrointestinal with 19(24.0%) and finally skin hypersensitivity skin reactions with 11(14.0%).

Drug Effects by Toxicity Grade

Table 8: Toxicity grading of TLD/3TC/DTG drug effects

Grouping	Drug Effects	Grade 1	Grade 2	Grade 3	Grade 4
Overall		69 (87.3%)	3 (3.8%)	6 (7.6%)	1 (1.3%)
Central Nervous System	Headaches	13 (16.5%)	0	2 (2.5%)	0
	Insomnia	18 (22.8%)	1 (1.3%)	0	0
	Psychiatric disorders (Depression/ Psychosis)	5 (6.3%)	1 (1.3%)	0	0
	Suicidal Ideation or Attempt	9 (11.4%)	0	0	0

Gastro-Intestinal Tract	Diarrhea	8 (10.1%)	0	0	0
	Nausea	6 (7.6%)	1 (1.3%)	1 (1.3%)	0
	Other	1 (1.3%)	0	0	0
	Vomiting	2 (2.5%)	0	0	0
Hypersensitivity skin Reactions	Pruritus	6 (7.6%)	0	2 (2.5%)	1 (1.3%)
	Rash	1 (1.3%)	0	1 (1.3%)	0

N=79: Percentages are based on the frequency of reported drug effects

Table 8 above summarizes the toxicity grading of DTG-based regimen adverse/side effects as reported by the respondents attending KNH CCC.

Grading of these side effects was adopted from the United States Division of AIDS in the order of increasing severity (Appendix 3). In most patients 69 (87.3%) of the drug effects were grade one, meaning they were mild and were not a hindrance to daily activities. 3 (3.8%) of the drug effects were moderate/ grade two and posed some bother to the patients, requiring them to seek medical attention. 6 (7.6%) of the drug effects were severe/ grade 3, though not life threatening to the patients, but required further intervention by their primary care givers. Only 1 (1.3%) of the drug effects was severe and potentially life threatening (grade 4).

4.3.2 Gastrointestinal Tract Side Effects

The study sought to describe gastrointestinal tract effects as reported by the respondents on the DTG-based regimen. The findings are summarized in table 9 below.

Table 9: Grading of Gastrointestinal Tract Side Effects

Variable	Characteristic	Frequency	Percent
Diarrhea	Grade 1	8	42.1
Nausea	Grade 1	6	31.6
	Grade 2	1	5.3
	Grade 3	1	5.3
Vomiting	Grade 1	2	10.5
Other	Grade1	1	5.3

N=19: Percentages are based on the frequency of reported GIT effects.

The most frequent gastrointestinal effect was grade 1 diarrhea 8 (42.1%), which is mild diarrhea lasting less than one week. There were 6 (31.6%) reported cases of grade 1 nausea-mild or transient but reasonable with food intake, and 1 (5.3%) case for both grade 2 and nausea (moderate discomfort with reduced food intake for less than 3 days or more than 3 days respectively). Vomiting was the least frequent gastrointestinal effect with 2 and 1 reported cases of grade 1 and 2 respectively. Grade one was described as 2-3 episodes of vomiting a day or mild vomiting for less than one week and grade 2 as 4-5 episodes a day or mild vomiting for more than one week. One participant reported a mild case of stomach discomfort in their first week of DTG-based regimen use.

4.3.3 Central Nervous System Effects

Grading of central nervous system side effects and adverse effects was done on the patients selected for the study. Table 10 presents the findings.

Table 10: Grading of Central Nervous System Effects

Variable	Characteristic	Frequency	Percent
Insomnia	Grade 1	18	36.7
	Grade 2	1	2.0
Suicidal Ideation or attempt	Grade 1	9	18.4
Psychiatric disorders (Depression/Psychosis)	Grade 1	5	10.2
	Grade 2	1	2.0
Headaches	Grade 1	13	26.5
	Grade 3	2	4.1

N=49: Percentages are based on the frequency of reported CNS effects.

Insomnia was the most frequent CNS effect with 18 (36.7%) and 1(2.0%) cases of grade 1 and 2 respectively. Grade 1 was described as mild difficulty in falling asleep, staying asleep, or waking up early and grade 2 as moderate difficulty in falling asleep, staying asleep, or waking up early. There were no cases of severe insomnia (grade 3 and 4) reported.

Psychiatric disorders were also reported by the study participants and were graded into four grades. Grade 1 was symptoms with intervention not indicated or behavior causing no or

minimal interference with usual social & functional; grade 2 was symptoms with intervention indicated or behavior causing greater than minimal interference with usual social & functional activities; grade 3 was symptoms with hospitalization indicated or behavior causing inability to perform usual social & functional activities; and grade 4 was threatened harm to self or others or acute psychosis or behavior causing inability to perform basic self-care functions. Grade 1 and 2 depression was reported as 5 (10.2%) and 1 (2.0%) respectively. Suicidal ideation or attempt was also reported highly in this cohort, with 9 (18.4%) reported cases of grade 1.

There were a total of 15 cases of headaches reported; 13 (26.5%) cases of mild/grade 1 headaches and 2 (4.1%) cases of severe/grade 3 headaches. Grade 1 (mild headaches) was described as symptoms causing no or minimal interference with usual social & functional activities and grade 3 (severe headaches) as symptoms causing inability to perform basic self-care functions.

Headache and Insomnia by time of taking medication

Table 11: Headache and Insomnia by time of taking medication

Side effect	Evening	Morning	p-value
Headache	5 (2.3%)	6 (2.7%)	1.0000
Insomnia	6 (2.7%)	11 (5.0%)	0.6141

N=219: Percentages are based on the total number of patients. Exact p-values were used.

Time of taking medication (evening) was suspected to determine occurrence of headaches and/or insomnia. In the table above, the p-values are both >0.05 at 95% confidence level. This shows that there is no statistical association between occurrence of headaches and/or insomnia with time of taking medication.

4.3.4 Skin Reactions

The study graded the extent to which the skin reactions effects as reported by the study participants on DTG-based ART regimen. Table 12 presents the findings.

Table 12: Grading of Skin Reactions

Variable	Characteristic	Frequency	Percent
Pruritus	Grade 1	6	54.5
	Grade 3	2	18.2
	Grade 4	1	9.1
Rash	Grade 1	1	9.1
	Grade 3	1	9.1

N=11: Percentages are based on the frequency of reported skin reactions.

The grading of pruritus was such that grade 1 was itching causing no or minimal interference with usual social & functional activities; grade 2 itching causing greater than minimal interference with usual social & functional activities and grade 3&4, Itching causing inability to perform usual social & functional activities. The finding shows that there was a total of 9 reported cases of pruritus with 6 (66.7%) being of grade 1, 2 cases of grade 3 and one case of grade 4. It is worth noting that 2 patients with grade 3 and 4 pruritus were stopped from the DTG-based regimen after suffering from intense itching for more than one month.

The study also graded rash into 4 grades. Grade 1 was localized rash, grade 2 was diffuse rash or Target lesions, grade 3 was diffuse rash and vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site, and grade 4 was extensive or generalized bullous lesions or ulceration of mucous membrane involving two or more distinct mucosal sites or Stevens-Johnson syndrome or toxic epidermal. The findings show that there were two reported cases of rash; one grade 1 and another of grade 3.

4.3.5 Weight changes among Adult HIV Patients on TDF/3TC/DTG Regimen Attending KNH CCC

This study also aimed at investigating weight changes among the respondents. A baseline weight (weight recorded on/before initiation of regimen) and a post baseline weight (weight after three, six months, twelve or twenty-four months into the regimen) were gotten from

electronic medical records and recorded.

Table 13: Weight changes among Adult HIV Patients on TDF/3TC/DTG Regimen Attending KNH CCC

	Result						Change from baseline					
Visit	**n**	**Mean**	**SD**	**Min**	**Median**	**Max**	**n**	**Mean**	**SD**	**Min**	**Median**	**Max**
Baseline	28	70.48	13.26	46.4	71.7	105						
3 months	144	71.15	15.09	36.9	70.6	120	16	0.69	3.07	-7.6	1.25	4.5
6 months	117	71.87	14.82	42.2	71.5	123	18	1.51	4.1	-4	0.5	16
12 months	108	73.13	14.87	42.8	72	122	6	2.68	4.88	-1	1.3	12.4
24 months	7	71.26	12.17	59	65.5	88.5	1	-1.2	NE	-1.2	-1.2	-1.2
Last Post baseline	174	72.09	14.5	36.9	72	122	26	1.6	2.89	-4	1.6	12.4

Baseline weight (weight before DTG-based regimen initiation) was generally small with data available for only 28 patients. These had an average weight of 70.48 kg (SD=13.26 kg). From 3 to 12 months data was available for (>100) of patients, and among with these, there was an increase in the average weight change from baseline to month 3 (0.69 kg) and to month 12 (2.68). The change of weight from baseline shows that a patient had the highest drop in weight (-7.6 kg) at 3 months, and the highest gain in weight at 12 (12.4 kg). The results at 24 months are inconclusive because of low weight reporting. The overall post-baseline changes indicate a general weight gain of 1.6 kg.

4.4 Patients' Adherence and Tolerance to DTG-based regimen

The study also collected information on whether the respondents adhered to clinical instructions while on the DTG-based regimen. Table 14 presents the findings.

Table 14: Adherence and Tolerance to DTG-based regimen

Variable	Characteristic	Response	Percent
Follows all instructions	Yes	213	97.3
	No	6	2.7
Forgets to take ARV medicine	Never	172	78.5
	Once in a while	35	16.0
	Often	12	5.5
Attendance of clinic appointments	Timely	159	72.6
	Not-timely	60	27.4
Percentage of days covered by medicine (Determined by pill count balances)	<50%	30	13.4
	50%-80%	183	83.6
	>80%	6	2.7
Tolerant to TDF/3TC/DTG regimen (Acceptance of the regimen)	Yes	198	90.4
	No	21	9.6
Reason for lack of Tolerance	Adverse drug effects	21	100
	Other	0	0

N=219: Percentages are based on the total number of patients.

The findings in Table 13 above show that majority (97.3 %) of the patients followed all the instructions given by their healthcare providers concerning taking their ARV medicine and 78.5% of the respondents responded they never forgot to take their medicine. However, 16.0% revealed to forget to take their ARV drugs once in a while and 12% forgot to take their ARV drugs often. Majority of the patients (72.6%) responded to attend their clinic appointments on time. Only 27.4% of the respondents reported some difficulties in keeping their clinical appointments. Pill count balance was used to determine the percentage of days covered by the ARV medicine. Majority (83.6%) of the respondents had >80 % days covered by the DTG-based the ARV medicine.

Tolerability of the DTG-based regimen was partly determined by acceptability of the regimen by the respondents, whom majority revealed to be unbothered by the regimen, and therefore tolerant to it. Among the respondents who never reported any drug effect, all responded to be tolerable to the regimen, however 21 (61%) of those who reported to be affected by the regimen, responded not to be tolerant to the regimen.

4.5 Viral Load changes among Adult HIV Patients on TDF/3TC/DTG Regimen Attending KNH CCC

In this section, the Principle Investigator extracted at least two viral load readings of the respondents from electrical medical records and noted. The findings were as presented in Table 15 below.

Table 15: Viral Load changes among Adult HIV Patients on TDF/3TC/DTG Regimen Attending KNH CCC

	Baseline				
Post-Baseline	**<50**	**50-200**	**200-400**	**Total**	**No Data**
<50	60 (95.2%)	1 (100%)	6 (85.7%)	67	3
50-200	2 (3.2%)	0	0	2	3
200-400	1 (1.6%)	0	1 (14.3%)	2	0
Total	63	1	7	71	6
No Data	67	6	6	79	63

Percentages are based on the column totals in the Total row; Viral Load = HIV viral copies per millimeter of blood; Baseline - viral load assessment before start of DTG regimen; Post-baseline – viral load assessment at the latest available assessment at 3, 6, 12 or 24 months.

Cumulatively, baseline viral data was available for a total of 150 (71+79) patients and post-baseline viral load data was available for 71 of the patients with baseline vial loads. Out of these, 60 (95.2%) out of 63 patients maintained a viral load of <50 HIV copies post-baseline. In the same category, viral loads of 2 patients increased to the 50-200 HIV viral copies category and 1 patient to the 200-400 HIV viral copies category post-baseline. At baseline, only 1 patient had 50-200 HIV copies, and moved to <50 HIV copies, post-baseline. Out of the 7 patients who had between 200-400 HIV copies at baseline, 6 moved to <50 HIV copies and 1 still had between 200-400 HIV copies post-baseline. A total of 67 patients had neither baseline nor post-baseline viral load data. 67, 6 and 6 patients had <50, 50-200 and >200 HIV copies respectively at baseline but no post-baseline data.

These findings show that there was a decline in the average viral load of the patients (with a total of 7 patients with >=50 HIV copies at baseline moving to <50 HV copies post-baseline) who were under the TDF/3TC/DTG treatment therapy.

4.6 Relationship between sociodemographic characteristics of study participants and reporting of DTG-based ARV drug effects

In this section, the relationship between social-demographic characteristics and reporting of drug effects by adult HIV patients attending KNH CCC was established using Exact Fisher's test and summerised in Table 16 below.

Table 16: Relationship between patients ever harmed by ARV and their socio-demographic characteristics

Variable	Characteristic	Ever Harmed by ARV?				p-value
		Yes		No		
		n (%)	CI (%,%)	n (%)	CI (%,%)	
Sex	Male	26 (11.9%)	(7.90, 16.91)	101 (46.1%)	(39.38, 52.96)	0.1123
	Female	28 (12.8%)	(8.67, 17.95)	64 (29.2%)	(23.29, 35.73)	
Age Group (Years)	18-34 (young adults)	6 (2.7%)	(1.01, 5.87)	20 (9.1%)	(5.30, 13.22)	0.5508
	35-49 (middle-age adults)	20 (9.1%)	(5.67, 13.75)	77 (35.2%)	(28.85, 41.88)	
	>=50 (elderly)	28 (12.8%)	(8.67, 17.95)	68 (31.1%)	(24.99, 37.63)	
BMI Group	Normal	3 (1.4%)	(0.01, 2.52)	26 (11.9%)	(1.59, 7.07)	0.0166
	Overweight	17 (7.8%)	(0.50, 4.61)	17 (7.8%)	(0.50, 4.61)	
	Obese	30 (13.7%)	(0.75, 5.25)	18 (8.2%)	(0.28, 3.95)	
	Missing	4 (1.8%)	(14.99, 26.02)	104 (47.5%)	(61.89, 74.59)	
Alcohol Intake	Yes	7 (3.2%)	(1.29, 6.47)	26 (11.9%)	(7.90, 16.91)	0.8267
	No	47 (21.5%)	(16.22, 27.50)	139 (63.5%)	(56.72, 69.85)	

Cigarette Smoking	Yes	1 (0.5%)	(0.01, 2.52)	5 (2.3%)	(0.75, 5.25)	1.0000
	No	53 (24.2%)	(18.68, 30.43)	160 (73.1%)	(66.67, 78.81)	

N=219 – Percentages are based on the total number of patients; CI – Exact Confidence Interval; BMI Group: Normal (>=18.5 to <25), Overweight (>=25 to <30), Obese (>=30).

DTG-based ART effects were reported by 26 (11.9%) male participants compared with 28 (12.8%) female participants. This difference in the reporting of DTG-regimen drug effects among the two sexes was not statistically significant, at p-value 0.1123. Similarly, age group, alcohol intake and cigarette smoking were not statistically significantly associated with DTG-based regimen drug reported effects, all having p-values >0.05. However, BMI was statistically significantly associated with drug effects, with a significant p-value of 0.0166, although BMI data was missing in almost half of the respondents.

4.7 Relationship between Clinical Information and DTG-based regimen reported drug effects

In this section, the relationship between clinical characteristics and reporting of DTG-based regimen drug effects by adult HIV patients attending KNH CCC was summarized in table 17 below.

Table 17: Relationship between clinical information and DTG-based regimen drug effects among adult HIV patients attending KNH CCC

Variable	Characteristic	Drug Effect		p-value
		Yes	No	
Duration on TDF/3TC/DTG Regimen (months)	<6	15 (6.8%)	38 (17.4%)	0.6689
	6-12	32 (14.6%)	98 (44.7%)	
	>12	7 (3.2%)	29 (13.2%)	
Duration of Onset of ADR [From DTG-based regimen start**] (months)**	<1	6 (2.7%)	2 (0.9%)	1.0000
	>=1	3 (1.4%)	2 (0.9%)	
	Missing	45 (20.5%)	161 (73.5%)	
Number of tablets/drugs taken in a day	1	42 (19.2%)	120 (54.8%)	1.0000
	2	2 (0.9%)	5 (2.3%)	

	>=3	10 (4.6%)	40 (18.3%)	
ART regimen taken Before or After Meals	Before	15 (6.8%)	42 (19.2%)	0.7243
	After	39 (17.8%)	123 (56.2%)	
Time of taking TDF/3TC/DTG Regimen	Morning	28 (12.8%)	97 (44.3%)	0.4291
	Evening	26 (11.9%)	68 (31.1%)	
Viral Load (copies/ml)	<50	20 (9.1%)	50 (22.8%)	0.5661
	50-200	0	5 (2.3%)	
	>200	0	2 (0.9%)	
	Missing	34 (15.5%)	108 (49.3%)	

N=219 – Percentages were based on the total number of patients.

In table 17, all p-values are >0.05 indicating that the occurrence of drug effects is not statistically significant on the clinical information. Generally, across all the variables, more patients did not experience drug effects.

CHAPTER FIVE: DISCUSSION

5.1 Discussion

A total of 219 adults HIV patients participated in the study. There were more (58%) male participants than female (42%) because during the optimization of DTG-based regimen in Kenya, the regimen was withdrawn and withheld from women of reproductive age. This was after a WHO communication on the regimen to potentially cause neural tube birth defects in babies born of mothers using DTG-based as reported in the Tsepamo study in Botswana. However, after rigorous quality data checks and birth defects surveillance studies, WHO has since withdrawn the restriction of use of DTG-based regimen in women of child bearing potential, albeit cautiously, as more studies are being carried about the same ('Additional Surveillance Data from Botswana', 2019), (*WHO Briefing April 2018*).

The mean age of the study participants was 47.6 years with most of them (44.3%) aged between 35 & 49 years, as the middle-aged participants. We also had the elderly (>=50 years) following closely at 43.8%. This concurs with local literature of HIV being most prevalent within this population (NASCOP, 2020). Body mass index (BMI) data was unavailable for almost half (49.3%) of the participants because height information was unavailable in those participants. Out of the 111 participants that had their BMI calculated, only 26.1% had normal BMI, 30.6% and 43.3% were overweight and obese respectively. The higher body mass indices established in the current study population is expected among this age set because of reduced metabolism and unhealthy lifestyles that set in with increased age (*Aging, Obesity, and Mortality*, 2004).

Prevalence of DTG-based ART drug effects in this study was 24.7% with an exact confidence interval of (19.10%, 30.92%) and an exact p-value of 0.2466. The one-sided Wald test for binomial proportions is significant at <.0001, indicating that we have sufficient statistical evidence to say that the proportion of patients harmed by the ARV regimen is <50%. The exact p-value, however, is not significant for the obtained proportion. In comparison, a country-wide prospective pharmacovigilance study carried out among adult

HIV patients on the TDF/3TC/DTG regimen in Brazil between April and December 2017 revealed the prevalence of DTG based regimen drug reactions to be 2.24% (Batista *et al.*, 2019b). This discrepancy may be due to the difference in study designs, such that the Brazilian study was a prospective study involving 79,742 patients on the DTG-based ART regimen, whereas the current study was a cross sectional study with a much smaller sample size. However, no adverse drug reactions were reported by participants in a South Indian year-long prospective study among 564 adult HIV patients on the TDF/3TC/DTG regimen (Kumarasamy *et al.*, 2017) . It is advisable, therefore, to do a wider study in Kenya, so as to obtain reliable and conclusive results.

In this study, most (87.3%) of the reported DTG-based ART regimen drug effects/ reactions, were minor (toxicity grade 1), 3.8% were grade 2, 7.6% were severe (grade 3) and only 1.3% life threatening (grade 4). There were no reported cases of mortality associated with DTG-based ART adverse drug reactions among adult HIV patients during this study, and also since the rollout of the regimen at KNH CCC. This data concurs with data from the Brazilian and clinical trial studies (STRIIVING, SAILING, SPRING-1 and 2, FLAMINGO) that showed adverse drug effects associated with DTG-based regimens to be mostly mild or moderate (Mondi *et al.*, 2019), (Batista *et al.*, 2019b).

There were a total of 54 patients who reported DTG-based ART regimen drug effects among adult HIV patients at the KNH CCC. The most (62.0%) frequent adverse drug effects were central nervous system (CNS) effects, followed by gastrointestinal (GIT) and then skin reactions at 24.0% and 14.0% respectively. Insomnia was the most (24.0%) frequent adverse effect, followed by headaches and skin reactions at 19.0% and 14.0% respectively. This differed with data from the Brazilian pharmacovigilance study which reported GIT effects to be more frequent than CNS effects. However, a follow up study in The Netherlands, like the current study, revealed CNS (insomnia and neuropsychiatric effects) to be most frequent (De Boer *et al.*, 2016). This disparity shows that pharmacokinetics and consequently adverse drug reactions are affected by race (Rabiu, Simbak and Haque, 2014). The mean duration of DTG-based regimen use before onset of adverse reactions was 0.923 months. This shows that most

DTG-based regimen drug reactions are experienced within the first month of use.

Almost half (54.4%) of the reported adverse drug effects resolved without any intervention. 25.3% of these drug effects required some intervention/ management. 17.7% were reported to be persistent and 2 severe skin reactions resulted in DTG-based regimen switch in two patients. Only 17.7 % of these adverse drug reactions were persistent, most being psychiatric (10 cases) and 4 cases of headaches. Contrary to the current study, the Brazilian study reported 50.39% of the DTG-based regimen drug effects to be persistent (Batista *et al.*, 2019b). Therefore, it is paramount for healthcare providers managing HIV patients on DTG-based regimens to be vigilant for neuropsychiatric symptoms and manage them accordingly (Hoffmann and Llibre, 2019).

In this study, insomnia was reported by 11 (5.0%) of patients taking the DTG-based regimen in the morning compared with 6 (2.7%) of patients taking the regimen at bedtime. Therefore, insomnia among adult HIV patients on the DTG-based ART regimen at KNH CCC was not likely to be associated with taking the regimen at bedtime. This is further supported by the insignificant fisher's p-value of 0.6141, which indicates no association between time of taking medication and occurrence of insomnia. Similarly, occurrence of headaches was not associated with time when the DTG-based regimen was taken; such that, headaches were reported in 6 (2.7%) patients who took the medication in the morning compared with 5 (2.3%) who took it at bedtime. With a fisher's p-value of 1.0000, this too was not statistically significant.

Among the reported neuropsychiatric disorders, the most frequent were suicidal ideations and depression at 11.4% and 7.6% respectively. All the reported psychiatric effects were grade 1 and 2, therefore mild to moderate. Clinical trial studies and post market surveillance studies on DTG-based ART regimen have reported depression in patients, especially among HIV patients with underlying psychosocial issues (Hoffmann *et al.*, 2017), (Cailhol *et al.*, 2017). In Sub-Sahara Africa, studies have established that HIV patients on combined ART are two to three times likely to be depressed compared to non-HIV patients (Nyongesa *et al.*, 2019). A study in Kenya (Nyongesa *et al.,* 2019) established the prevalence of depression

among HIV patients to be 13.8%. However, a 2014/ 2016 study in The Netherlands (De Boer *et al.*, 2016) reported unexpected severe depression and suicidal ideations in 5.6 % of their study participants. This figure was substantially high than stated in clinical trial studies. In this study, none of these psychiatric effects affected adherence to DTG-based ART treatment.

There has been compelling data from a South African case study (*Dolutegravir- why new does not automatically mean better • Spotlight*, 2019) and European pharmacovigilance studies (Menard *et al.*, 2017) on weight increase in patients on DTG-based ART regimes. This may be explained by the increased accumulation/ distribution of body fat caused by dolutegravir and other ARV drugs used in the fixed dose combinations ART regimens. In this study, an overall of 26 patients reported increase in weight. From the last available post-baseline weight measurement at month 3, 6, 12 and 24, the 26 patients had a mean weight increment of 1.6 kilograms. The mean increase was 0.69, 1.51 and 2.68 kilograms after 3, 6 and 12 months of DTG-based regimen treatment respectively.

One of the reasons for WHO recommendation for adoption of DTG-based regimens as first line ART was the remarkable ability of DTG-based regimens to suppress HIV virus replication in patients within a few weeks of treatment (Mondi *et al.*, 2019) (WHO, 2017a). In this study, most 60 (95.2%) out of 63 patients with post baseline viral loads after DTG-based regimen use had undetectable (<50 HIV copies per milliliter of blood) viral loads, 2 (0.9%) and 2 (0.9%) had viral loads of within 50-200 and 200-400 viral copies per milliliter of blood respectively. Therefore, all patients were virally suppressed after DTG-based regimen use. This implies that the therapy was effective in reducing the level of viral load among patients and agrees with Wainberg and Han, (2015) that the primary goal of HAART is to achieve full and long-term suppression of HIV- RNA plasma viral load by inhibiting and suppressing viral replication. A reduction in HIV viral load allows the rejuvenation of the host's immune system and ability to mount a strong response to contain the HIV virus. This is especially very promising and in line with the National HIV program targets of at least 90% of HIV patients on care to be virally suppressed (NASCOP, 2020).

Adherence to the TDF/3TC/DTG regimen by adult HIV patients attending KNH CCC was

generally good (≥80% in almost all aspects). Adherence level was determined by number of days covered by ART regimen and fidelity of patients to keep clinic appointments. 83.6% of the respondents had 50%-80% days covered with DTG-based ART regimen. Almost all (97.3%) of the patients responded to follow their health care providers' instructions concerning their ARV drugs take. Low level of adherence was associated with intolerance of DTG-based regimen in patients experiencing severe and potentially life-threatening adverse drug reactions. A good percentage (90.4%) of the participants responded to tolerate the DTG-based ART regimen. 21 (9.6%) patients responded to be intolerant (bothered by their ART regimen) and reported adverse drug effects as the reason for intolerance. This is concurrent with literature on effect of ARV adverse drug reactions being the major reason for intolerance and non-adherence among HIV patients (Wasti *et al.*, 2012). Consequently, this can result to treatment failure and rapid clinical deterioration in the affected patients. Therefore, there should be a deliberate close monitoring for adverse drug reactions in all HIV patients.

5.2 Conclusion and Recommendations

This study established that DTG-based regimen was associated with some adverse drug reactions; most of the reactions were mild and resolved without medical intervention. Skin reactions were the least tolerated and resulted in DTG- based regimen switch. Generally, the DTG-based regimen had an acceptable safety profile and was tolerated by HIV patients attending KNH CCC.

There is limited safety data on the recently rolled out DTG-based ART regimen in Africa and other low-income countries. For full adoption of DTG-based regimen by other African and low-income countries, WHO recommends continuous active and passive pharmacovigilance in countries who have already rolled out DTG-based regimens for the management of HIV. Therefore, after three years of roll out of DTG-based ART regimens in Kenya, country wide follow up safety studies are recommended to provide the much necessary safety data on these new DTG-based regimens.

5.3 Study Limitations

This study relied on patient reported information. Therefore, response and recall biases could have resulted and affected the credibility of the data. More so, cross sectional studies with small samples like the current study are not as statistically powerful as follow up observational studies in providing safety data of drugs. Furthermore, the reported adverse effects could not be pinned on a particular ARV as the DTG-based ART regimen is a fixed dose combination of three antiretroviral drugs. This study did not establish the role of other confounding effects in patient reported adverse drug effects. These confounding effects include and not limited to the HIV disease, concomitant disease and physiological states and other drugs/medicinal products. All these cause or exacerbate adverse drug effects/reactions. Therefore, future studies should investigate the role of these confounding effects in the occurrence of adverse drug effects among patients on DTG-based ART regimens.

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APPENDICES

Appendix 1: Adult participant information and consent form

Appendix 2: Maelezo na fomu ya ridhaa ya washiriki ambao ni watu wazima

Appendix 3: Grading of side effects and adverse drug reactions

Appendix 4: Data Collection Questionnaire

Appendix 1: Adult participant information and consent form

STUDY TITLE: Safety profile, Tolerability and Adherence of DTG-based Regimens among Adult HIV patients attending KNH CCC in the months of October/November 2019

Introduction

My name is Caroline Kaeni, a postgraduate student in the School of Tropical & Infectious Diseases at the University of Nairobi. I am inviting you to take part in this research study and would like to give you information that will help you decide whether or not to participate in this study. Feel free to stop me and ask any questions about the purpose of this study, any risks or benefits, what happens if you participate and anything else about the study that is not clear. Once I have answered the questions to your satisfaction, you may then decide to sign your name on this form to be in the study. It is also good to understand that the decision to participate in this study is voluntary; you are free to withdraw from the study at any time without giving a reason. Refusal to participate will not in any way affect the services you are entitled to at Kenyatta National Hospital. I will give you a copy of this form for your record.

May I continue? YES/NO

What is this research study about?

The researcher listed above is interviewing individuals who are taking antiretroviral drugs. The purpose of the interview is to find out if the medication they are taking is working and whether they have experienced or are experiencing any side effects from their medication. Participants in this research study will be asked questions about their experience with the antiretroviral drugs they are taking, whether they are on any other medication or have any other medical problems.

There will be approximately 384 participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

What will I be asked to do if I decide to participate in this research study?

If you agree to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 10 minutes. The interview will mainly focus on the medication you are taking but we may also ask you a little bit about yourself.

After the interview has finished, you will then proceed to the hospital laboratory where you will have a sample of your blood taken to test your blood sugar level and your liver function.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include seeking clarification on the information you have given us or if there are any concerns regarding your test results.

Are there any risks to my participation in this study?

One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. To protect your privacy, your name will not be filled on the data collection instruments. For this study, you will be assigned a unique number that I will use to identify you in a password-protected database. All the records will be kept under lock and key and only I will be able to access and use it. The results from this study may be published or presented at professional meetings but your name will not be used or

associated with the findings.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

You may also feel some slight pain when your blood is being drawn but we do not anticipate any injury or complications arising from this.

Are there any benefits to me if I decide to take part in this study?

We will refer you to doctors at this clinic for care and support where necessary. Also, the information you provide will help us better understand the benefits and harms of the medication you are taking. This information is a contribution to science and may help in making future decisions on the choice of antiretroviral drugs.

Are there any costs or payments for participating in this study?

There will be no costs to you for taking part in this study. You will not receive money or any form of compensation for taking part in this study.

What are my rights as a research study participant?

Your participation in this study is voluntary. Withdrawal or refusal to participate in the study will not affect in any way the treatment you are receiving or your hospitalization, both now and in the future.

Who can I talk to if I have questions?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 Email: uonknh_erc@uonbi.ac.ke. or Caroline Kaeni

School of Tropical & Infectious Diseases, University of Nairobi karolkaeni@yahoo.com, 0725 776 613

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study staff. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	**Yes**	**No**
I agree to provide contact information for follow-up:	Yes	No

Participant name: ____

Participant signature/Thumb stamp_____Date_____

Researcher's Agreement

I confirm that the participant has been given an opportunity to ask questions about the study, and all the questions have been answered correctly and to the best of my ability. I confirm that the participant has understood and knowingly given consent.

Researcher's signature _____ Date_____

Appendix 2: Maelezo na fomu ya ridhaa ya washiriki ambao ni watu wazima

Ufanisi, usalama na utumishi bora wa Dolutegravir miongoni mwa wagonjwa wa virusi vya ukimwi katika Hospitali Kuu ya Kenyatta (Kenya)

Utangulizi

Jina langu ni Caroline Kaeni. Mimi ni mwanafunzi wa shahada ya uzamili katika Shule ya Tropical & Infectious Diseases ya Chuo Kikuu cha Nairobi. Ningependa kukualika kushiriki katika utafiti huu. Kabla ya kufanya uamuzi wako, nitakupa maelezo yote kuhusu utafiti huu itakayokusaidia kuamua iwapo utashiriki au la. Jisikie huru kunikatiza wakati wowote kwa ajili ya kuuliza maswali kuhusu madhumuni ya utafiti huu, madhara au faida yoyote inayowezatokea kutokana na kushiriki katika utafiti huu au jambo lingine lolote linalohusiana na utafiti huu. Ikiwa utahisi umeridhika na maelezo kuhusu utafiti huu na baada ya maswali yako yote kujibiwa, utahitajika kutia sahihi yako kwenye fomu ya ridhaa iwapo utaamua kushiriki. Pia ni vema kuelewa kwamba uamuzi wa kushiriki katika utafiti huu ni kwa hiari yako na uko huru kujiondoa kwenye utafiti wakati wowote bila ya kutoa sababu . Kukataa kushiriki haitaathiri kwa njia yoyote huduma ambayo una haki ya kupata katika Hospitali Kuu ya Kenyatta. Nitakupa nakala ya fomu hii kwa rekodi yako.

Naweza kuendelea? NDIO LA

Utafiti huu umeidhinishwa na kamati ya Maadili na Utafiti ya Hospitali Kuu ya Kenyatta-Chuo Kikuu cha Nairobi. Nambari ya usajili.....

Utafiti huu ni wa nini?

Mtafiti aliyeorodheshwa hapo juu anahoji watu ambao wanatumia dawa za kupunguza

makali ya virusi vya ukimwi. Lengo la mahojiano haya ni kujua kama dawa wanazozitumia zinafanya kazi na ikiwa wamewahi pata au wanapata madhara yoyote kutokana na dawa hizo. Washiriki katika utafiti huu wataulizwa maswali kuhusu dawa za kupunguza makali ya virusi vya ukimwi wanazotumia, ikiwa wanatumia dawa zingine zozote au kama wana matatizo mengine ya kiafya. Washiriki pia watakuwa na chaguo la kufanyiwa vipimo viwili vya maabara; moja ya kupima viwango vya sukari kwa damu yao na kingine cha kuangalia kama maini yao yanafanya kazi vizuri.

Kutakuwa na washiriki wapatao 384 waliochaguliwa kwa nasibu katika utafiti huu. Tunaomba ridhaa yako ili ushiriki katika utafiti huu.

Je, nitatarajiwa kufanya nini ikiwa nitaamua kushiriki katika utafiti huu?

Ikiwa utakubali kushiriki katika utafiti huu, mambo yafuatayo yatatokea: Utahojiwa na mtafiti katika eneo la faragha ambako utajisikia huru kujibu maswali. Mahojiano yatachukua kama dakika kumi na yatazingatia dawa ambazo unazitumia. Hata hivyo, tunaweza pia kukuuliza maswali kidogo juu yako binafsi.

Baada ya mahojiano, utaombwa uelekee kwenye maabara ya hospitali ambapo sampuli ya damu yako itachukuliwa ili kupima kiwango cha sukari kwenye damu na kuangalia ikiwa ini lako linafanya kazi vizuri.

Tutaomba namba ya simu ambayo tunaweza kutumia kuwasiliana nawe iwapo kutakuwa na sababu. Ikiwa utakubali kutoa maelezo yako ya mawasiliano, itatumiwa tu na watu wanaofanya kazi kwa ajili ya utafiti huu na kamwe hautapewa mtu mwingine yeyote. Sababu ambazo tunaweza kuwasiliana na wewe ni pamoja na kutafuta ufafanuzi juu ya maelezo uliyotoa au ikiwa kuna matatizo yoyote kuhusu matokeo yako ya vipimo vya maabara.

Je, kuna hatari yoyote itakayonikumba nikishiriki katika utafiti huu?

Hatari moja ya kuwa katika utafiti ni uwezekano wa kupoteza faragha. Tutaweka mikakati kuweka maelezo yote utakayotupa siri. Njia moja ya kutekeleza wajibu huu itakuwa ni

kutoandika jina lako katika vyombo vyetu vya ukusanyaji data. Badala ya jina, utapewa nambari ya kipekee itakayotumika kukutambua kwenye hifadhidata yetu itakayohifadhiwa na nenosiri. Kumbukumbu zote zitahifadhiwa katika kabati kitakachofungwa wakati wote kwa kufuli ili kuhakikisha ya kwamba ni mimi tu ndiye nitakayeweza kuzifikia au kuzitumia. Matokeo ya utafiti huu yanaweza kuchapishwa au kupelekwa kwenye mikutano ya kitaaluma lakini jina lako halitatumiwa au kuhusishwa na matokeo.

Vilevile, kuna uwezekano wa maswali mengine kuwa magumu au ya kibinafsi. Ikiwa kuna maswali yoyote usiyotaka kuyajibu, unaweza kuyaruka. Una haki ya kukataa mahojiano au maswali yoyote yaliyoulizwa wakati wa mahojiano.

Kuna faida yoyote kwangu ikiwa nitaamua kushiriki katika utafiti huu?

Tutakuelekeza kwa madaktari katika kliniki hii kwa ajili ya huduma na msaada zaidi ikiwa kutakuwa na sababu. Pia, maelezo utakayoyatoa yatatusaidia kuelewa vizuri faida na madhara ya dawa unazozitumia. Maelezo hayo vilevile yatachangia maarifa ya kisayansi na yanaweza kusaidia kufanya maamuzi ya baadaye juu ya uchaguzi wa dawa za kupunguza makali ya virusi vya ukimwi.

Je, kuna gharama au malipo itakayotokana na kushiriki katika utafiti huu?

Hakutakuwa na gharama kwako kwa kushiriki katika utafiti huu. Hutapata fedha au aina yoyote ya fidia kwa kushiriki katika utafiti huu.

Je, haki zangu kama mshiriki katika utafiti huu ni zipi?

Kushiriki kwako katika utafiti huu ni kwa hiari. Kujiondoa au kukataa kushiriki katika utafiti hautaathiri kwa namna yoyote matibabu unayopokea katika hospitali hii sasa na siku za usoni.

Ninaweza kuwasiliana na nani ikiwa nina maswali?

Ikiwa una maswali zaidi au mahangaiko juu ya kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe mfupi wa simu kwa wafanyakazi wa utafiti huu kwa namba iliyotolewa mwishoni mwa maelezo haya.

Kwa habari zaidi juu ya haki zako kama mshiriki wa utafiti unaweza kuwasiliana na Katibu / Mwenyekiti, Kamati ya Maadili na Utafiti ya Hospitali Kuu ya Kenyatta-Chuo Kikuu cha Nairobi; Nambari ya simu 2726300 Ext. 44102 E mail: uonknh_erc@uonbi.ac.ke .

FOMU YA RIDHAA (TAARIFA YA RIDHAA)

Taarifa ya Mshiriki

Nimesoma au nimesomewa maelezo yaliyoko katika fomu hii ya ridhaa. Nimekuwa na fursa ya kujadili utafiti huu na mfanyikazi wa utafiti. Maswali yangu yote yamejibiwa kwa lugha ninayoelewa. Nimeelezewa kuhusu hatari na faida za utafiti huu. Ninaelewa kuwa kushiriki kwangu katika utafiti huu ni kwa hiari na kwamba ninaweza kujiondoa wakati wowote. Ninakubali kwa hiari kushiriki katika utafiti huu.

Ninaelewa kwamba jitihada zote zitafanywa kuweka taarifa kuhusu utambulisho wangu siri.

Kwa kutia sahihi fomu hii ya ridhaa, sijasalimisha haki yangu yoyote ya kisheria kama mshiriki katika utafiti.

Nakubali kushiriki katika utafiti huu:	**Ndiyo**	**Hapana**
Nakubali kutoa maelezo ya mawasiliano kwa ufuatiliaji:	Ndiyo	Hapana

Jina la mshiriki : ___

Sahihi / Alama ya kidole_____Tarehe _____

Mkataba wa Mtafiti

Ninathibitisha kuwa mshiriki amepewa fursa ya kuuliza maswali kuhusu utafiti, na maswali yote yamejibiwa kwa usahihi kadri ya uwezo wangu. Ninathibitisha kuwa mshiriki ameelewa na kutoa idhini yake kwa kusudi.

Sahihi ya Mtafiti _____Tarehe_

Appendix 3: Grading side effects and adverse effects (Adapted from the United States Division of AIDS)

GRADE 1 (Mild) - Transient (goes away after a short time) or mild discomfort; no limitation in your daily activity; no medical intervention/ therapy required

GRADE 2 (Moderate) - Daily activity is affected in a mild to moderate way – some assistance might be needed; no or minimal medical intervention/therapy required.

GRADE 3 (Severe) - Daily activities is markedly reduced – some assistance usually required; medical intervention/therapy required hospitalization or hospice care possible.

GRADE 4 (Potentially life threatening) - Extreme limitation to daily activity, significant assistance required; significant medical intervention/therapy, hospitalization or hospice care very likely. Grading for some common side effects

A: Grading of Gastrointestinal tract side effects and adverse effects

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Diarrhoea	3-4 loose stools a day OR mild diarrhea lasting less than one week	5-7 loose stools a day OR diarrhea lasting more than one week	Bloody diarrhea or over 7 loose stools a day OR needing IV treatment OR feeling dizzy when standing	Hospitalization required (Possibly also for grade 3)
Nausea	Mild OR transient but reasonable food intake	Moderate discomfort OR intake decrease for less than 3 days	Severe discomfort OR minimal food intake for more than 3 days	Hospitalization required
Vomiting	2-3 episodes a day OR mild	4-5 episodes a day OR mild	Severe vomiting of all	Hospitalization for IV treatment

	vomiting for less than one week	vomiting for more than one week	food and fluids over 24 hours OR needing IV treatment OR feeling dizzy when standing	(possibly also for grade 3)

B: Grading of central nervous system side effects and adverse effects

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	Not applicable
Psychiatric disorders (Depression/ Psychosis)	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social &	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or attempt	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 Hospitalization indicated	Suicide attempted

Headaches	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic

C: Grading of hypersensitivity skin reactions

PARAMETER	**GRADE 1 (MILD)**	**GRADE 2 (MODERATE)**	**GRADE 3 (SEVERE)**	**GRADE 4 (POTENTIALLY LIFE THREATENING)**
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	Not applicable
Rash	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Appendix 4: Data collection Questionnaire (Adapted from HIV i-Base: HIV treatment information for healthcare professionals and HIV-positive people)

Questionnaire

STUDY TITLE: Safety profile, Tolerability and Adherence of DTG-based Regimens among Adult HIV patients attending the Kenyatta National Hospital

Patient Unique Number: ..... Date: ……

1. **SOCIO-DEMOGRAPHICS**

a. Age (years) …… Date of Birth …….

b. Gender

Male ☐ Female ☐

Weight (kgs) …….....

Height (m) ……

c. BMI ……..

d. Marital Status

Married ☐ Married ☐ Divorced ☐ Separated ☐

e. Education

Primary ☐ Secondary ☐ Tertiary ☐ Informal ☐

f. Cigarette smoker

Yes ☐ No ☐

g. No. of cigarettes per day ……

h. Alcohol Intake

Yes ☐ No ☐

No. of bottles per day ……..

2. CLINICAL INFORMATION

(I) ARV drug information

a. Current regimen: TDF/3TC/DTG Date started ……

b. Other regimen after DTG based regimen change (Choose the most appropriate)

1. TDF/3TC/EFV- AF2B
2. TDF/3TC/ATVr- AF2D
3. Other

c. For patients who were previously on TDF/3TC/DTG but were changed to other regimens, fill the able below:

Reason for change:	**CODE**	
Virological treatment failure	1 ☐	
Clinical treatment failure	2 ☐	
Adverse Drug reaction (Tick the most appropriate)	3 ☐	

S/E	CODE
GIT	3a
CNS	3b
Hepatotoxicity	3c
Skin Hypersensitivity	3d
Weight Changes	3e
Sugar Deregulations	3f
Reproductive System	3g

d. Approximately how long have you been on your current DTG based regimen? (Mo

e. What time do you normally take your medicine?

f. Morning evening anytime other

g. How many tablets do you take daily? I II III IV

h. Do you take your medicine before or after meals?

Before After

(II) Laboratory Tests (where available)

a.

Test	Value 1	Value 2	Value 3	~~Comment~~ Normal	Abnormal
Liver function					

tests					
Kidney function tests					
CD4 counts					

b. General comments on above tests

……
….

……
…..

……
……
…….

c. The following table will be used to determine the viral load suppression of DTG based regimen.

Viral load (copies/ml)	**(copies/ml)**	**Change(1-Increase,2-Decrease,3- No change)**
On DTG initiation		
3 months after DTG initiation		
6 months after DTG initiation		
12 months after DTG		
24 months after DTG		

(III) This section will be used to assess and profile side effects reported above by adult HIV patients on TDF/3TC/DTG regimen

a. Has your ARVs ever harmed you in any way? Yes ☐ No ☐

If yes, fill in the table below:

SE	Grade	Duration of onset of S/E after starting DTG-based regimen	Outcome: 1-Resolved 2-Required further management 3-Required regimen withdrawal

Additional comments/description of S/Es

……

……

……

……

……..

b. Do you have any allergies? Yes ☐ No ☐

(If yes, please specify).....

The following charts will be used to assess the side/adverse effects of adult HIV patients on TDF/3TC/DTG

A: **Grading of Gastrointestinal tract side effects and adverse effects**

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Diarrhea	3-4 loose stools a day OR mild diarrhea lasting less than one week	5-7 loose stools a day OR diarrhea lasting more than one week	Bloody diarrhea or over 7 loose stools a day OR needing IV treatment OR feeling dizzy when standing	Hospitalization required (Possibly also for grade 3)
Tick if applicable				
Nausea	Mild OR transient but reasonable food intake	Moderate discomfort OR intake decrease for less than 3 days	Severe discomfort OR minimal food intake for more than 3 days	Hospitalization required
Tick if applicable				
Vomiting	2-3 episodes a day OR mild vomiting for less than one week	4-5 episodes a day OR mild vomiting for more than one week	Severe vomiting of all food and fluids over 24 hours OR needing IV treatment OR feeling dizzy when standing	Hospitalization for IV treatment (possibly also for grade 3)
Tick if applicable				

B: **Grading of hypersensitivity skin reactions**

PARAMETER	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (POTENTIALLY
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	Not applicable
Tick if applicable				
Rash	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Tick if applicable				

C: **Grading of central nervous system side effects and adverse effects**

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	Not applicable
Tick if applicable				
Psychiatric disorders (Depression/ Psychosis)	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Tick if applicable				
Suicidal Ideation or attempt	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 Hospitalization indicated	Suicide attempted
Tick if applicable				
Headaches	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with
Tick if applicable				

IV) The following questions will be used to assess the effects of DTG on the reproductive system

If Female:

a. Have you reached menopause? Yes ☐ No ☐

b. If no, have you had a regular menstrual cycle since starting TDF/3TC/DTG regimen?

Yes ☐ No ☐

c. If yes, how long after starting TDF/3TC/DTG did you experience irregular menstrual cycles? (State in weeks)…….

d. If no, is there a known underlying cause of the irregular menstrual cycle?

Yes ☐ No ☐

e. Are you using any family planning method? Yes ☐ No ☐

f. Have you experienced any loss of libido since starting TDF/3TC/DTG?

Yes ☐ No ☐

g. If yes, how long after starting the TDF/3TC/DTG regimen?

(State in weeks).....

If male:

a. Have you experienced any erectile dysfunction since starting TCF/3TC/DTG regimen?

Yes ☐ No ☐

b. If yes, how long after starting the DTG regimen? (State in weeks).....

c. Have you experienced loss of libido since starting TDF/3TC/DTG?

Yes ☐ No ☐

d. If yes, how long after starting the DTG regimen? (State in weeks)……..

e. Is there any known cause of erectile dysfunction or loss of libido above?

Yes ☐ No ☐

(V) The following questions will be used to assess the effects of DTG on Weight changes

	Weight (kgs)
Weight on DTG initiation	
Weight 3 months after DTG initiation	
Weight 6 months after DTG initiation	
Weight 12 months after DTG initiation	
Weight 24 months after DTG initiation	

From above table, what is the weight trend since starting DTG regimen?

☐ Increase (kgs)……..

☐ Decrease (kgs)……..

☐ No change

(VI) This section will show the action and outcome of side/adverse effect experienced

S/ no	Action Taken	Tick	Code	OUTCOME	Tick	Code
1	Drug withdrawn		1	Recovering/resolving		1
2	Dose increased		2	Recovered/resolved		2
3	Dose decreased		3	Requires or prolongs hospitalization		3
4	Dose not changed		4	Causes a congenital anomaly		4
5	Unknown		5	Requires intervention to prevent permanent damage		5
				unknown		6

a. Were you on any other drugs at the time? Yes☐ No☐

b. If yes in (a), which drugs? .....

.....

c. What were the drugs in (b) for? .....

(VII) The following section will be used to assess Adherence

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

A n s w e r	**C o d e**
Never ☐	1
Once in a while ☐	2
Sometimes ☐	3
U s u a l l y ☐	4

a. Can you generally say that you follow all the instructions given by your doctor concerning taking your medicine? Yes ☐ No ☐

b. How many pills have you brought back with you today?.....

c. How many days were meant to be covered by those pills from your last visit?.....

d. What is the percentage of days covered by medicines? Data collector to calculate as (Number on days with medicines/ Number of days without medicines) / 100……..

e. When were you supposed to attend this clinic appointment?

☐ Today or 3 days earlier or later

☐ 30 days or more earlier

☐ You don't remember

f. What are the reasons or challenges responsible for your delayed clinic appointment attendance? (Where applicable)

……

……

……

S/no	Total positive checks	Adherence (%)

(VIII)This section will be used to assess Tolerability to DTG-based regimen

a. Do you have any concerns regarding your medications? No (0) Yes (1)

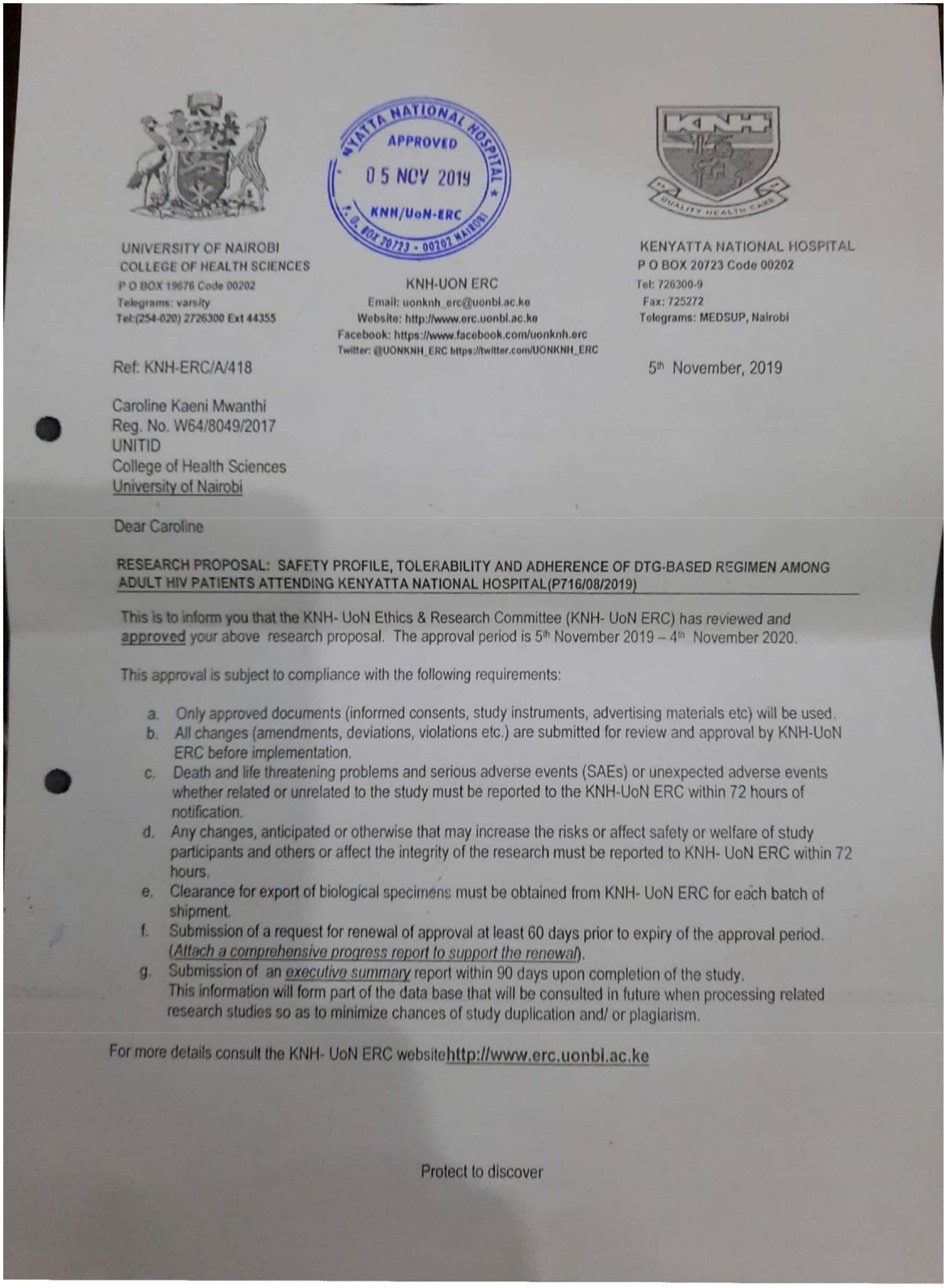
b. If yes to question above, what are the concerns?

Is the number of pills a concern? No (0) Yes (1)

c. Is the number of times you take drugs a concern? No (0) Yes (1)

d. Do you have any concern about side-effects of medications?

Appendix 5: ERC Approval



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Ref: KNH-ERC/A/418

5th November, 2019

Caroline Kaeni Mwanthi
Reg. No. W64/8049/2017
UNITID
College of Health Sciences
University of Nairobi

Dear Caroline

RESEARCH PROPOSAL: SAFETY PROFILE, TOLERABILITY AND ADHERENCE OF DTG-BASED REGIMEN AMONG ADULT HIV PATIENTS ATTENDING KENYATTA NATIONAL HOSPITAL(P716/08/2019)

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 5th November 2019 – 4th November 2020.

This approval is subject to compliance with the following requirements:

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

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

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Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
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