ASSESSMENT OF THE CLINICAL EFFECTIVENESS OF DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY AMONG ADULTS LIVING WITH HIV AT THE KENYATTA NATIONAL HOSPITAL

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This research dissertation has been evaluated and approved with our permission as the University supervisors.

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DEDICATION

I dedicate this work to my father, Prof. John A. Shiundu, and my mother Mrs. Sarah O. Shiundu for their continued support, encouragement, and prayers throughout my studies.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immuno-Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
BD	Twice daily
CCC	Comprehensive Care Clinic
COR	Crude Odds Ratio
DHIS	District Health Information System
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
ELV	Elvitegravir
GFR	Glomerular filtration rate
GI	Gastrointestinal
H	Hours
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Inhibitor
KNH	Kenyatta National Hospital
LDL	Low-density lipoprotein
NASCOP	National AIDS & STI Control Programme
NCD	Non-communicable disease
NRTI	Nucleoside Reverse Transcriptase Inhibitor

OD	Once daily
PLHIV	People living with HIV
QoL	Quality of life
RAL	Raltegravir
$T_{1/2}$	Half-life
TDF	Tenofovir disoproxil fumarate
TE	Treatment-experienced
TLD	Tenofovir Lamivudine Dolutegravir
TN	Treatment-naive
VL	Viral load
WHO	World Health Organization

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OPERATIONAL DEFINITION OF TERMS

Adverse drug event: Medical occurrence temporarily associated with the use of a medicinal product, but not necessarily causally related.

Adverse drug reaction: A response to a drug that is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modifications of physiological function.

Antiretroviral therapy: The use of a combination of antiretroviral drugs in the treatment of HIV infection.

The Area under the curve (AUC): The area under the plasma concentration vs time profile of a drug that represents the rate and extent to which the active ingredients/ moiety is absorbed from a drug product and becomes available at the site of drug action.

Clinical effectiveness: The performance of an intervention under 'real-world' conditions or during routine clinical use.

Clinical efficacy: The performance of an intervention under ideal and controlled circumstances such as randomized controlled trials.

Comprehensive Care Clinic: A clinic in a hospital dedicated to the management of HIV/AIDS patients

Switch rate: The rate at which a drug is stopped or discontinued either by the patient or by the clinician due to drug toxicities, poor clinical response, or other reasons.

Opportunistic infection: Infections that occur more frequently and are more severe in people with weakened immune systems, including people with HIV.

Undetectable viral load: Where ART has reduced the viral load to such small quantities that it can no longer be detected by standard blood tests - defined as having less than 50 copies of HIV per milliliter of blood.

Viral load suppression: If taken as prescribed, ART reduces the viral load to a very low level, which keeps the immune system working and prevents illness. This is called viral suppression - defined as having less than 400 copies of HIV per milliliter of blood.

ABSTRACT

Background: Dolutegravir is highly effective, with a high genetic barrier to HIV drug resistance, and is well tolerated. International studies have assessed the efficacy and non-inferiority of dolutegravir, but more studies are required to assess its clinical effectiveness in resource-constrained settings.

Objective: To assess the clinical effectiveness of dolutegravir-based antiretroviral therapy among adults living with HIV at the Kenyatta National Hospital (KNH).

Methods: A cross-sectional study was done on 154 participants at the KNH comprehensive care center where secondary data was obtained from a review of patient files/records. Simple random sampling involving computer-generated random numbers gave a representative sample of files. Microsoft-excel 2019 was used to create the database and analysis was done using STATA version-13. Association between sociodemographics and clinical effectiveness of dolutegravir was assessed using the Chi-square test. Forward-stepwise logistic regression modeling was carried out to determine the relationship between independent variables and the outcome variables at a p-value ≤ 0.05.

Results: Participants' mean age was 45.2 (SD $\pm$ 10.6) years, comprising mostly females (95, 61.7%). Majority (143, 92.9%) were treatment-experienced, with TDF/3TC/DTG being the most common regimen (148, 96.1%). Viral load suppression was 92.6% and 95.5% at 6 and 12 months respectively. The regimen TDF/3TC/DTG (aOR = 21.607; 95% CI 1.118-417.591; p = 0.042) gave higher odds of VL suppression at 6 months. Prevalence of opportunistic infections decreased after dolutegravir initiation with bacterial pneumonia (6, 3.9%) being most prevalent. Males (aOR = 0.354; 95% CI 0.133-0.941; p = 0.037) had lower odds of having OIs before dolutegravir initiation. Being treatment-experienced (aOR = 0.066; 95% CI 0.005-0.886; p = 0.040) resulted in lower odds of OIs after dolutegravir initiation. Adverse drug reactions to dolutegravir were infrequent though headache (11, 7.1%), weight-gain (3, 1.9%), and insomnia (2, 1.3%) featured. Males (aOR = 0.222; 95% CI 0.061-0.814; p = 0.023) had lower odds of having ADRs. No instances of dolutegravir switch were recorded.

Conclusion and Recommendations: Dolutegravir-based regimens are clinically effective and well-tolerated achieving above 90% viral load suppression rate at 6 and 12 months with minimal ADRs experienced. Clinicians should continue prescribing and monitoring the

effectiveness of dolutegravir therapy. Further, a large prospective cohort study with participants on different dolutegravir-based regimens should be done to compare their safety, clinical appropriateness, drug interactions, and resistance patterns, if any.

CHAPTER ONE: INTRODUCTION

1.1 Background of the study

The HIV virus is a retrovirus of the Retroviridaé family, *Léntivirus* genus. The HIV virus has an envelope and has two plus-sense single-stranded RNA genomes. The single-strand RNA undergoes conversion to a DNA intermediate (a provirus), that persists in host-cell DNA upon integration (1). Since the first case of HIV/AIDS reported in 1981, infections worldwide have continued to rise and the pandemic remains a major concern. There was about thirty-eight million PLHIV globally at the close of 2019, of which 54% were in eastern and southern Africa and 13% in central and western Africa (2,3). The prevalence of HIV among adults in Kenya was 4.9%, which translates to approximately 1.3 million adults living with HIV in Kenya as of 2019 (4).

Over the years, several drugs have been used for the management of HIV as part of various combinations referred to as ART regimens. Several region-specific guidelines are available for preferred first, second and third-line regimens based on WHO guidelines. The drugs used in the management of HIV target various stages in the replication cycle of the virus. Commonly used classes of ART include co-receptor (CCR5) antagonists, HIV integrase strand transfer inhibitors, fusion inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protéase inhibitors (PIs) (5).

The WHO recommends dolutegravir (DTG) plus a NRTI backbone to be preferred when initiating PLHIV on ART (6). For instance, in Kenya, NASCOP guidelines recommend the regimen "TDF/3TC/DTG" as the first-line for adult HIV patients (7). Dolutegravir, which is a second-generation INSTI, is known to be better tolerated, has high potency, and has a high genetic barrier to HIV drug resistance. Dolutegravir-based antiretroviral therapy was introduced in Kenya in 2017 and has become the most commonly used regimen with an estimated 839,953 patients as of 2019 (8).

The use of ART provides primary benefit to the HIV-infected patient by improving CD4 count and suppressing VL thus reducing the incidence of opportunistic infections which leads to improved quality of life and reduced mortality (9). The use of ART also provides secondary prevention by reducing HIV transmissibility in discordant couples when the HIV-infected partner consistently takes ART and is virally suppressed (2,10). Concerted efforts

in response to HIV have seen coverage of services steadily increase but the pandemic remains a significant health concern in the world and Kenya as well. Though the clinical effectiveness of DTG is well established in other populations, the same cannot be said locally where there exists a paucity of data. This study, therefore, seeks to fill this gap by providing data on the clinical effectiveness of dolutegravir.

1.2 Problem statement

While the HIV pandemic is still not fully controlled, scientific advances have continued to see the evolution of ART with the development of newer improved drugs. An ideal medicine would show high effectiveness with little or no adverse effects. In the context of HIV, the effectiveness of a drug would be indicated by the ability to suppress the viral load and ultimately lead to undetectable viral load (< 50 viral copies/ml). Several factors can influence viral load suppression including, adherence, long- and short-term toxicities, pharmacogenomics, drug-drug and drug-food interactions, and drug product factors such as pill burden or availability (11).

Changes made on various ART regimens since the beginning of the pandemic have been aimed at improving viral suppression while decreasing side effects (12). Changes of constituent drugs in ART regimens are usually based on efficacy studies conducted in randomized control trials and non-inferiority studies against current regimens (12). However, there are limited studies on the effectiveness of recommended regimens in routine clinical settings. Africa suffers greatly since most studies are done on high-income populations and findings generalized to all settings. While many international studies have been done to show the efficacy and non-inferiority of dolutegravir, more studies are required to investigate the effectiveness of the drug in clinical use locally. This study, therefore, aims to assess the clinical effectiveness of dolutegravir-based ART among adult PLHIV at the Kenyatta National Hospital over a period of three years from January 2017 to December 2020.

1.3 Purpose of the study

The purpose of this study was to assess the clinical effectiveness of DTG-based ART regimens as shown by the extent of viral suppression and prevalence of opportunistic infections, as well as the safety profile of DTG indicated by the prevalence of ADRs and drug switch. This study also assessed the impact of associated factors on the outcome variables. The findings of this study directly benefited the KNH CCC and its patients by

providing objective information about the effectiveness of the DTG-based ART regimens. The study also provided objective pharmacovigilance information that can further inform policy.

1.4 Research questions

The study sought to answer the following questions:

I. To what extent do adult patients on dolutegravir-based ART regimens at KNH CCC achieve viral load suppression?

II. What proportion of adult patients on dolutegravir-based ART regimens at KNH CCC develop opportunistic infections?

III. How many adult patients on dolutegravir-based ART regimens at KNH CCC experience ADRs?

IV. What is the rate of switch of dolutegravir among adult patients on DTG-based ART regimens at KNH CCC?

1.5 Objectives of the study

1.5.1 Main objective

To assess the clinical effectiveness of dolutegravir-based ART among adults living with HIV enrolled for care at the Kenyatta National Hospital CCC.

1.5.2 Specific objectives

The specific objectives of the study were to:

I. Determine the prevalence of viral load suppression and associated factors among adult patients on dolutegravir-based ART regimens at KNH CCC.

II. Analyze the prevalence of opportunistic infections and risk factors among patients on dolutegravir-based ART regimens at KNH CCC.

III. Determine the prevalence of adverse drug effects and associated factors among patients on dolutegravir-based ART regimens at KNH CCC.

IV. Assess the rate of switch of dolutegravir and associated factors among patients on dolutegravir-based ART regimens at KNH CCC.

1.6 Significance of the study

There have been several changes in the international and local HIV treatment guidelines that have resulted in the addition of new drugs and the replacement of others. There is a need to ensure that new regimens are assessed for safety and effectiveness once in routine clinical use. Many differences exist between American or European populations compared to African populations and these differences necessitate continued post-market surveillance and re-assessment of the clinical effectiveness of newer drugs. Differences such as sociodemographic factors, drug availability, genetics, adverse drug effects, regimen combinations, and comorbidities among others are possible confounding variables that affect the clinical effectiveness of a new drug introduced in a new population.

Various studies done on DTG in the American and European populations have demonstrated various ADRs related to the drug. However, in our local setup, there are limited studies following up on the same. Moreover, there are limited studies on the Kenyan population done to assess the clinical effectiveness of dolutegravir since its introduction in 2017. This study, therefore, aims to address the knowledge gap on the local assessment of the clinical effectiveness of DTG-based ART regimens and the effect of various independent variables such as sociodemographic characteristics in the Kenyan population. The findings of the study can be used to improve patient care and add to the existing body of knowledge available to medical professionals.

The findings will also be useful in describing the clinical picture of patients managed by DTG-based ART regimens which can influence policy at the KNH CCC. From a pharmacovigilance point of view, the findings of this study will evaluate the prevalence of ADRs and their impact on the use of DTG-based regimens. The findings of this study will be of importance in shaping regional and international policy by providing objective findings as to the performance of DTG based ART regimens and thus inform future policy decisions. The findings of the study will be disseminated and made available to all stakeholders.

1.7 Delimitations

This study was carried out at the comprehensive care clinic of the Kenyatta National Hospital. The study only focused on adult HIV patients (18 years and above) who were attending the clinic at the KNH CCC and was only limited to patients who were on dolutegravir based ART regimens. Dolutegravir based ART regimens were introduced in

Kenya in 2017, therefore the study was limited to the period between January 2017 and December 2020.

1.8 Limitations

One of the limitations of this study was the type of viral load test conducted, specifically, whether it was plasma-based or based on dry blood samples. The Covid-19 pandemic was another limitation in that it influenced participant availability and recruitment into the study. Since the study was limited to adult HIV patients, it was not possible to generalize the findings to the pediatric population. The study was also limited by the availability of documented outcomes of interest during the extraction of data from records. The study was also limited by confounders such as age, patient adherence, marital status, and disclosure status.

1.9 Conceptual framework

The management of HIV heavily relies on the efficacy and effectiveness of ART. Efficacy is usually determined under controlled conditions; thus, an efficacious drug needs to prove effective in real-world conditions. Dolutegravir has unique advantages that have made DTG-based ART regimens to be preferred when initiating adult PLHIV on ART. Dolutegravir has been shown in several studies to be very efficacious at viral suppression, it is better tolerated and easier to take, it has a high barrier to resistance and it is also affordable (13–16).

The exposure variable in this study was the use of a DTG-based ART regimen while the outcome variable was clinical effectiveness. The clinical effectiveness of DTG-based ART regimens was assessed by looking at the viral load suppression, opportunistic infections, adverse drug reactions, and DTG discontinuation rates among adult HIV patients at KNH CCC. An effective drug is expected to have a high viral load suppression rate which would ensure a reduced prevalence of opportunistic infections. An effective drug is also expected to have minimal ADRs which would lead to a reduced rate of discontinuation.

During routine clinical use of medications, several factors determine whether the drug will produce its desired effects. Variability among patients using a drug such as age, genetics, comorbidities, pill burden, and gender influence the effectiveness of the drug. Factors related to the drug itself such as availability, innate potency, physical size, and shape also influence the effectiveness of the drug.

Conceptual framework

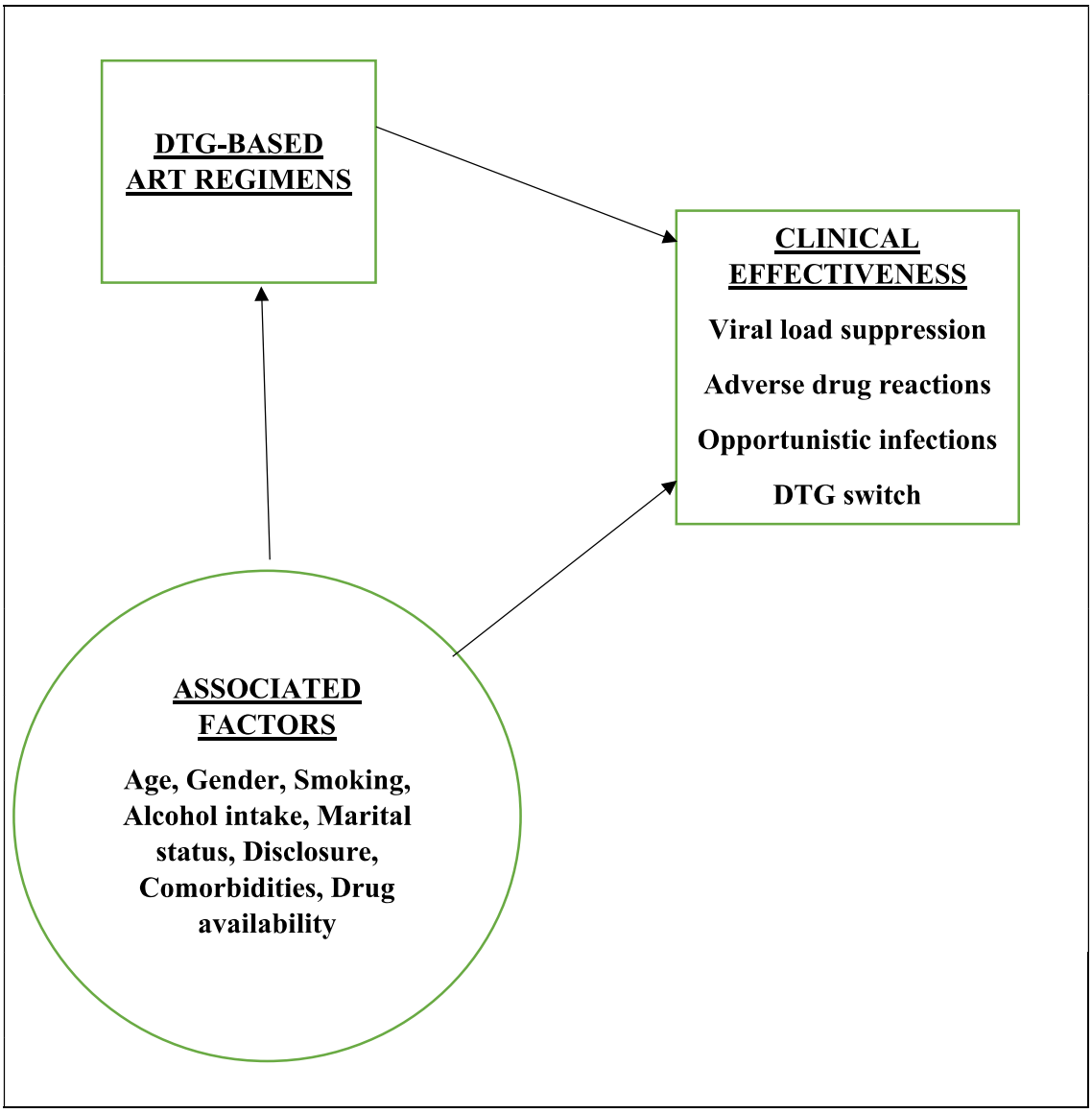

Figure 1.1: Conceptual framework (Author, 2021)

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Literature on dolutegravir regarding its pharmacology, efficacy studies, and safety profile will be discussed. This chapter will also review the literature on aspects of the clinical effectiveness of ART including viral load suppression, adverse drug reactions, and drug switch.

2.2 Pharmacology of dolutegravir

The HIV virus attaches to a target CD4 cell via surface receptors such as GP120 on the virus envelope and chemokine co-receptors such as CCR5 on the CD4 cell membrane. After entry occurs, the reverse transcriptase enzyme converts the single-strand RNA to a double-strand DNA intermediate (the provirus) (17). Incorporation of the provirus into the DNA of the infected CD4 cell then occurs and this is catalyzed by the integrase enzyme which is encoded by the 3'-end of the pol gene of the HIV (17). The incorporation of HIV provirus into the genome of the infected CD4 cell is complex and critical for viral replication and this multistep process utilizes a divalent metal cation such as magnesium attached on the active site of the enzyme (18).

Integrase strand inhibitors, including dolutegravir, can chelate metal cations bound to the enzyme, and this prevents the HIV provirus from being integrated into the genome of the host (18), as shown in Figure 2.1. Dolutegravir differs structurally and functionally from first-generation INSTIs (raltegravir and elvitegravir) which makes it active in cases of mutations causing ELV and RAL drug resistance (19). Dolutegravir effectively displaces viral DNA from the integrase enzyme's catalytic site and the resulting complex has a much slower dissociation rate which accounts for DTG's higher barrier to resistance and activity in resistance to first-generation INSTIs (20).

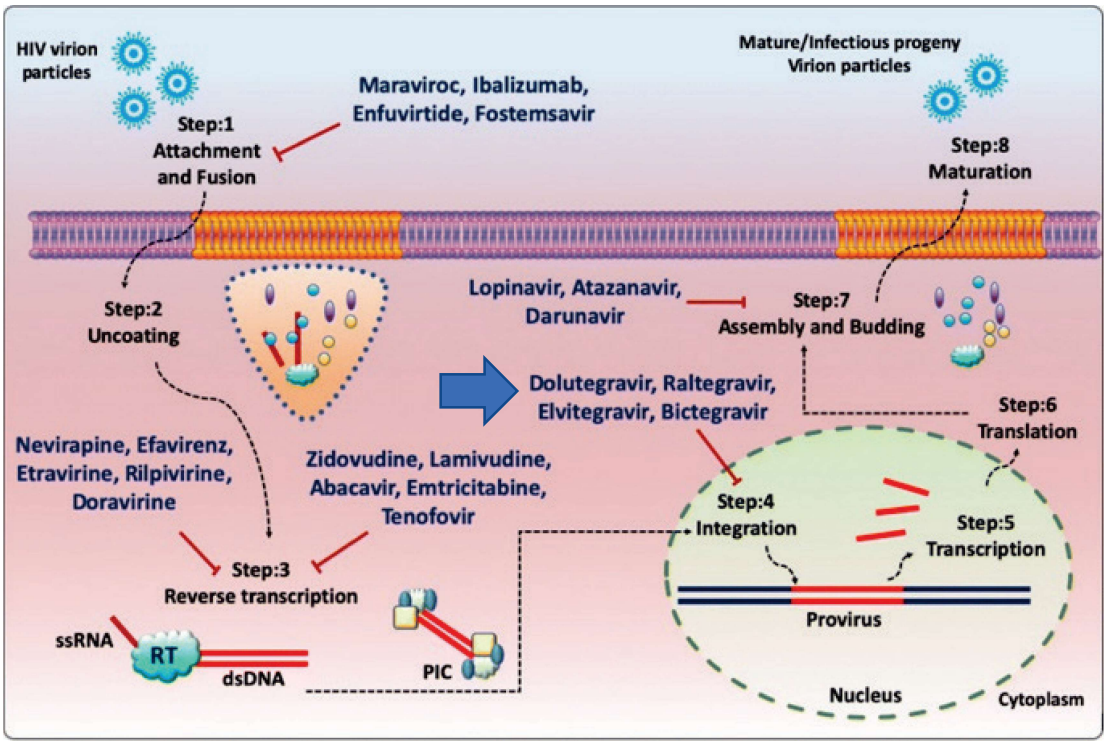

Figure 2.1: Mode of action of dolutegravir (source: "Recent Advances in the Development of Integrase Inhibitors for HIV Treatment" by Trivedį *et al.* (21))

2.3 Pharmacokinetics of dolutegravir

Dolutegravir achieves the highest serum concentration within hours of administration because of its rapid absorption. Dolutegravir has a terminal $T_{1/2}$ of 12h and requires OD administration without pharmacological boosting (7,22). Dolutegravir inhibits the organic cation transporter 2 (OCT2), a renal transporter; this diminishes renal elimination of creatinine leading to increased serum levels that are not progressive. Dolutegravir-induced changes in creatinine concentration are unrelated to GFR or worsening renal function (22).

Dolutegravir's major pathway for metabolism is the uridine diphosphate glucuronosyltransferase 1A1 while its minor pathway is the cytochrome P450 (CYP)-3A4. Dolutegravir does not induce or inhibit CYP isoenzymes therefore it has very few drug-drug interactions (22). A study by Patel *et al.* that evaluated the effect of antacids on DTG found that concurrent administration of antacid with DTG reduced DTG's area under the curve (AUC) by 74% and staggering the antacid dosing significantly minimized this interaction, thus antacids should be administered either 6 hours after or 2 hours before DTG administration (23).

The interaction between DTG and Metformin has been evaluated in several studies. Dolutegravir inhibits the "multidrug and toxin extrusion transporter 1" and the "organic cation transporter 2" which are involved in the metabolism of metformin, thus taking DTG and metformin concurrently drastically increases metformin serum availability (24). The current recommendation is to adjust the metformin dose (usually half the normal dose to a maximum of 1g) and track glycaemic control (7).

The other major drug-drug interaction for DTG is with Rifamycins, which are a major constituent of antituberculosis drug regimens. Rifampicin induces the cytochrome P450 (CYP) pathway, which reduces serum concentrations of several antiretroviral drugs to subtherapeutic levels (25). Rifampicin also induces the "uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes" and interferes with many drugs, including dolutegravir, which can be metabolized by this pathway (26). The current recommendation is to give additional DTG 50 mg to PLHIV on rifampicin (7).

2.4 Clinical effectiveness of dolutegravir

Advancements in ART have significantly reduced the progression and mortality of HIV allowing patients to live a close to normal life. Antiretroviral therapy aims to: maintain an undetectable VL (< 50 copies/ml) for as long as possible which reduces HIV transmission, increase the CD4+ count above 200 cells/mm3 ensuring opportunistic infections or development of AIDS is unlikely, and improve the QoL and years lived minus unpleasant adverse drug reactions (5). Several studies have evaluated the clinical effectiveness of Dolutegravir-based ART regimens.

2.4.1 Viral load suppression with dolutegravir

Many efficacy studies and non-inferiority studies have been conducted for dolutegravir targeting both TE and TN patients. Notable efficacy studies carried out on treatment-naïve patients include Study-ING11446 (SINGLE study), Study-ING112276 (SPRING-1 study), Study-ING111762 (SPRING-2 study), and Study-ING114915 (FLAMINGO study) (13–15,27). Notable efficacy studies carried out on treatment-experienced patients include Study-ING111762 (SAILING study) and Study- ING112574 (VIKING-3 study) (28,29).

The "SINGLE study" was a Phase III, randomized and double-blind study which was comparing DTG 50mg OD plus ABC-3TC backbone to EFV-TDF-FTC OD in TN patients. The main endpoint of the SINGLE study was viral load suppression (< 50 copies per milliliter), while other endpoints were baseline CD4+ count change and time to viral

suppression. Results from the study showed that by the 48th week, more participants (88%) on DTG compared to 81% on EFV/TDF/FTC had an undetectable VL (p = 0.003). The study concluded that DTG plus ABC-3TC was better tolerated and was more effective through 48 weeks compared to EFV/TDF/FTC (14).

The "SPRING-2 study" was a 96-week, Phase III randomized double-blind, non-inferiority study that compared DTG 50mg OD to RAL/r 400/100mg BD with TDF/FTC or ABC/3TC backbone among treatment-naïve patients. By the 48th week, 88% of patients on DTG compared to 85% of patients on RAL had undetectable VL. By the 96th week, 81% of patients on DTG compared to 76% on RAL had undetectable VL. The SPRING study concluded that DTG 50mg OD was non-inferior to BD raltegravir in TN patients. The study also concluded that since DTG does not require a pharmacokinetic booster and it is taken OD, dolutegravir-based ART is preferable among HIV-1-infected TN patients (13,27).

The "FLAMINGO study" was a 96-week multicentre open-label, Phase IIIb, non-inferiority study comparing DTG 50mg OD to DRV/r 800/100mg OD plus either ABC/3TC or TDF/FTC backbone among TN patients. By the 48th week, 90% of patients on DTG compared to 83% on DRV/r had undetectable VL. The conclusion was that DTG was superior to DRV/r (p=0.025), with higher rates of virologic response and lower rates of switch (15).

The "SAILING study" was a 48-week Phase III randomized non-inferiority study comparing DTG 50mg OD with RAL 400mg BD plus an NRTI backbone in ART experienced, INSTI-naïve HIV-infected adults. Participants who had resistance to 2/more ART drug classes, as well as those with advanced disease (VL > 50000) and AIDS were included. By the 48th week, 71% of participants using DTG compared to 64% on RAL had undetectable VL. The study found DTG to be statistically superior to RAL (p=0.03). The SAILING study thus concluded that DTG 50mg OD plus a suitable NRTI backbone is better tolerated with greater virological effect compared to raltegravir 400mg BD in treatment-experienced patients (28).

The VIKING-3 study was an open-label, single-arm, phase III study in which TE adults with INSTI-resistant virus maintained their failing regimen and received DTG 50 mg BD for one week, after which the regimen was adjusted with 2 active drugs and DTG continued. In the study, the mean VL change from baseline at day 8 and the prevalence of subjects with undetectable VL by the 24th week were assessed. Results on the 8th day showed significant change in VL from the baseline with 69% having undetectable VL. Findings of the study

informed the FDA's approval for use of DTG 50mg BD in patients suspected to have HIV integrase resistance (18). The VIKING-3 study thus concluded that DTG 50 mg BD was effective in managing TE patients with resistance to other INSTIs (29).

In a retrospective, observational, multicentre cohort study by Nasreddine *et al.* which included 4101 adult PLHIV on DTG-based ART from April 2014 to December 2017, "VL suppression rate was 96%, probability of experiencing loss of VL suppression was 7%, and the mean increase in CD4+ cell count was 100 cells/µl". (30). The effectiveness of dolutegravir was assessed in a retrospective one-arm study done in Western India by Pujari *et al.* which found that DTG had immunological and virological clinical effectiveness and was well tolerated in both TN and TE PLHIV-2 (31). Data from the Icona Cohort that included about 1679 participants (932 TN, 747 TE) assessed the effectiveness of DTG-based ART regimens as 1st line or switch ART and also concluded that dolutegravir was highly efficacious and had a good safety profile (32).

2.4.2 Occurrence of opportunistic infections

A major cause of stigma and deterioration of the QoL among PLHIV is the occurrence of opportunistic infections. While many opportunistic infections are readily treatable and preventable, opportunistic infections still account for significant morbidity and mortality among HIV patients. Opportunistic infections occur due to a fall in the CD4+ count as HIV VL increases, thus a patient who adheres appropriately to an effective ART regimen, such as a DTG-based ART regimen, is likely to have a very low incidence of OIs.

A systematic analysis conducted by Low *et al.* comprised 126 studies looking at the occurrence of OIs and the impact of ART among adult PLHIV in low and middle-income states (33). Among TN patients, the summary risk was highest (>5%) for bacterial pneumonia, herpés zoster, oral candidiasis, and tuberculosis. The first 12 months of ART provided the greatest reduction in occurrence for all OIs (range 57%–91%) except for TB and was largest for pneumocystis pneumonia, oral candidiasis, and toxoplasmosis. The study concluded that the use of ART caused a significant decrease in risk for many OIs, especially within the 1st year of therapy resulting in reduced costs due to OIs averted.

During the initiation of treatment or switch to a more effective regimen, immune reconstitution inflammatory syndrome (IRIS) may occur, caused by exacerbation of previously silent opportunistic infection due to immune system recovery. Dolutegravir rapidly reduces HIV plasma VL and induces CD4+ T-cell proliferation which may cause

IRIS. In a retrospective analysis study of a one-arm cohort (Athena) conducted by Wijting *et al*., treatment with INSTIs (DTG and RAL) was independently associated with IRIS (OR 2·17, 95% CI:1·45–3·25) (34). Examples of opportunistic infections that can predispose a patient to IRIS include atypical mycobacteria, oral candidiasis, cerebral toxoplasmosis, cryptococcosis, cytomegalovirus (CMV) infection, extra-pulmonary, herpes zoster, pneumonia, Kaposi's sarcoma, and tuberculosis.

2.4.3 Adverse drug effects associated with dolutegravir

Dolutegravir has been shown to have a good safety profile with just a few mild to moderate adverse effects. The most notable adverse events from efficacy studies on treatment-naive HIV-positive patients were insomnia, headache, nausea, diarrhea, rash, and liver abnormalities, which were mostly mild to moderate. The SINGLE study reported that DTG was better tolerated compared to EFV, with rash and psychiatric adverse reactions (anxiety, dizziness, strange dreams, and drowsiness) being noted (14). In the FLAMINGO study, "diarrhea (DTG 41 [17%] patients vs DRV/r 70 [29%] patients), headache (37 [15%] vs 24 [10%]) and nausea (39 [16%] vs 43 [18%])" were the most commonly reported (>10%) ADRs (15). Patients on DTG experienced less LDL values of grade 2 or higher compared to patients on DRV/r (11 [2%] vs 36 [7%]; p=0.0001) (15).

An active pharmacovigilance project for DTG monitoring set up in Brazil in 2017 provided valuable information reported in a study by Batista *et al* (35). A total of 79,742 participants on DTG-based ART in Brazil were included in the project, of which 2.24% reported adverse reactions to DTG. Among participants who experienced ADRs, about 74% were on 1st-line ART regimens, and about a quarter were on 3rd-line treatments. Looking at some demographics of the participants who reported ADRs to DTG, the mean age was 39 years, 69% were male, and 31% were female. About half of the ADRs experienced were considered persistent, with nausea (13%), diarrhea (9%), and headaches (9%) being the most frequent.

In a systematic review carried out by Patel *et al.* that was conducted to identify phase III/IV RCTs with participants on a DTG plus NRTI backbone regimen, dolutegravir was compared with ATV/r, DRV/r, EFV, LPV/r, and RPV in terms of total cholesterol, LDL and triglycerides changes. The study found that DTG had a good lipid profile and lower odds of ADRs and switch (36). A randomized placebo-controlled single and multiple dose-escalation study by Sherene Min *et al.* looked at the safety profile and pharmacokinetics of DTG in healthy participants and reported headache as the main adverse event (37).

The safety of DTG in pregnancy continues to be under review with initial surveillance data indicating possible neural tube defects in newborns when DTG is used early during pregnancy (38–40). Currently, DTG is considered safe during pregnancy when initiated 8 weeks after conception and when breastfeeding; proper counseling and dual contraception should be offered to women at risk of becoming pregnant while on DTG (7).

2.4.4 Dolutegravir switch

The decision to switch an ART regimen or a constituent drug, either temporarily or permanently, can be made by the patient or by the provider. Providers may recommend switching a drug due to treatment failure, ADRs, intervening illness, surgery, or conditions that do not allow oral therapy such as intubation, or drug unavailability (41). Incidences of Dolutegravir switch have been documented in several studies.

The SPRING-2 study reported that drug switches due to ADRs occurred in only 2% (10 patients in both arms) and were thus uncommon in both arms of the study (13,27). The FLAMINGO study found that DTG switch due to ADRs was less frequent (four [2%] patients) compared to DRV/r (ten [4%] patients) which caused a difference in response rates (15). The SAILING study found that both DTG and RAL were well tolerated with very few switches (28). The VIKING-3 study also found that DTG 50mg BD had a low (3%) ADR-induced switch rate, comparable to INSTI-naive subjects initiating on DTG 50mg OD (29).

A cohort study by Boer *et al.* that included 556 TN and TE participants initiating DTG-based ART regimens found that the main ADRs resulting in DTG switch were “insomnia and sleep disturbance (5.6%), psychiatric symptoms such as anxiety, depression, and psychosis (4.3%) and GI complaints (4.3%)”. The study also found that the DTG switch rate was higher in regimens that included abacavir (adjusted relative risk 1.92, 95% CI 1.09-3.38, P log-rank 0.01) (42).

A retrospective, observational, multicentre cohort study by Nasreddine *et al.* reported 785 (19.1%) switches of DTG (8.9 switches per 100 patient-years) mostly due to ADRs, with psychiatric ADRs being the most prevalent (5.2%; 2.4 switches per 100 patient-years) (30). In a retrospective cohort study of 2260 PLHIV conducted by Menard *et al.* which reviewed the clinical profile of dolutegravir specifically focusing on neuropsychiatric ADRs, the most common reasons for DTG switch were irritability and sleep disturbances (43).

Hoffmanń *et al.* carried out a retrospective analysis on a cohort of PLHIV in 2 outpatient clinics in Germany from 2007 to 2016 who had initiated an INSTI. Neuropsychiatric ADRs (dizziness, insomnia, sleep disturbances, and painful paraesthesia) causing switch of DTG were "observed more frequently in women [hazard ratio (HR) 2.64; 95% CI: 1.23–5.65; P = 0.012], in patients older than 60 years (HR: 2.86; 95% CI: 1.42–5.77; P = 0.003) and in human leucocyte antigen (HLA) B*5701-negative patients who initiated abacavir at the same time (HR: 2.42; 95% CI: 1.38–4.24; P = 0.002)" (44).

2.5 Summary of the literature

Studies assessing the efficacy of DTG and studies assessing the effectiveness of DTG under real-world conditions indicate that DTG is effective, achieving remarkable viral suppression, and is well tolerated among the majority of patients with insomnia, headache, nausea, diarrhea, rash, and liver abnormalities being the commonly reported adverse effects. However, since DTG-based regimens have been introduced in our local set up fairly recently, local data on their clinical effectiveness remains scanty.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter focuses on the research methods that were employed to achieve the objectives of the study. It comprises the study design, study site, study population, sample size, sampling techniques, data collection tools, data analysis, and logistical and ethical considerations.

3.2 Study design

The study design was a descriptive hospital-based Cross-sectional study, where data was obtained through a review of adult HIV patient records for the period between January 2017 to December 2020. A Cross-sectional study design was relevant for this study because it allowed multiple outcomes from the exposure to be studied from records. In this study, the outcome variables included viral load suppression, opportunistic infections, adverse drug reactions, and DTG drug switches. A Cross-sectional study allowed data on all the variables to be collected at the same time and prevalence determined.

3.3 Location of the study

The study was conducted at the Comprehensive Care Clinic (CCC) of the Kenyatta National Hospital (KNH). The KNH CCC offers a wide range of HIV and TB care services, including testing and counseling, pharmaceutical care, nutrition care, prevention of mother to child transmission (PMTCT), and laboratory services, among others. The KNH CCC has a staff establishment comprising of doctors, pharmacists, nurses, and support staff and serves approximately 200 patients per day. The KNH is located in Kibra constituency, Woodley/Kenyatta Golf Course ward, and is the country's national referral hospital and the teaching hospital for the University of Nairobi, College of Health Sciences. The KNH is one of the largest referral hospitals in East and Central Africa. The hospital is a level 6 hospital with about a 2000 bed capacity, 50 wards, 24 theatres (16 specialized), 22 out-patient clinics, and an accident & emergency department.

3.4 Study population

The target population was adult HIV patients on dolutegravir-based ART regimens in Kenya. There are about 1.4 million adult HIV patients on various DTG-based ART regimens in Kenya according to the November 2020 MoH-729A report in the DHIS (45). The study population was all adult HIV patients on dolutegravir-based ART regimens who had

attended the KNH CCC between January 2017 and December 2020. As per KNH's November 2020 MoH-729A report in the DHIS, there were about 7263 patients on Dolutegravir based ART regimens at the KNH CCC (45).

3.5 Eligibility criteria

3.5.1 Inclusion criteria

Patients were included in the study if they:

1. Were HIV infected adults aged 18 years and above attending the clinic at KNH CCC
2. Had been on a dolutegravir based ART regimen for at least 6 months to allow adequate exposure for assessment of the outcome variables
3. Had documented viral load readings at 6 and 12 months within the study period
4. Gave consent to participate in the study

3.5.2 Exclusion criteria

Patients were excluded from the study if they were:

1. Declared Loss to Follow-up at KNH CCC at any point within the study period
2. Taking antituberculosis medication at any point within the study period since the doubled dose of dolutegravir will misrepresent the findings.
3. Having no documented baseline viral load reading during the switch to DTG-based ART regimen.

3.6 Sampling

3.6.1 Sample size calculation

The study design was a descriptive Cross-sectional study design and the outcome variables were categorical. The main outcome variables included prevalence of viral load suppression, opportunistic infections, adverse drug reactions, and Dolutegravir switch rate. Therefore, the Cochran formula described by Cochran was applied (46).

$n = t^2 . p (1-p) / d^2$

Where,

n – Sample size

t – t value at an alpha level of 0.05 (t = 1.96)

p – expected prevalence of viral suppression with DTG (p = 90% based on findings by NASCOP reported in the World AIDS day report 2020 (8) and findings in a previous study by Pujari *et al.* (31))

d – accepted level of deviation. (d = 0.05 since the outcome variable is categorical)

The calculated sample size based on the considerations above was 139 participants. This sample size was inflated by 10% to cater for non-response bias, giving a sample size of 153 participants. A total of 154 participants were finally included in the study.

3.6.2 Sampling technique

Simple random sampling with replacement was used. The KNH CCC patient register provided a complete list of all adult HIV patients actively attending the clinic and their respective ART regimens. The study population, which comprised adult HIV patients on dolutegravir based ART regimens attending KNH CCC, was adequately described from the patient register. Availability of the list of adult HIV patients on DTG based ART regimens at KNH CCC, which formed the sampling frame, meant the entire study population was known thus making simple random sampling an appropriate method. Once the eligible participants from the sampling frame had been serialized, excel was used to generate random numbers to create a simple random sample. A replacement was done if an eligible file was picked but found to fall short of data.

3.7 Research instruments

Secondary data were extracted from patient records covering the study period and entered into the data collection form (Appendix 4). Secondary data sources that were used included adult HIV patient files for eligible patients at KNH CCC and electronic databases containing records for eligible participants. Electronic databases included the DHIS, Kenya-EMR, and Pharmacy Web-ADT.

3.8 Pre-testing

Pre-testing of the research instruments was done on 10 eligible participant files which were later excluded during the actual study. The data collection form was also tested on secondary data sources capturing data for the selected 10 patients for piloting purposes. After pre-testing, the data collection tool was restructured based on improvements identified during piloting. Changes made included the addition of two new parameters under chronic

conditions, a section capturing ART status before DTG initiation, and a summary section under viral load suppression to categorize viral load suppression at 6 months and 12 months.

3.9 Validity

3.9.1 External validity

In this study, external validity was ensured by having inclusion and exclusion criteria that did not lock out any particular sub-set of the population to ensure the sample was representative. External validity was also guaranteed by obtaining a representative non-biased sample by use of the simple random sampling method.

3.9.2 Internal validity

The accuracy and preciseness of research instruments play an important role in ensuring internal validity. In this study, the main research instrument was the data collection form. Internal validity was ensured by structuring the data collection tool in simple, clear, and acceptable language with no ambiguity of questions. Internal validity was also assessed during piloting.

3.10 Reliability

Reliability can be looked at in terms of dependability, consistency, and unambiguity of measurements. The data collection tools were structured in simple, clear, and acceptable language. Pre-testing was used to assess reliability after which restructuring was done based on areas of improvement identified.

3.11 Data collection techniques

3.11.1 Participant file identification

The participant file was identified at the KNH CCC with the help of the records officer and recruitment done by the principal investigator. The participant's unique identifier was used to identify the participant's records through various electronic databases. No research assistants were recruited during the study. The principal investigator was responsible for all data collection activities.

3.11.2 Data abstraction using data collection forms

Each study participant's patient file was retrieved with assistance from the records department. The patient file was used to identify the corresponding patient record from the

electronic patient database for extraction of requisite data. The requisite data was extracted from the patient file and electronic records and entered into the data collection forms by the principal investigator. Verification and reconciliation of data entry were done by the principal investigator. All reviews of patient files were done at the KNH CCC and no files were removed. All filled data collection forms were securely stored under lock and key.

3.11.3 Covid-19 infection prevention measures

The Covid-19 pandemic continued to be a major concern and in this study, all measures were taken to ensure infection prevention for all parties involved. Social distancing was ensured by maintaining at least one meter apart during data collection activities. All parties involved were properly wearing face masks and there was no physical contact between individuals. Use of hand sanitizers was encouraged. All data collection activities at the KNH CCC were conducted in a well-ventilated room and all MOH Guidelines on Covid-19 Infection prevention were adhered to.

3.12 Data analysis

This study aimed to assess the effectiveness of dolutegravir-based ART among adult HIV patients at KNH CCC. The outcome variables of the study included prevalence of viral load suppression at 6 months and at 12 months, the prevalence of opportunistic infections before and after dolutegravir initiation, the prevalence of adverse drug reactions before and after dolutegravir initiation, and dolutegravir switch rate at 12 months and at 18 months. Prevalence was obtained by dividing the total number of participants with the outcome by the total number of subjects over a period of 6 months and 12 months.

The exposure variable was the use of a DTG-based ART regimen, while the main outcome variables included viral load suppression, opportunistic infections, adverse drug reactions, and DTG switch. Secondary data was entered into an excel worksheet version 2019 to create the database. Data were cleaned and exported to the STATA version 13 software which was used to carry out data analysis. Descriptive summary statistics including frequency and percentages for categorical variables and mean (standard deviation) for normally distributed continuous variables were used on sociodemographic characteristics of participants such as age, gender, level of education, employment status among others, which was presented in form of tables and graphically. Descriptive statistics were used to summarize clinical data such as regimen details, viral load suppression, adverse drug reactions, and comorbidities, which were presented in tables and graphically.

The STATA version 13 software was used to carry out Pearson's Chi-square and Fischer's exact Chi square tests to determine the association between sociodemographics and clinical effectiveness of DTG. Logistic regression was carried out to determine the relationship between various independent variables such as age and gender and the outcome variable. The bivariate analysis gave the crude measures of association and multivariate analysis gave the adjusted odds ratios. Information criteria were used in forward stepwise model building. Statistical significance was set at a confidence interval of 95% and any p-value ≤ 0.05 was considered statistically significant.

3.13 Logistical and ethical considerations

All data collection activities were carried out at the KNH CCC after obtaining approval from the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC), approval study number P93/02/2021. Confidentiality of all participants' information was maintained and a unique study code was used while personal identifiers were omitted from research instruments. All data collection tools were stored under lock and key. Any digital data was stored in password-protected folders and the computer was password protected. No data records were taken away from the KNH CCC premises.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter outlines the results obtained after descriptive, inferential, and logistic regression data analyses. It comprises the sociodemographic and clinical characteristics of the study population, patterns of outcome variables among participants, associations, and predictors of outcome variables.

4.2 Sociodemographic characteristics of participants

A total of 154 participants were recruited into the study. The distribution of sociodemographic characteristics of the participants is summarised in Table 4.1. The mean age of the participants was 45.2 (SD $\pm$ 10.6) years and a range of 19 to 70 years. The majority of the participants (95, 61.7%) were females. Most of the participants (75, 49%) were married. Participants with secondary education comprised the majority (69, 47.0%) with tertiary education making up 60 (40.8%). Most of the participants (75, 49.3%) were self-employed. Almost all the participants did not smoke cigarettes (152, 98.7%) and did not drink alcohol (151, 98.0%). The mean duration living with HIV among the participants was 9.1 (SD $\pm$ 4.6) years (Table 4.1).

4.3 Clinical characteristics of participants

A majority of the participants (82, 53.2%) did not have any chronic condition. Hypertension was the most prevalent (44, 28.6%) comorbidity. The distribution of chronic conditions is shown in Figure 4.1. Most of the participants (143, 92.9%) were treatment-experienced at the time of initiation to a Dolutegravir based ART regimen. The mean duration on a dolutegravir based ART regimen among the participants was 21.3 (SD $\pm$ 6.5) months. The regimen comprising TDF/3TC/DTG was the most common among participants (148, 96.1%). The ART regimen details of the participants are summarised in Table 4.2.

Table 4.1: Sociodemographic characteristics of the study population

Variables	Total (N=154)	%
Sex; n (%)		
Male	59	38.3
Female	95	61.7
Age in years; mean (SD)	45.221 (10.570)	
Marital status; n (%)		
Single	36	23.5
Married	75	49.0
Widowed	20	13.1
Separated	20	13.1
Divorced	2	1.3
Education; n (%)		
Primary	18	12.2
Secondary	69	47.0
Tertiary	60	40.8
Employment; n (%)		
Self employed	75	49.3
Employed	36	23.7
Unemployed	36	23.7
Retired	5	3.3
Smoking status; n (%)		
Yes	2	1.3
No	152	98.7
Alcohol use; n (%)		
Yes	3	2.0
No	151	98.0
Duration LHIV in years; mean (SD)	9.091 (4.601)	

Table 4.2: ART regimen characteristics of the study population

Variables	Total (N=154)	%
ART Status on DTG initiation		
Treatment experienced	143	92.9
Treatment naïve	11	7.1
Duration on DTG based regimen in months; mean (SD)	21.273 (6.520)	
DTG-based regimen of participants		
TDF/3TC/DTG	148	96.1
AZT/3TC/DTG	2	1.3
ABC/3TC/DTG	2	1.3
TDF/3TC/DTG (2nd Line)	2	1.3

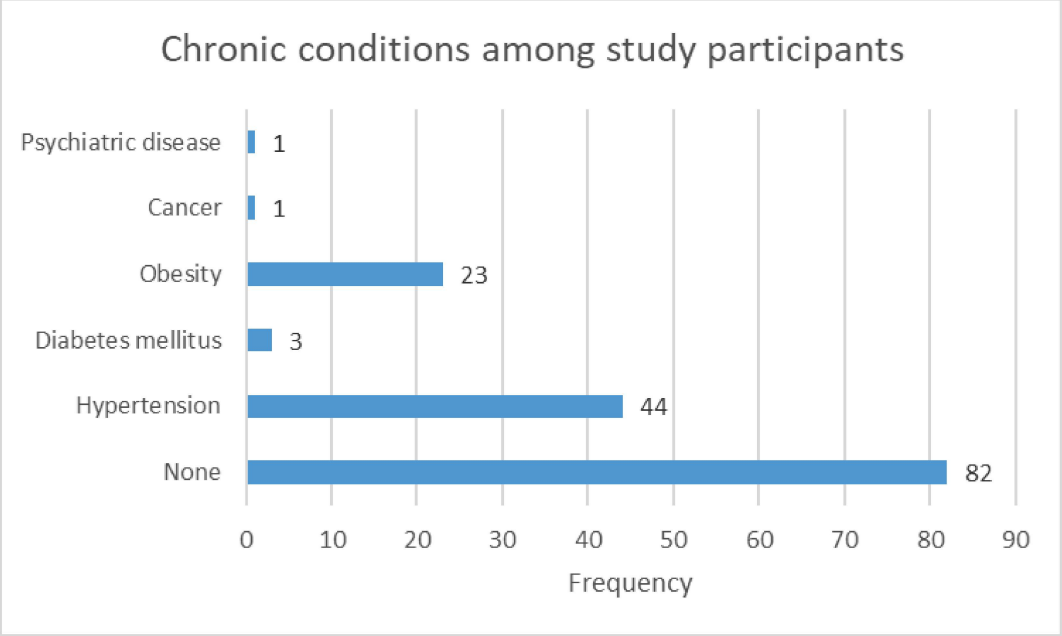

Figure 4.1: Distribution of chronic conditions among study participants

4.3.1 Viral load suppression

The pattern of viral load suppression among participants was assessed at 6 months and 12 months on a dolutegravir based ART regimen over the study period and key findings are summarized in Table 4.3. At 6 months on a DTG based ART regimen, a majority (137, 92.6%) of the participants were virally suppressed. At 12 months as well, a majority (105, 95.5%) of the participants were virally suppressed.

Table 4.3: Viral load suppression among the study population

Variables	Total	%
Viral load suppression at 6 months of DTG (N=148)		
Virally suppressed	137	92.6
Not virally suppressed	11	7.4
Viral load suppression at 12 months of DTG (N=110)		
Virally suppressed	105	95.5
Not virally suppressed	5	4.5

4.3.2 Opportunistic infections

Before initiation of a DTG based ART regimen, a majority (120, 77.9%) of the participants did not have any opportunistic infection. Among the opportunistic infections recorded, bacterial pneumonia was the most prevalent (20, 13.0%). After initiation of a dolutegravir based ART regimen, there was a bigger proportion (142, 92.2%) of the participants who did not have any opportunistic infections, while bacterial pneumonia was the most prevalent among cases (6, 3.9%). Figure 4.2 provides a comparison of the distribution of OIs among participants before and after DTG initiation. A paired t-test was conducted to determine the effect of dolutegravir on the prevalence of opportunistic infections among study participants. There was a significant difference in prevalence of OIs with regards to dolutegravir initiation before (mean = 0.221; SD $\pm$ 0.034) and after (mean = 0.078; SD $\pm$ 0.022); $t(153) = 3.612$, $p < 0.001$. Initiation of a DTG based ART regimen resulted in a reduction in the number and range of opportunistic infections among participants.

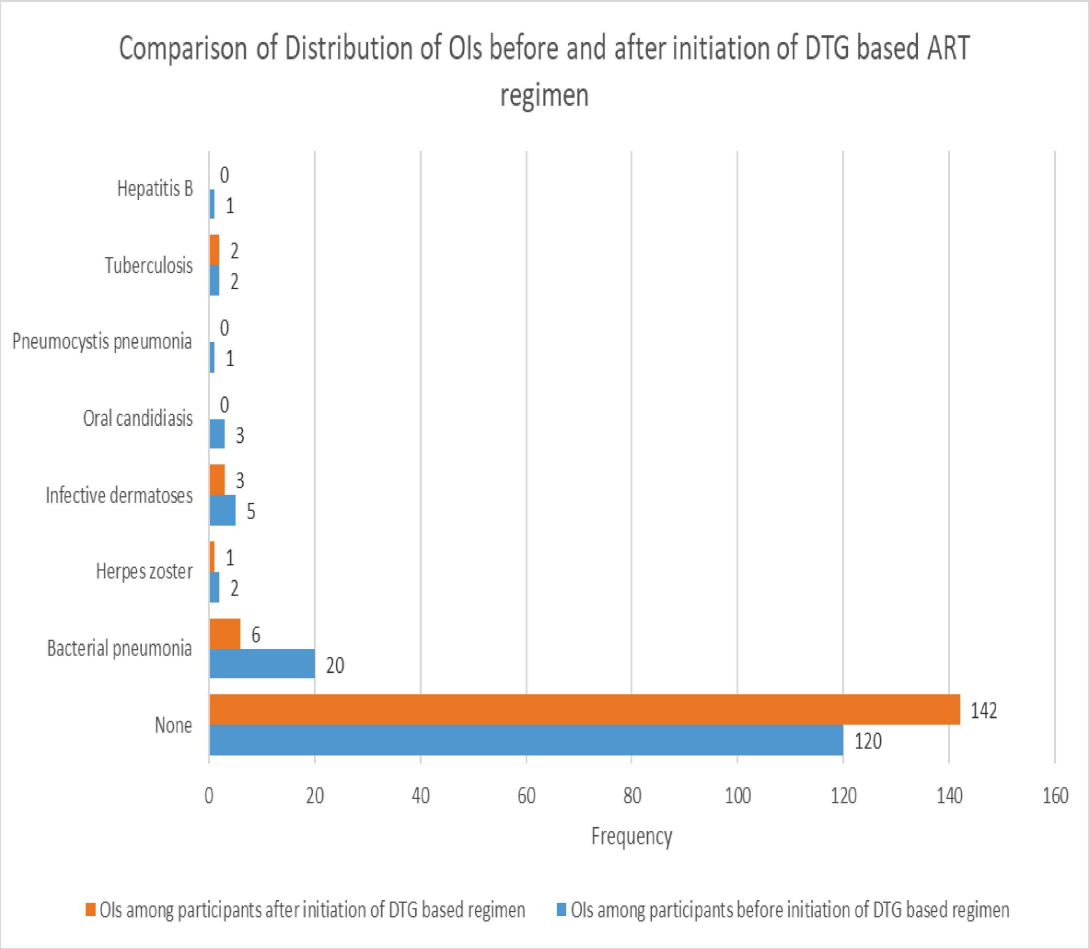

Figure 4.2: Comparison of the distribution of OIs before and after initiation of DTG based ART regimen

4.3.3 Adverse drug reactions

Before initiation of a dolutegravir based ART regimen, a majority (123, 79.9%) of the participants recorded no adverse drug reaction, with the most prevalent ADRs being GI discomfort (3, 2.0%) and paraesthesia (3, 2.0%). After initiation of a dolutegravir based ART regimen, a majority (126, 81.8%) of the participants did not experience any ADR, with headache being the most prevalent ADR (11, 7.1%). Figure 4.3 provides a comparison of the distribution of ADRs among participants before and after DTG initiation.

A paired t-test was conducted to determine the effect of dolutegravir on prevalence of adverse drug reactions among study participants. There was no significant difference in prevalence of ADRs with regards to dolutegravir initiation before (mean = 0.201; SD $\pm$ 0.032) and after (mean = 0.182; SD $\pm$ 0.031); t (153) = 0.456, p = 0.324.

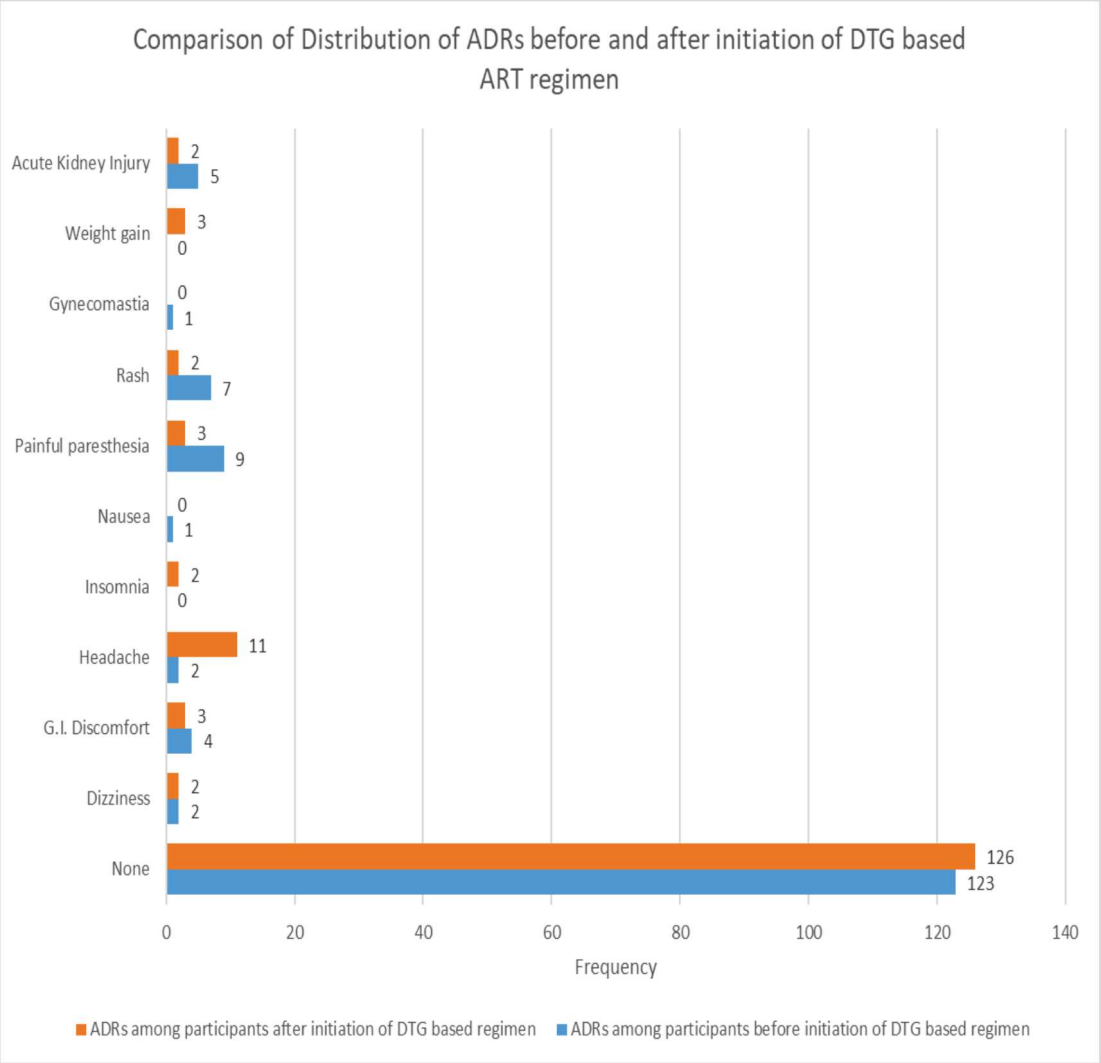

Figure 4.3: Comparison of the distribution of ADRs before and after initiation of DTG based ART regimen

4.3.4 Dolutegravir switch

All the participants included in the study did not record any instances in which dolutegravir was switched for any given reason, and for the entire duration of the study, all participants were continuing with their DTG based ART regimen.

4.4 Association between viral load suppression and sociodemographic characteristics

The association between viral load suppression at 6 months and at 12 months on a dolutegravir based ART regimen with sociodemographic characteristics was assessed. Pearson's and Fischer's exact Chi-square tests were used for the assessment and findings are presented in Table 4.4. For viral load suppression at 6 months, only marital status was found to have a statistically significant association ($p = 0.02$). For viral load suppression at 12 months, only smoking status showed a statistically significant association ($p = 0.045$) (Table 4.4).

4.5 Association between viral load suppression and clinical characteristics

The association between viral load suppression at 6 months and 12 months with the medical characteristics of participants was assessed. The findings of the assessment of the association between viral load suppression and clinical characteristics of the participants are presented in Table 4.5. The DTG based regimen of the participants had a statistically significant association with viral load suppression at 6 months ($p = 0.017$). The other clinical characteristics did not show statistically significant associations with viral load suppression (Table 4.5).

Table 4.4: Association between viral load suppression and sociodemographic characteristics

	VL suppression at 6 months (n=148)			VL suppression at 12 months (n=110)		
Variable	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**
Age in years						
< 45	63 (92.6)	5 (7.4)	0.973	45 (97.8)	1 (2.2)	0.301
≥ 45	74 (92.5)	6 (7.5)		60 (93.7)	4 (6.3)	
Sex						
Male	52 (91.2)	5 (8.8)	0.623	58 (95.1)	3 (4.9)	0.603
Female	85 (93.4)	6 (6.6)		47 (95.9)	2 (4.1)	
Marital status						
Single	31 (91.2)	3 (8.8)	**0.02**	19 (95.0)	1 (5.0)	0.372
Married	71 (98.6)	1 (1.4)		57 (96.6)	2 (3.4)	
Widowed	15 (78.9)	4 (21.1)		12 (85.7)	2 (14.3)	
Separated	18 (90.0)	2 (10.0)		14 (100.0)	0 (0.0)	
Divorced	2 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
Alcohol use						
Yes	2 (66.7)	1 (33.3)	0.208	1 (50.0)	1 (50.0)	0.089
No	135 (93.1)	10 (6.9)		104 (96.3)	4 (3.7)	
Smoking status						
Yes	1 (50.0)	1 (50.0)	0.144	0 (0.0)	1 (100.0)	**0.045**
No	136 (93.1)	10 (6.9)		105 (96.3)	4 (3.7)	
Duration LHIV in years						
< 9	65 (94.2)	4 (5.8)	0.349	54 (98.2)	1 (1.8)	0.182
≥ 9	72 (91.1)	7 (8.9)		51 (92.7)	4 (7.3)	
Employment						
Self employed	67 (93.1)	5 (6.9)	0.391	51 (96.2)	2 (3.8)	0.869
Employed	32 (91.4)	3 (8.6)		24 (92.3)	2 (7.7)	
Unemployed	33 (97.1)	1 (2.9)		23 (95.8)	1 (4.2)	
Retired	4 (80.0)	1 (20.0)		5 (100.0)	0 (0.0)	
Education						
Primary	15 (88.2)	2 (11.8)	0.53	9 (90.0)	1 (10.0)	0.38
Secondary	62 (92.5)	5 (7.5)		49 (94.2)	3 (5.8)	
Tertiary	54 (94.7)	3 (5.3)		41 (97.6)	1 (2.4)	

Table 4.5: Association between viral load suppression and medical characteristics

	VL suppression at 6 months (n=148)			VL suppression at 12 months (n=110)		
Variable	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**
Chronic Condition						
Present	65 (95.6)	3 (4.4)	0.165	48 (96.0)	2 (4.0)	0.586
Absent	72 (90.0)	8 (10.0)		57 (95.0)	3 (5.0)	
ART Status on DTG Initiation Treatment						
Sensitive	126 (92.0)	11 (8.0)	0.414	97 (95.1)	5 (4.9)	0.681
Treatment naïve	11 (100.0)	0 (0.0)		8 (100.0)	0 (0.0)	
Duration on DTG based regimen in months						
< 20	63 (92.6)	5 (7.4)	0.973	32 (94.1)	2 (5.9)	0.493
≥ 20	74 (92.5)	6 (7.5)		73 (96.1)	3 (3.9)	
DTG-based regimen of participants						
TDF/3TC/DTG	133 (93.7)	9 (6.3)	**0.017**	104 (95.4)	5 (4.6)	0.955
AZT/3TC/DTG	2 (100.0)	0 (0.0)				
ABC/3TC/DTG	2 (100.0)	0 (0.0)				
TDF/3TC/DTG (2nd Line)	0 (0.0)	2 (100.0)		1 (100.0)	0 (0.0)	

4.6 Association between opportunistic infections and sociodemographic characteristics

The association between opportunistic infections occurring among participants and sociodemographic characteristics was assessed before and after initiation of a dolutegravir based ART regimen. Pearson's and Fischer's exact Chi-square tests were used for the assessment and the findings are presented in Table 4.6. Looking at the prevalence of opportunistic infections before initiation of a dolutegravir based ART regime, sex was found to have a statistically significant association (p = 0.016). None of the variables showed statistically significant associations after initiation of a dolutegravir based ART regimen.

Table 4.6: Association between opportunistic infections and sociodemographic characteristics

	OIs before initiation of DTG (n=154)			OIs after initiation of DTG (n=154)		
Variable	**Present; n (%)**	**Absent; n (%)**	**p value**	**Present; n (%)**	**Absent; n (%)**	**p value**
Age in years						
< 45	17 (23.9)	54 (76.1)	0.606	4 (5.6)	67 (94.4)	0.269
≥ 45	17 (20.5)	66 (79.5)		8 (9.6)	75 (90.4)	
Sex						
Male	7 (11.9)	52 (88.1)	**0.016**	6 (10.2)	53 (89.8)	0.386
Female	27 (28.4)	68 (71.6)		6 (6.3)	89 (93.7)	
Marital status						
Single	10 (27.8)	26 (76.2)	0.074	2 (5.6)	34 (94.4)	0.632
Married	13 (17.3)	62 (82.7)		5 (6.7)	70 (93.3)	
Widowed	2 (10.0)	18 (90.0)		3 (15.0)	17 (85.0)	
Separated	8 (40.0)	12 (60.0)		2 (10.0)	18 (90.0)	
Divorced	1 (50.0)	1 (50.0)		0 (0.0)	2 (100.0)	
Alcohol use						
Yes	0 (0.0)	3 (100.0)	0.47	1 (33.3)	2 (66.7)	0.217
No	34 (22.5)	117 (77.5)		11 (7.3)	140 (92.7)	
Smoking status						
Yes	0 (0.0)	2 (100.0)	0.606	0 (0.0)	2 (100.0)	0.85
No	34 (22.4)	118 (77.6)		12 (7.9)	140 (92.1)	
Duration LHIV in years						
< 9	14 (19.4)	58 (80.6)	0.46	6 (8.3)	66 (91.7)	0.814
≥ 9	20 (24.4)	62 (75.6)		6 (7.3)	76 (92.7)	
Employment						
Self employed	21 (28.0)	54 (72.0)	0.395	8 (10.7)	67 (89.3)	0.263
Employed	6 (16.7)	30 (83.3)		1 (2.8)	35 (97.2)	
Unemployed	7 (19.4)	29 (80.6)		2 (5.6)	34 (94.4)	
Retired	0 (0.0)	5 (100.0)		1 (20.0)	4 (80.0)	
Education						
Primary	4 (22.2)	14 (77.8)	0.62	2 (11.1)	16 (88.9)	0.256
Secondary	18 (26.1)	51 (73.9)		6 (8.7)	63 (91.3)	
Tertiary	11 (18.3)	49 (81.7)		2 (3.3)	58 (96.7)	

4.7 Association between opportunistic infections and clinical characteristics

The association between opportunistic infections and medical characteristics of the participants was also assessed before and after initiation of a dolutegravir based ART regimen and the findings are summarised in Table 4.7. None of the variables showed statistically significant associations before initiation of a DTG based ART regimen.

However, after initiation to a DTG based ART regimen, the ART status of the participant i.e., whether treatment-experienced or treatment naïve, showed a statistically significant association (p = 0.042).

Table 4.7: Association between opportunistic infections and medical characteristics

	OIs before DTG			OIs after DTG		
Variable	**Present; n (%)**	**Absent; n (%)**	**p value**	**Present; n (%)**	**Absent; n (%)**	**p value**
Chronic Condition						
Present	17 (23.6)	55 (76.4)	0.667	4 (5.6)	68 (94.4)	0.254
Absent	17 (20.7)	65 (79.3)		8 (9.8)	74 (90.2)	
ART Status on DTG Initiation						
Treatment Experienced	33 (23.1)	110 (76.9)	0.254	9 (6.3)	134 (93.7)	**0.042**
Treatment naïve	1 (9.1)	10 (90.9)		3 (27.3)	8 (72.7)	
Duration on DTG based regimen in months						
< 20				5 (6.9)	68 (93.2)	0.679
≥ 20				7 (8.6)	74 (91.4)	
DTG-based regimen of participants						
TDF/3TC/DTG				11 (7.4)	137 (92.6)	0.391
AZT/3TC/DTG				0 (0.0)	2 (100.0)	
ABC/3TC/DTG				0 (0.0)	2 (100.0)	
TDF/3TC/DTG (2nd Line)				1 (50.0)	1 (50.0)	

4.8 Association between adverse drug reactions and sociodemographic characteristics

Sex showed a statistically significant association before initiation of a DTG based ART regimen (p = 0.044). After initiation of a DTG based ART regimen, none of the sociodemographic characteristics showed a statistically significant association with adverse drug reactions (Table 4.8).

Table 4.8: Association between adverse drug reactions and sociodemographic characteristics

	ADR before DTG			ADR after DTG		
Variable	**Present; n (%)**	**Absent; n (%)**	**p value**	**Present; n (%)**	**Absent; n (%)**	**p value**
Age in years						
< 45	10 (14.1)	61 (85.9)	0.084	15 (21.1)	56 (78.9)	0.381
≥ 45	21 (25.3)	62 (74.7)		13 (15.7)	70 (84.3)	
Sex						
Male	7 (11.9)	52 (88.1)	**0.044**	8 (13.6)	51 (86.4)	0.241
Female	24 (25.3)	71 (74.7)		20 (21.1)	75 (78.9)	
Marital status						
Single	5 (13.9)	31 (86.1)	0.117	6 (16.7)	30 (83.3)	0.607
Married	12 (16.0)	63 (84.0)		13 (17.3)	62 (82.7)	
Widowed	6 (30.0)	14 (70.0)		5 (25.0)	15 (75.0)	
Separated	7 (35.0)	13 (65.0)		3 (15.0)	17 (85.0)	
Divorced	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
Alcohol use						
Yes	1 (33.3)	2 (66.7)	0.493	1 (33.3)	2 (66.7)	0.455
No	30 (19.9)	121 (80.1)		27 (17.9)	124 (82.1)	
Smoking status						
Yes	1 (50.0)	1 (50.0)	0.363	1 (50.0)	1 (50.0)	0.332
No	30 (19.7)	122 (80.3)		27 (17.8)	125 (82.2)	
Duration LHIV in years						
< 9	15 (20.8)	57 (79.2)	0.838	12 (16.7)	60 (83.3)	0.648
≥ 9	16 (19.5)	66 (80.5)		16 (19.5)	66 (80.5)	
Employment						
Self employed	18 (24.0)	57 (76.0)	0.27	9 (12.0)	66 (88.0)	0.162
Employed	9 (25.0)	27 (75.0)		8 (22.2)	22 (77.8)	
Unemployed	4 (11.1)	32 (89.9)		10 (27.8)	26 (72.2)	
Retired	0 (0.0)	5 (100.0)		1 (20.0)	4 (80.0)	
Education						
Primary	6 (33.3)	12 (66.7)	0.161	5 (27.8)	13 (72.2)	0.353
Secondary	10 (14.5)	59 (85.5)		10 (14.5)	59 (85.5)	
Tertiary	14 (23.3)	46 (76.7)		13 (21.7)	47 (78.3)	

4.9 Association between adverse drug reactions and clinical characteristics

The association between adverse drug reactions and various clinical characteristics of the participants before and after initiation of a DTG based ART regimen was assessed and the findings are presented in Table 4.9. Before initiation, none of the variables showed a statistically significant association. After initiation of a DTG based ART regimen, the DTG regimen of the participant had a statistically significant association (p = 0.048).

Table 4.9: Association between adverse drug reactions and medical characteristics

	ADRs before DTG			ADRs after DTG		
Variable	**Present; n (%)**	**Absent; n (%)**	**p value**	**Present; n (%)**	**Absent; n (%)**	**p value**
Chronic Condition						
Present	14 (19.4)	58 (80.6)	0.842	11 (15.3)	61 (84.7)	0.381
Absent	17 (20.7)	65 (79.3)		17 (20.7)	65 (79.3)	
ART Status on DTG Initiation						
Treatment Sensitive	31 (21.7)	112 (78.3)	0.077	25 (17.5)	118 (82.5)	0.32
Treatment naïve	0 (0.0)	11 (100.0)		3 (27.3)	8 (72.7)	
Duration on DTG based regimen in months						
< 20				16 (21.9)	57 (78.1)	0.254
≥ 20				12 (14.8)	69 (85.2)	
DTG-based regimen of participants						
TDF/3TC/DTG				25 (16.9)	123 (83.1)	**0.048**
AZT/3TC/DTG				0 (0.0)	2 (100.0)	
ABC/3TC/DTG				2 (100.0)	0 (0.0)	
TDF/3TC/DTG (2nd Line)				1 (50.0)	1 (50.0)	

4.10 Independent predictors of viral load suppression

Viral load suppression was considered a categorical variable, suppressed or not suppressed. Logistic regression analysis was used to determine predictors of viral load suppression at 6 months and 12 months on a DTG based ART regimen. Looking at viral load suppression at 6 months, marital status was statistically significant on bivariable analysis (COR = 9.682; 95% CI 1.194, 78.511; p = 0.034). Marital status was categorized into two broad groups, married (reference group) and not married (single, widowed, divorced, or separated). The findings on bivariable analysis implied that married individuals were 9.682 times more likely to be virally suppressed at 6 months on a dolutegravir based ART regimen compared to non-married individuals. The statistical significance of marital status was however lost on multivariable analysis.

The DTG based regimen of the participant, i.e., whether the participant was on TDF/3TC/DTG (reference group) or on any other DTG based regimen, was a statistically significant predictor (COR = 7.389; 95% CI 1.189, 45.909; P = 0.032 and AOR = 21.607; 95% CI 1.118, 417.591; P = 0.042). However, based on the relatively wide 95% confidence interval, the precision of this finding was considered low. A participant on TDF/3TC/DTG regimen was 96% more likely to be virally suppressed at 6 months compared to a participant on any other DTG based regimen. The most parsimonious model from forward stepwise model building was a model containing marital status, DTG based regimen, and alcohol use as the independent predictor variables. The findings of the analysis of predictors of viral load suppression at 6 months are presented in Table 4.10.

Logistic regression analysis of viral load suppression at 12 months on a DTG based ART regimen with various predictor variables did not show any statistically significant independent predictors. Alcohol use (reference group – use of alcohol) had a significant effect on bivariable analysis (COR = 0.038; 95% CI 0.002,0.732; p = 0.030). The findings implied that alcohol use was a harmful predictor variable, with individuals who use alcohol having a 4% chance of being virally suppressed at 12 months on a dolutegravir based ART regimen compared to an individual who did not use alcohol. However, the statistical significance of alcohol use was lost on multivariable analysis. The findings of the logistic regression analysis of predictor variables for viral load suppression at 12 months are summarised in Table 4.11.

Table 4.10: Independent predictors of viral load suppression at 6 months

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	1.006 (0.949, 1.066)	0.852	1.025 (0.941, 1.116)	0.571
Sex	0.734 (0.213, 2.527)	0.624	4.667 (0.392, 55.561)	0.223
Marital status	9.682 (1.194, 78.511)	**0.034**	6.234 (0.670, 58.028)	0.108
Alcohol use	0.148 (0.012, 1.778)	0.132	0.019 (<0.001, 1.349)	0.068
Smoking status	0.074 (0.004, 1.265)	0.072	-	
Duration LHIV in years	0.903 (0.785, 1.038)	0.150	0.882 (0.733, 1.063)	0.187
Employment	0.669 (0.136, 3.296)	0.621	0.476 (0.069, 3.287)	0.451
Education	1.933 (0.375, 9.968)	0.431	0.810 (0.044, 15.011)	0.888
Chronic condition	2.407 (0.613, 9.461)	0.208	3.834 (0.539, 27.292)	0.180
Duration on DTG based regimen in months	0.987 (0.900, 1.082)	0.775	0.913 (0.787, 1.060)	0.232
DTG based regimen of participant	7.389 (1.189, 45.909)	**0.032**	21.607 (1.118, 417.591)	**0.042**

Table 4.11: Independent predictors of viral load suppression at 12 months

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	1.023 (0.937, 1.117)	0.606	1.081 (0.934, 1.251)	0.296
Sex	1.216 (0.195, 7.578)	0.834	2.013 (0.155, 26.133)	0.593
Marital status	1.819 (0.292, 11.345)	0.522	0.644 (0.052, 8.033)	0.733
Alcohol use	0.038 (0.002, 0.732)	**0.030**	-	
Duration LHIV in years	0.921 (0.751, 1.130)	0.431	0.765 (0.535, 1.095)	0.144
Employment	0.670 (0.072, 6.252)	0.725	0.182 (0.006, 5.426)	0.325
Education	2.500 (0.252, 24.834)	0.434	24.116 (0.528, 1101.636)	0.103
Chronic condition	1.263 (0.203, 7.874)	0.802	0.640 (0.052, 7.812)	0.727
Duration on DTG based regimen in months	1.048 (0.885, 1.240)	0.588	1.077 (0.835, 1.388)	0.568

4.11 Independent predictors of opportunistic infections

Opportunistic infection was a categorical variable, present or absent. Logistic regression analysis was carried out to determine independent predictors of opportunistic infections before and after initiation of a DTG based ART regimen. Analysis of the predictor variables before DTG initiation revealed sex (reference group – male) to be a statistically significant predictor of opportunistic infections (COR = 0.339; 95% CI 0.137, 0839; p = 0.019 and AOR = 0.354; 95% CI 0.133, 0.941; p = 0.037). Male sex was a protective predictor variable as male participants had a 75% lower risk of developing an opportunistic infection before initiation of a DTG based ART regimen compared to female participants. A summary of the findings of logistic regression analysis before DTG initiation is presented in Table 4.12.

Table 4.12: Independent predictors of opportunistic infections before DTG initiation

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	0.978 (0.943, 1.014)	0.222	0.967 (0.927, 1.001)	0.126
Sex	0.339 (0.137, 0.839)	**0.019**	0.354 (0.133, 0.941)	**0.037**
Marital status	0.569 (0.261, 1.241)	0.156	0.558 (0.238, 1.311)	0.181
Duration LHIV in years	1.031 (0.949, 1.120)	0.474	1.037 (0.938, 1.146)	0.478
Employment	1.561 (0.621, 3.925)	0.344	2.315 (0.840, 6.380)	0.105
Education	1.015 (0.310, 3.322)	0.980	0.852 (0.234, 3.106)	0.808
Chronic condition	1.182 (0.552, 2.533)	0.667	1.062 (0.447, 2.526)	0.891
ART status on DTG initiation	3.000 (0.370, 24.306)	0.303	1.833 (0.179, 18.795)	0.610

Looking at the predictor variables of opportunistic infections after initiation of a DTG based ART regimen, the ART status of the patient i.e., whether treatment-experienced (reference group) or treatment naïve was statistically significant (COR = 0.179; 95% CI 0.040, 0.794); p = 0.024 and the AOR = 0.066; 95% CI 0.005, 0.886; p = 0.040). Being treatment-experienced was a protective predictor variable since a treatment-experienced participant had an 85% lower risk of having an opportunistic infection compared to a treatment naïve individual. The findings of logistic regression analysis of opportunistic infections after DTG initiation are presented in Table 4.13.

Table 4.13: Independent predictors of opportunistic infections after DTG initiation

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	1,019 (0.962, 1.079)	0.524	1.021 (0.958, 1.088)	0.527
Sex	1.679 (0.515, 5.474)	0.390	1.091 (0.193, 6.170)	0.922
Marital status	0.724 (0.219, 2.391)	0.597	0.395 (0.086, 1.810)	0.232
Alcohol use	6.364 (0.534, 75.813)	0.143	-	
Duration LHIV in years	1.017 (0.894, 1.156)	0.798	1.116 (0.932, 1.335)	0.232
Employment	1.118 (0.287, 4.349)	0.873	1.111 (0.238, 5.177)	0.893
Education	0.529 (0.103, 2.713)	0.445	0.303 (0.046, 1.990)	0.214
Chronic condition	0.544 (0.157, 1.889)	0.338	0.498 (0.104, 2.379)	0.382
ART status on DTG initiation	0.179 (0.040, 0.794)	**0.024**	0.066 (0.005, 0.886)	**0.040**
Duration on DTG based regimen in months	1.024 (0.939, 1.117)	0.588	1.054 (0.934, 1.190)	0.391
DTG based regimen of participant	0.401 (0.043, 3.745)	0.423	0.395 (0.021, 7.344)	0.533

4.12 Independent predictors of adverse drug reactions

Adverse drug reaction was a categorical variable, present or absent. Logistic regression analysis was carried out to assess independent predictors of adverse drug reactions among participants before and after initiation of a DTG based ART regimen. The analysis of predictor variables before DTG initiation showed that sex (reference group – male) was a statistically significant predictor variable (COR = 0.398; 95% CI 0.160, 0.994; p = 0.049 and the AOR = 0.318; 95% CI 0.107, 0.942; p = 0.039). Male sex was a protective predictor variable since male participants had a 72% lower risk of experiencing an adverse drug reaction before DTG initiation compared to female participants.

The analysis also showed that employment was a statistically significant predictor of adverse drug reactions on multivariable analysis (COR = 2.973; 95% CI 0.971, 9.104; p = 0.056) and the AOR = 5.386; 95% CI 1.496, 19.392; p = 0.010). Employment was categorized into two broad groups; employed (i.e., formally employed and self-employed) which was the reference group, and non-employed (i.e., unemployed and retired). Individuals who are employed were 84% more likely to have an adverse drug reaction before DTG initiation compared to unemployed individuals. The findings of logistic regression analysis for adverse drug reactions before DTG initiation are presented in Table 4.14.

Table 4.14: Independent predictors of adverse drug reactions before DTG initiation

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	1.026 (0.987, 1.066)	0.196	1.047 (0.991, 1.106)	0.104
Sex	0.398 (0.160, 0.994)	**0.049**	0.318 (0.107, 0.942)	**0.039**
Marital status	0.591 (0.264, 1.323)	0.201	0.572 (0.226, 1.451)	0.240
Alcohol use	2.017 (0.177, 22.988)	0.572	-	
Smoking status	4.067 (0.247, 66.904)	0.326	-	
Duration LHIV in years	0.985 (0.904, 1.074)	0.732	0.937 (0.836, 1.050)	0.263
Employment	2.973 (0.971, 9.104)	0.056	5.386 (1.496, 19.392)	**0.010**
Education	0.457 (0.156, 1.340)	0.154	0.358 (0.100, 1.278)	0.114
Chronic condition	0.923 (0.418, 2.036	0.842	0.590 (0.233, 1.493)	0.265

After initiation of a Dolutegravir based ART regimen, sex (reference group – male) was found to be a statistically significant predictor variable of adverse drug reactions on multivariable analysis (COR = 0.588; 95% CI 0.241, 1.438; p = 0.245 and the AOR = 0.222; 95% CI 0.061, 0.814; p = 0.023). Male sex was a protective predictor variable with male participants having an 82% lower risk of having an adverse drug reaction compared to female participants after DTG initiation.

The DTG based regimen of the participant (reference group - TDF/3TC/DTG regimen) was also found to be a statistically significant predictor of adverse drug reactions after DTG initiation (COR = 0.203; 95% CI 0.039, 1.066; p = 0.059 and the AOR = 0.090; 95% CI 0.012, 0.690; p = 0.021). Participants on TDF/3TC/DTG regimen had a 90% lower risk of experiencing an ADR after DTG initiation compared to participants initiated on any other DTG based ART regimen. The findings of logistic regression analysis for adverse drug reactions after DTG initiation are summarised in Table 4.15.

Table 4.15: Independent predictors of adverse drug reactions after DTG initiation

	Bivariable analysis		Multivariable analysis	
Variable	**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
Age in years	1.026 (0.987, 1.066)	0.196	0.984 (0.941, 1.030)	0.496
Sex	0.588 (0.241, 1.438)	0.245	0.222 (0.061, 0.814)	**0.023**
Marital status	0.881 (0.387, 2.002)	0.762	1.249 (0.498, 3.134)	0.635
Alcohol use	2.296 (0.201, 26.248)	0.504	8.741 (0.395, 193.323)	0.170
Smoking status	4.630 (0.281, 76.349)	0.284	-	
Duration LHIV in years	1.013 (0.927, 1.108)	0.769	1.068 (0.953, 1.198)	0.259
Employment	0.493 (0.208, 1.169)	0.108	0.563 (0.217, 1.464)	0.239
Education	0.564 (0.183, 1.739)	0.319	0.384 (0.104, 1.410)	0.149
Chronic condition	0.689 (0.299, 1.589)	0.383	0.505 (0.184, 1.383)	0.184
ART status on DTG initiation	0.565 (0.140, 2.280)	0.423	0.268 (0.039, 1.832)	0.180
Duration on DTG based regimen in months	0.988 (0.926, 1.053)	0.708	1.092 (0.999, 1.194)	0.054
DTG based regimen of participant	0.203 (0.039, 1.066)	0.059	0.090 (0.012, 0.690)	**0.021**

CHAPTER FIVE: DISCUSSION, CONCLUSION. AND RECOMMENDATIONS

5.1 Introduction

This chapter provides an in-depth review of key findings obtained in this study. It comprises the discussion of key findings, summary, conclusion, and recommendations.

5.2 Discussion

The clinical effectiveness of dolutegravir based ART regimens was found to be high based on remarkable viral load suppression, low prevalence of opportunistic infections, and good tolerability among our participants. A total of 154 adult HIV-positive participants attending the clinic at the Kenyatta National Hospital were included in this study. A majority of the participants in this study were treatment-experienced, with the regimen comprising TDF/3TC/DTG being the most common on initiation or transition to a dolutegravir based ART regimen. This finding is in line with recommendations by NASCOP on preferred first-line dolutegravir based regimens among adults as well as recommendations by WHO on preferred first-line ART regimens among adults (6,7).

The prevalence of viral load suppression among the participants in this study was 92.6% at 6 months and 95.5% at 12 months on a dolutegravir based ART regimen. These findings are comparable to findings in a study by Mehari *et al*. that reported a proportion of 92% virological suppression among patients on TDF/3TC/DTG for 12 months (47). Similar findings were also reported in a study in Uganda by Nabitaka *et al*. that found 94% of the study's participants were virally suppressed at 6 months (48). The viral load suppression rates were above the national estimates by NASCOP reported in the World AIDS day report 2020 that placed overall viral suppression at 73.4% and viral suppression among patients on dolutegravir based ART regimens at about 90% (8). This finding correlates with those reported in the Kenya Population-based HIV Impact Assessment (KENPHIA) 2018 preliminary report (4). The UNAIDS is adopting new targets through 2025 that proposes a target of 95-95-95 in the management of the HIV pandemic (49). The findings of this study indicate that indeed dolutegravir based ART regimens can be a key factor in achieving the UNAIDS targets.

Many factors, sociodemographic or clinical, can have an impact on the viral suppression of a patient on HAART. In this study, there was a significant difference in viral load suppression at 6 months among various categories of marital status. However, multivariable logistic regression analysis did not demonstrate that marital status was an independent

predictor of viral load suppression. While marital status can have a significant influence on other factors that influence viral load suppression such as disclosure, adherence, a stable sexual partner, and social support system (50–52), many other studies agree with our findings that marital status is not an independent predictor (53–55). However, a study by Meshesha *et al*. found that the divorced/separated individuals had threefold higher odds of virological failure (AOR=3.03, 95% CI 1.356 to 6.778) than married individuals (56).

In this study, there was a significant difference in viral load suppression at 6 months among participants on different dolutegravir based ART regimens. Multivariable logistic regression analysis with TLD as the reference group showed that the DTG based ART regimen was an independent predictor of VL suppression. However, due to the low number of participants on regimens other than first-line TLD (AZT/3TC/DTG - 2, 1.3%, ABC/3TC/DTG - 2, 1.3%, and second-line TLD - 2, 1.3%), the precision of these findings may be low. Previous studies have demonstrated no significant difference in VL suppression when combining DTG with ABC/3TC compared to a combination with TDF/3TC (16,32,57).

Participants on second-line TLD are individuals who have been switched to TLD from a previous PI/r based second-line regimen. Their odds of having viral load suppression may be different from those on first-line TLD as implied by our study. However, a study by Gatell *et al*. found that switching from a PI/r based ART regimen to a DTG based regimen did not result in virological failure (58). A large clinical trial (NCT04229290) by Ombajo *et al*. is currently ongoing that is assessing "the non-inferiority of switching to a DTG containing regimen relative to maintaining a PI/r containing second-line regimen in virologically suppressed, INSTI-naive HIV-1 positive adults (≥ 18 years old) as determined by having HIV-1 RNA ≥ 50 copies/ml at week 48" (59). Perhaps the findings from this study may ascertain the revelation of the present research.

The clinical effectiveness of any ART regimen correlates with its ability to prevent the emergence of opportunistic infections which indicates a well-preserved immune system. In this study, there was a general reduction in the number and range of opportunistic infections among participants comparing before and after initiation of a dolutegravir based ART regimen. This indicates that the dolutegravir based ART regimen was effective at preventing deterioration of the immune system and thus improving the individual's QoL. The most prevalent opportunistic infection before and after initiation of a DTG based ART regimen was bacterial pneumonia. This is comparable to findings in several other studies that also

found bacterial pneumonia to be among the most common opportunistic infections affecting PLHIV (60,61).

In this study, there was a significant difference in the prevalence of opportunistic infections with gender before initiation of a DTG based ART regimen but lost after initiation. Male sex was also independently associated with lower odds of having an opportunistic infection before DTG initiation. The fact that gender ceases to be a significant factor in relation to the prevalence of opportunistic infections after initiation of a DTG based ART regimen further underscores the effectiveness of dolutegravir. These findings are comparable to those of a study done in Uganda by Rubaihayo *et al*. which found that OIs such as bacterial pneumonia, infectious diarrhea, helminths, candidiasis, and genital ulcer disease occurs more frequently in women ($p < 0.05$) before and after ART (62). Women may be more predisposed to OIs due to biological and hormonal differences as well as factors such as GBV, early/forced marriage, lack of access to information, and a reduced negotiating power or economic autonomy (63). The high prevalence of opportunistic infections among women compared to men can also be attributed to higher survival rates among women than in men which results in an overall higher prevalence of OIs (64).

This study demonstrated that the ART status of the patient including whether treatment-experienced or treatment naïve was a statistically significant predictor of opportunistic infections. Prompt initiation of HAART is meant to prevent severe destruction of the immune system by controlling the rate of viral replication as early as possible, thus an individual who is not on HAART will be more likely to have OIs. These findings are comparable to findings in the systematic review by Low *et al*. which concluded that ART reduced the risk for most OIs especially in the first year of treatment (33).

A major downside of highly potent medications is the likelihood of drug-related toxicities leading to a deterioration in the QoL of the patient. In this study, the general prevalence of ADRs was comparable before and after DTG initiation. However, after DTG initiation headache, weight gain, and insomnia were more prevalent. Weight gain correlates with the high prevalence of obesity reported in this study population. These findings are similar to findings of a study by Hoffman *et al*. that found the most prevalent DTG associated ADRs were insomnia and sleep disorders, as well as "anxiety, depression, dizziness, headache, paraesthesia, muscle-skeletal pain, reduced concentration, and slow thinking" (65). In this study, we found that patients on DTG based ART regimens had reduced contact time with

clinicians since they were deemed stable based on viral load suppression, and most were on fast-track differentiated care with extended TCAs. However, neuropsychiatric adverse drug reactions are difficult to detect and patients are unlikely to recognize and share such problems freely. These findings point to the need for a higher index of suspicion for neuropsychiatric ADRs among caregivers.

This study demonstrated that male sex was independently associated with lower odds of developing adverse drug reactions before and after initiation of a dolutegravir based ART regimen. These findings are similar to findings in a study by Hoffman *et al*. that found neuropsychiatric adverse events resulting in DTG switch occurred 2.64 times more frequently in women (P = 0.012) (44). The reason for this disparity may be because women have "a lower lean body mass, a reduced hepatic clearance, differences in the activity of cytochrome P450 enzymes and metabolize drugs at different rates compared with men", as well as hormonal and immunological differences (66).

The type of DTG based regimen showed statistical significance as a predictor of ADRs on multivariable logistic regression analysis, with regimens other than TLD having higher odds. However, the small number of participants on regimens other than TLD prevents any meaningful conclusions. Nonetheless, in the study by Boer *et al*. one of the conclusions was that DTG was switched more frequently due to ADRs if the regimen contained ABC (42). In our study, none of the participants recorded any instances of switch of dolutegravir due to ADRs or any other reason, and this may be a testament to the fact that DTG based ART regimens are well tolerated.

This study highlighted the extent of viral load suppression using DTG based ART regimens in the Kenyan population and brought out the most prevalent DTG associated ADRs that patients experience. In this study, the participants were drawn using simple random sampling thus the findings can be generalized to the wider study population. However, the small number of participants who were on DTG based ART regimens other than TLD was a weakness. Similarly, there was a very small number of participants who were smokers or used alcohol which limited our ability to associate these two predictors with outcomes of interest. Given the relative time constraints, the use of a cross-sectional study design and ample access to all relevant patient records granted to us at the KNH CCC enabled us to follow up the patients through the study period to obtain the required information. However, the use of patient records to obtain the requisite data exposed the study to information bias.

Information bias in this study could have been brought about by bias by the clinicians in recording outcomes inpatient records, or by the patients in providing information to the clinicians.

5.3 Conclusion

Dolutegravir based ART regimens are clinically effective and well-tolerated treatments achieving more than 90% viral load suppression rate at 6 and 12 months with headache, weight gain, and insomnia being the most common ADRs experienced.

5.4 Recommendations

5.4.1 Recommendations for policy and practice

1. Clinicians are encouraged to continue prescribing dolutegravir but with enhanced screening and documentation of ADRs, especially neuropsychiatric ADRs such as depression and anxiety, to ensure prompt diagnosis and linkage to care.
2. Institute well-equipped NCD clinics with provision for treatment and follow-up alongside provision of HAART within the CCCs instead of simply screening and sending clients to NCD clinics outside the CCC.

5.4.2 Recommendations for future research

1. A prospective cohort study with a large number of participants on various dolutegravir based regimens should be done to compare their safety, clinical appropriateness, drug interactions as well as resistance patterns if any.

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APPENDICES

Appendix 1: Eligibility screening form

KNH Comprehensive Care Clinic

Unique Identifier:

CRITERIA	REMARK	
HIV infected adults aged 18 years and above attending the clinic at KNH CCC	Yes ☐	No ☐
Have been on a Dolutegravir based ART regimen for at least 6 months	Yes ☐	No ☐
Have documented viral load readings at 6 and 12 months within the study period	Yes ☐	No ☐
Give consent to participate in the study	Yes ☐	No ☐
Not Declared Loss to Follow-up at KNH CCC at any point within the study period	Yes ☐	No ☐
Not Taking antituberculosis medication at any point within the study period	Yes ☐	No ☐
Have documented baseline viral load reading during switch to DTG-based ART regimen.	Yes ☐	No ☐

If all YES, proceed to data abstraction.

Appendix 2: Data abstraction tool

STUDY TITLE: Assessment of the clinical effectiveness of dolutegravir-based antiretroviral therapy among adults living with HIV at the Kenyatta National Hospital

Serial number: _____.

Date: ……. /……../……..

Unique Identifier number: _____ .

A. Socio-demographic characteristics

1. Gender: (1) Male ☐ (2) Female ☐

2. Age:_____ years

3.Marital status? (1) single ☐ (2) married ☐ (3) widowed ☐

(4) separated ☐ (5) divorced ☐

4. Level of education**?** (1) informal ☐ (2) primary ☐

(3) secondary ☐ (4) tertiary ☐

5. Employment status: (1) self-employed ☐ (2) employed ☐

(3) unemployed ☐ (4) retired ☐

6. Consumption of alcohol? (1) yes ☐ (2) no ☐

7. Smoking cigarettes? (1) yes ☐ (2) no ☐

8. Denomination? (1) atheist ☐ (2) Christian ☐ (3) Hindu ☐

(4) Muslim ☐ (5) Traditional ☐ (6) Other ☐ _____ .

9. Area of residence? (1) Urban ☐ (2) Rural ☐

B. Clinical Profile

10. Duration living with HIV? _____years.

11. Other chronic conditions patient is living with?

(1) Yes ☐ (2) No ☐

12. If yes in (11), please tick the condition(s) below:

(1) Diabetes mellitus ☐ (3) Cancer ☐ (4) Cardiovascular disease ☐

(5) Chronic renal disease ☐ (6) Psychiatric disease ☐ (7) Respiratory disease ☐

(8) Others ☐ specify _____ .

For treatment-naïve patients who initiated on DTG-based art regimen and have been on the regimens for at least 6 months

13. Regimen initiated: (1) AF2E (TDF-3TC-DTG) ☐ (2) AFID (AZT-3TC-DTG) ☐

(3) AF4C (ABC-3TC-DTG) ☐

(4) Other ☐ specify _____.

14. Baseline viral load at initiation: _____copies/ml

15. Date of initiation on regimen ……/…..... /……

For treatment-experienced patients switching to DTG-based art regimen and have been on the regimen for at least 6 months

16. Date of switch to DTG-based regimen: ……/…..... /……

17. DTG-based regimen switched to:

1st line: (1) AF2E (TDF-3TC-DTG) ☐ (2) AFID (AZT-3TC-DTG) ☐

(3) AF4C (ABC-3TC-DTG) ☐

2nd line: (4) ASIC (AZT-3TC-DTG) ☐ (5) AS2B (TDF-3TC-DTG) ☐

(6) AS5C (ABC-3TC-DTG) ☐

3rd line: (7) AT2D (TDF-3TC-DTG-DRV/r) ☐

(8) Other ☐ specify _____.

18. Regimen switched from: _____.

19. Baseline viral load during switch: _____ copies/ml

20. Participant is currently continuing with DTG-based ART regimen? (1) Yes ☐ (2) No ☐

21. If yes in (20), duration on DTG-based ART regimen:_____months

Viral load suppression

22. Most recent viral load test:

Date	Result
	copies/ml

23. Last 3 viral load tests:

Date	Result
	copies/ml
	copies/ml
	copies/ml

Opportunistic infections

24. Documented OIs within the study period

(1) Bacterial Pneumonia (2) Cryptococcal meningitis (3) Herpes zoster

(4) Infective dermatoses (5) Oral candidiasis (6) Pneumocystis pneumonia

(7) Toxoplasmosis (8) Tuberculosis (9) Other, specify

Date	OI (coded)	Treatment	Outcome

Adverse drug reactions to Dolutegravir

25. Documented ADR(s) within the study period

(1) Anxiety (2) Depression (3) Diarrhea (4) Dizziness (5) Gastrointestinal discomfort

(6) Headache (7) Insomnia (8) IRIS (9) Irritability (10) Nausea (11) Painful paresthesia (12) Psychosis (13) Rash (14) Sleep disturbance (15) Other

Date	ADR (coded)	Action taken	Outcome

For participants who have had Dolutegravir switched

26. Date of DTG switch: ……/…..… /……

27. DTG-based regimen being switched:

1st line: (1) AF2E (TDF-3TC-DTG) ☐ (2) AFID (AZT-3TC-DTG) ☐

(3) AF4C (ABC-3TC-DTG) ☐

2nd line: (4) ASIC (AZT-3TC-DTG) ☐ (5) AS2B (TDF-3TC-DTG) ☐

(6) AS5C (ABC-3TC-DTG) ☐

3rd line: (7) AT2D (TDF-3TC-DTG-DRV/r) ☐

(8) Other ☐ specify_____.

28. Duration on regimen being switched: _____months.

29. Baseline viral load during switch from DTG-based art regimen:

_____ copies/ml.

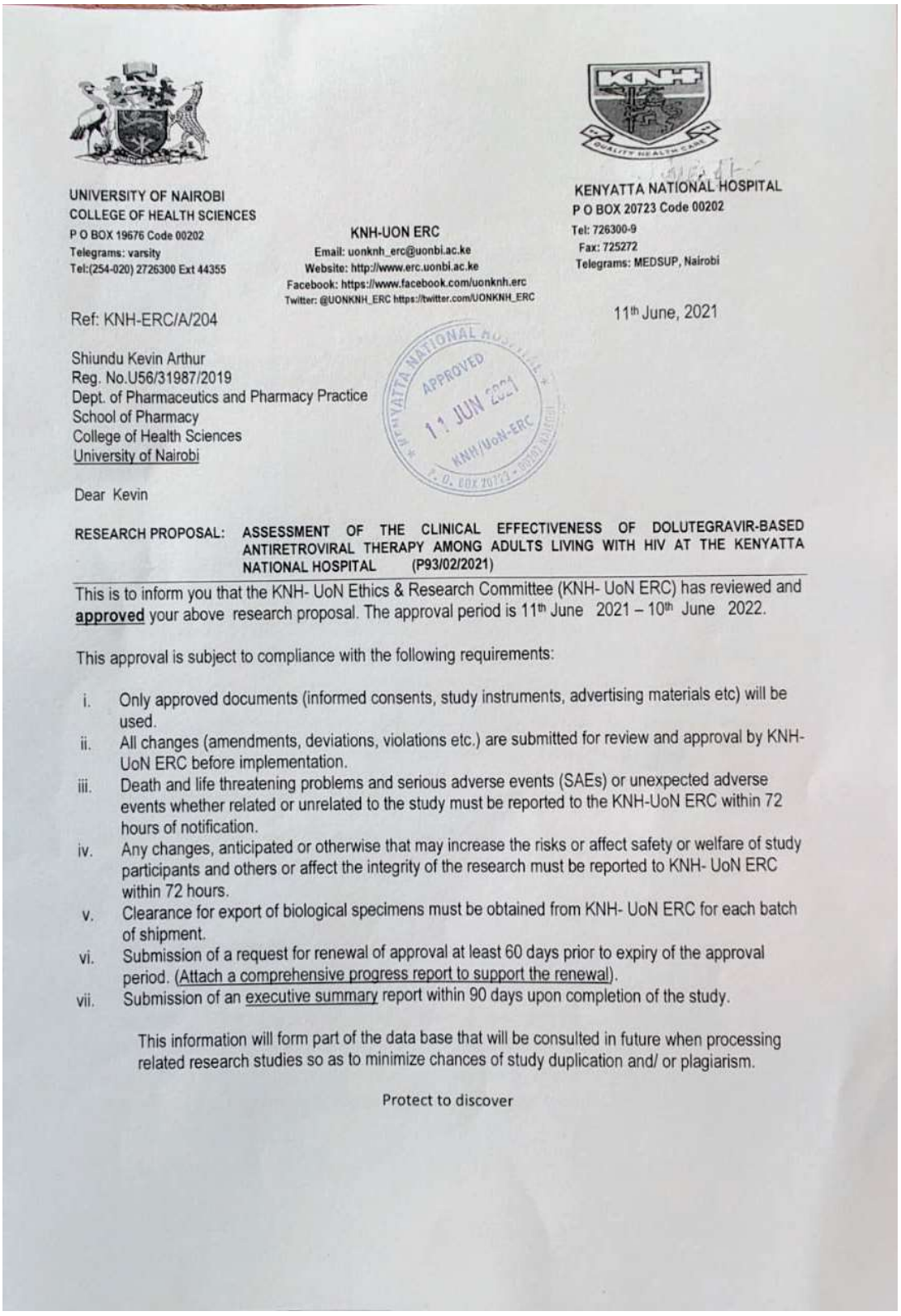
30. Reason(s) for switching: (1) ADR ☐ specify _____.

(2) Drug unavailability ☐ (3) Treatment failure ☐

(4) Other ☐ specify_____.

31. New switch regimen: _____ .

Appendix 3: Copy of KNH/UoN ERC approval letter – page 1



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KNH-UON ERC
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Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

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

Ref: KNH-ERC/A/204

11th June, 2021

APPROVED 11 JUN 2021 KNH/UoN-ERC

Shiundu Kevin Arthur
Reg. No.U56/31987/2019
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Kevin

RESEARCH PROPOSAL: ASSESSMENT OF THE CLINICAL EFFECTIVENESS OF DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY AMONG ADULTS LIVING WITH HIV AT THE KENYATTA NATIONAL HOSPITAL (P93/02/2021)

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 11th June 2021 – 10th June 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. 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.
iv. 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.
v. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
vi. 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).
vii. 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.

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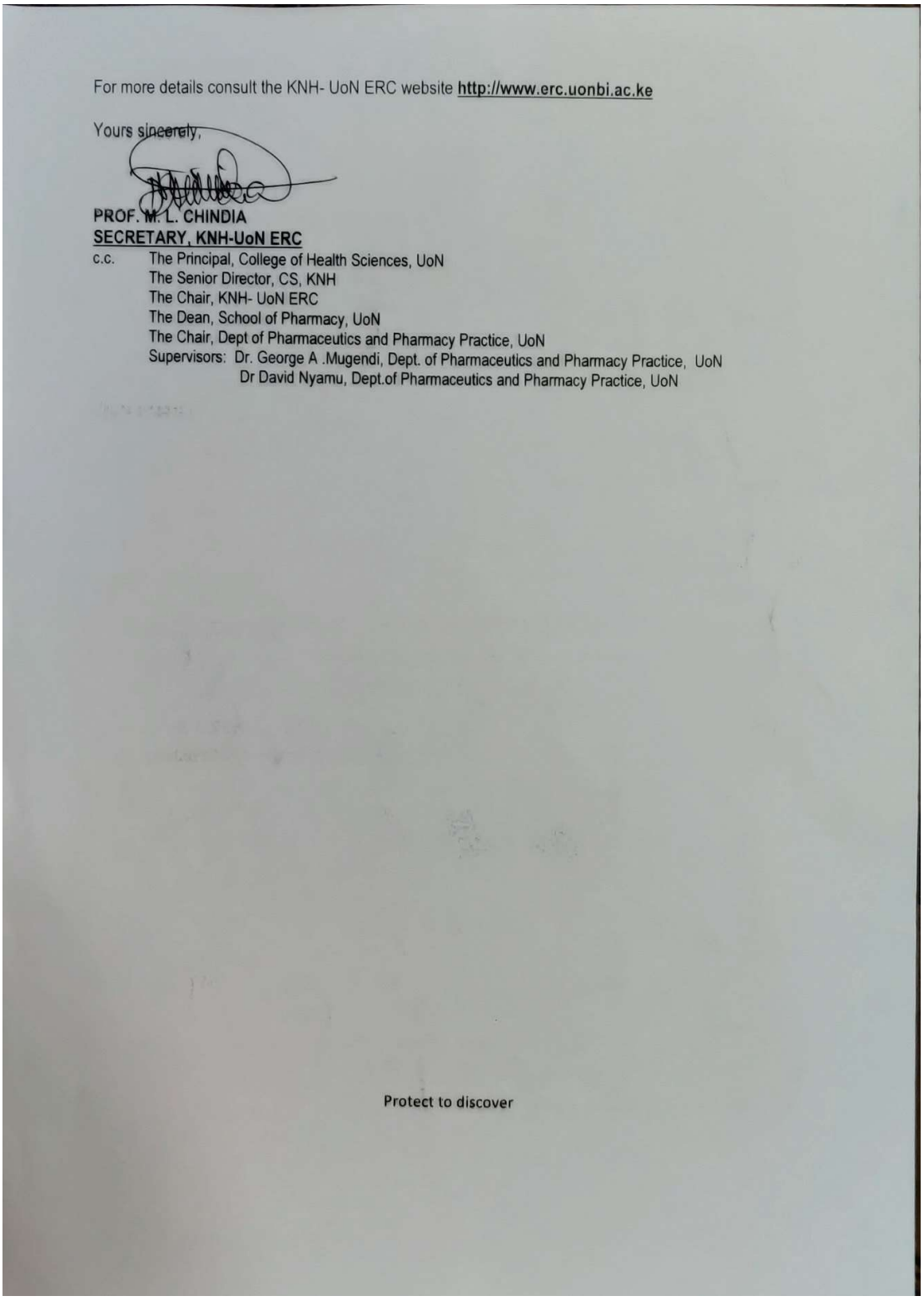
Appendix 3: Copy of KNH/UoN ERC approval letter – page 2



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

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. George A .Mugendi, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Dr David Nyamu, Dept.of Pharmaceutics and Pharmacy Practice, UoN

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Appendix 4: Copy of study registration certificate

KNH/R&P/FORM/01

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

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email:

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   SHIUNDU KEVIN ARTHUR
2. Email address: shiundukevinarthur@gmail.com Tel No. 0704586011
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   ASSESSMENT OF THE CLINICAL EFFECTIVENESS OF DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY AMONG ADULTS LIVING WITH HIV AT THE KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted KNH CCC
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted.
   Name: Dr. Simon Wathome Signature ..... Date 15/06/2021
8. KNH UoN Ethics Research Committee approved study number P93/02/2021
   (Please attach copy of ERC approval)
9. I Shiundu Kevin Arthur commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature..... Date 16/06/2021
10. Study Registration number (Dept/Number/Year) CCC /116/ 202
    (To be completed by Medical Research Department)
11. Research and Program Stamp 15 JUN 2021

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

Version 2: August, 2014

Appendix 5: Similarity index

KABiiri 19/11/2021

To assess the clinical effectiveness of dolutegravir-based ART among adults living with HIV enrolled for care at the Kenyatta National Hospital CCC.

18/11/2021

ORIGINALITY REPORT

14%	11%	8%	2%
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Submitted to University of Pretoria