SAFETY AND EFFECTIVENESS OF NEVIRAPINE AND DOLUTEGRAVIR BASED REGIMENS IN HIV PATIENTS AT THE KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA

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DEDICATION

I dedicate this work to my spouse for her perseverance, encouragement and support during my studies and to my parents for their immense sacrifices throughout my life.

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I wish to thank the Almighty God from whom all good things come and without who I would not have made it this far.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AMPATH	Academic Model Providing Access to Healthcare
ART	Antiretroviral Therapy
ARV	Antiretroviral
CCC	Comprehensive Care Centre
CDC	Centres for Disease Control and Prevention
CYP450	Cytochrome P450
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EFV	Efavirenz
EVG	Elvitegravir
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
KNH	Kenyatta National Hospital
KNH/UoN-ERC	Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
MoH	Ministry of Health

NASCOP	National AIDS and STIs Control Programme
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside and Nucleotide reverse transcriptase inhibitors
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
PIs	Protease inhibitors
RAL	Raltegravir
RBS	Random Blood Sugar
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UGT	Uridine diphosphate glucurunosyl transferase
ULN	Upper limit of normal
UNAIDS	United Nations Programme for HIV/AIDS

DEFINITION OF TERMS

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

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

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

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

Viral load: Number of HIV RNA copies in 1 millilitre of blood.

Viral suppression: HIV serum viral load of less than 1000 copies per millilitre.

ABSTRACT

Background: The antiviral drug Dolutegravir (DTG) is relatively new in the Kenyan market having been launched for use in mid 2017. This Integrase Strand Transfer Inhibitor has been shown to have a faster viral suppression rate, less susceptibility to viral mutations and favourable tolerability. These properties have led to a sharp increase in its use as a drug of choice in various scenarios in the management of the Human Immunodeficiency Virus (HIV). As a strategy for treatment optimization of HIV, there is an ongoing transition of HIV positive patients from a Nevirapine (NVP) based to a DTG based regimen. However, available data on the safety and effectiveness of DTG largely came from clinical trials and from studies done in the developed countries hence the need for this study.

Main objective: To compare the safety and effectiveness of a DTG and a NVP based regimen in HIV patients at the Kenyatta National Hospital.

Methods: This study which used a mixture of cross-sectional and historical cohort study designs was conducted at the Comprehensive Care Centre of Kenya's largest hospital, the Kenyatta National Hospital. Data on patient demographics, routine viral load test results and documented adverse drug reactions (ADRs) was extracted from electronic and physical patient records using a structured data collection tool. Additional data on ADRs was obtained from patient interviews using a pre-tested questionnaire. Two laboratory tests to assess liver function and glucose levels were also carried out on each participant. The Chi-square test was used to assess for any difference in viral suppression between the two groups. The influence of other variables was tested by use of multivariable logistic regression.

Results: A total of 111 patients met the eligibility criteria and were enrolled into the study (86 on TDF/3TC/DTG and 25 on TDF/3TC/NVP). Overall, the TDF/3TC/DTG regimen had a statistically significant (p=<0.001) higher viral suppression rate (93%) than the TDF/3TC/NVP regimen (56%). There was no statistically significant difference between the two regimens in the prevalence of hepatotoxicity (p=0.549) and hyperglycaemia (p=1.0). The TDF/3TC/NVP regimen had a slightly higher prevalence of Grade I headaches (8%) than TDF/3TC/DTG (7%) which was statistically significant (p=0.01). Similarly, the prevalence of Grade I pruritus was found to be

statistically significantly higher in the TDF/3TC/NVP arm (16%) than the TDF/3TC/DTG arm (5.8%) (p=0.008).

Conclusion: The TDF/3TC/DTG regimen was more effective in viral suppression and had a better safety profile than the TDF/3TC/NVP regimen.

CHAPTER ONE: INTRODUCTION

1.1 Background

In 2015, an estimated 1.6 million Kenyans were living with Human Immunodeficiency Virus (HIV) [1]. Out of these, about 900,000 were on lifelong antiretroviral therapy (ART) [2]. Jointly, HIV/Acquired Immune Deficiency Syndrome (AIDS) and Tuberculosis (TB) are the number two cause of death in Kenya after diarrheal diseases [3]. The year 2015 alone witnessed about 35,822 AIDS related deaths in Kenya [4].

In a bid to curb the spread of HIV and to reduce the mortality and morbidity associated with it, the World Health Organisation (WHO) is constantly changing the treatment guidelines to accommodate newer and more effective drugs as they become available. These guidelines in turn form the basis for many country-specific guidelines of individual member countries.

Dolutegravir (DTG), alongside Raltegravir (RAL) and Elvitegravir (EVG) is an Integrase Strand Transfer Inhibitor (INSTI) [5]. A number of studies have shown that DTG has a shorter median time to viral suppression, a higher genetic barrier to mutation, relatively fewer interactions with other drugs and a favourable tolerability [6–8]. For these reasons, there has been a sharp increase in the use of DTG the world over. In fact, it is projected that by 2021, DTG-based regimens will have a market share of about 59% up from the current 14% [9].

WHO introduced DTG in its HIV treatment guidelines in 2016 [10]. Since then, many countries including Kenya, Botswana, Uganda and Brazil have adopted its use [11]. One of the main donor partners, the United States President's Emergency Plan for AIDS Relief (PEPFAR) has also given a recommendation for a rapid scale up of DTG in its major target countries [12]. In Kenya, the Ministry of Health (MoH) through the National AIDS and STIs Control Program (NASCOP) incorporated DTG in the treatment guidelines [2] but the drug only became available in 2017 [9].

Through a circular released mid June 2017, the MoH announced the availability of DTG in the national supply chain and recommended its use in combination with dual fixed dose combination of Tenofovir and Lamivudine (TDF/3TC) in three scenarios [13]. These include its use as an alternative first line regimen in intravenous drug users, in people who cannot tolerate Efavirenz (EFV) and as a constituent of third line regimen in combination with other drugs [13]. As a result,

by the end of July 2017, approximately 1,400 patients were on DTG with a planned recruitment of more by the end of that year [9].

As a strategy towards ART optimization by scaling up the use of DTG in Kenya, the Academic Model Providing Access to Healthcare (AMPATH) program released an interim guidance document to clinicians [14]. In that document, additional recommendations for the use of DTG were given, chief among them being its use as a substitute for Nevirapine (NVP) in all patients on TDF/3TC/NVP who had achieved a viral load of less than 1000 copies/mL [14].

In line with this, Kenya's largest Teaching and Referral Hospital, Kenyatta National Hospital (KNH) with an approximated 10,000 HIV patients attending the Comprehensive Care Centre (CCC) clinic, embarked on an exercise to increase the number of patients on DTG. So far, the hospital has a total of about 700 patients on DTG. Out of this, about 400 were as a result of a transition from a TDF/3TC/NVP to a TDF/3TC/DTG regimen.

However, DTG is not free of adverse effects. The documented ones include nausea, diarrhoea, hyperglycaemia, hypersensitivity, hepatotoxicity and Immune Reconstitution Inflammatory Syndrome (IRIS) [2,6,10,14]. It has also been associated with a number of central neuropsychiatric adverse effects that include depression, suicidal ideation and dizziness. Others include abnormal dreams,insomnia and headache [14].

DTG is a relatively new drug in Kenya and Africa. Documented data on its safety in the Kenyan population is still scanty or at best anecdotal. The need for further safety assessment of this promising drug is perhaps exemplified by preliminary data from a study that is yet to be completed in Botswana which has identified four cases of children born with neural tube defects [15–17]. These were children whose mothers were already on DTG at the time of conception.

This study aimed at identifying the adverse effects experienced so far and assessing the effectiveness of DTG among patients at the KNH.

1.2 Statement of the problem.

With new safer and more effective drugs being discovered, HIV treatment guidelines are constantly changing to adopt their use. In line with this, the MoH launched the use of DTG in Kenya for the treatment of HIV [13]. Since then, there has been a rapid scale up of the use of

DTG. One of the strategies being employed is a mass transition of patients who are virally suppressed from a TDF/3TC/NVP to a TDF/3TC/DTG regimen.

Unlike NVP, DTG is a relatively new drug in Kenya and in Africa and therefore, data on its safety and effectiveness is not well documented. Even though this data exists from clinical trials and other studies done in the developed countries, the same cannot be directly extrapolated to our setting because of differences in the genetic makeup, race, co-morbidities and conditions of use [18].

The limited data notwithstanding, decisions have been made to switch patients en masse to DTG-based regimens. Should there be any future significant safety and/or efficacy concerns associated with the use of DTG in our population, the consequences of these decisions would be catastrophic not only to the patients, but also to the government and financiers of HIV treatment programs. These include additional costs incurred in the management of ADRs and transition of patients to alternative treatment regimens. ADRs have also been associated with negative treatment outcomes including increased morbidity and mortality [18]. Preliminary data from an ongoing cohort study in Botswana has reported four cases of neural tube defects out of four hundred and twenty six women who conceived while taking DTG.

The aim of this study therefore, was to compare the effectiveness and prevalence of ADRs of TDF/3TC/DTG and TDF/3TC/NVP. The information obtained will go a long way in providing insight to decision makers at KNH regarding the rapid scale up of patients on DTG.

1.3 Research questions

1. Is there a difference in the effectiveness in viral load suppression of NVP and DTG based regimens in HIV positive patients at KNH?
2. Is there a difference in the prevalence of drug induced hepatotoxicity, hyperglycaemia, CNS effects and hypersensitivity reactions between patients on NVP and DTG based regimens at KNH?
3. What other types of ADRs (apart from the ones targeted in question 2) are associated with DTG based regimens in HIV patients at KNH?

1.4 Objectives

1.4.1 Main objective

The main objective of the study was to compare the safety and effectiveness of DTG and NVP based regimens used in the treatment of HIV at Kenyatta National Hospital, Nairobi, Kenya.

1.4.2 Specific objectives

The specific objectives of the study were to:

1. Compare the effectiveness in viral load suppression of TDF/3TC/NVP and TDF/3TC/DTG based regimens in CCC patients at KNH
2. Compare the prevalence of hepatotoxicity, hyperglycaemia, CNS effects and hypersensitivity reactions associated with TDF/3TC/NVP and TDF/3TC/DTG regimens in HIV patients at KNH
3. Document other types of ADRs (apart from the ones targeted in the second objective) associated with the TDF/3TC/DTG regimen in HIV patients at KNH

1.5 Study justification

Over the years ARV drugs have been proven beyond any reasonable doubt to be lifesaving. In Kenya, over 423,000 AIDS related deaths have been averted so far since 2004 [4]. However, these drugs are also associated with significant safety issues. The Pharmacy and Poisons Board Kenya reported in 2014 that 74% of all ADR reports they received during that year were ARV related [19].

The introduction of DTG in Kenya, an arguably superior drug in terms of efficacy and safety [6] has sparked a lot of interest among stakeholders in HIV management. There is an ongoing rapid scale up of the use of DTG at KNH and in the country in general. The main strategy being employed is the mass transition of patients from a TDF/3TC/NVP regimen to a TDF/3TC/DTG one [14]. So far, about 400 patients have undergone this transition with many others expected to join them by the end of the year. The ultimate aim is to phase out the TDF/3TC/NVP regimen.

However, the safety of DTG is not as well documented in Kenya as in other countries. ADRs have been shown to affect the comfort of patients and to increase both morbidity and mortality. This in

turn reduces patient adherence to medication and may eventually lead to drug resistance and negative treatment outcomes [20].

The information obtained from this study sheds light on the types and extent of ADRs associated with DTG among HIV patients at KNH. In addition to this, the information obtained gives insight into the differences in the safety profile and effectiveness between a DTG and an NVP based regimen and hence provide scientific and clinical justification for the transition or the switch in therapy.

The findings of this study will be informative to policy makers and other stakeholders involved in the fight against HIV at KNH and in the country. Specifically, this study provides data in support of the decision to transition patients on a TDF/3TC/NVP regimen to a TDF/3TC/DTG one at KNH and by extension in the country.

These findings will be published in peer reviewed journals and disseminated to policy makers at the MoH, healthcare workers and other stakeholders via policy briefs, conferences and/or continuous medical education forums.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This study sought to compare DTG and NVP based regimens used in the treatment of HIV among patients at KNH with regard to effectiveness and safety. Viral suppression was used as a measure of effectiveness while safety was based on the occurence of a number of ADRs namely hyperglycaemia, hepatotoxicity, CNS effects and hypersensitivity. This section gives an overall review of the HIV disease in the general literature review segment and summarises findings on safety and effectiveness of the two regimens from other researches in the empirical literature review segment.

2.2 General Literature Review

2.2.1 HIV Disease burden

For over three decades HIV has been a pandemic. About 35 million people are living with the disease worldwide 70% of whom are in sub-Saharan Africa [21]. In 2017, the number of people living with HIV in Kenya was about 1.5 million [22].

The social and economic burden that HIV/AIDS has brought about over the years is enormous the world over. In 1999, the Government of Kenya declared the disease a national disaster owing to the huge socioeconomic impact witnessed due to the HIV/AIDS scourge [23].

According to the United Nations Programme for HIV/AIDS (UNAIDS), about 1 billion United States Dollars was spent in Kenya on HIV related activities and interventions in 2017 [24]. The same organisation estimates the number of orphaned children whose parents died due to HIV/AIDS in Kenya to be between 450,000 and 740,000 [22].

2.2.2 HIV replication cycle

The HIV-1 replication cycle roughly comprises two phases namely the early and the late phase [25]. The first phase starts with viral attachment to the host cell membrane and concludes with the integration of the viral deoxyribonucleic acid (DNA) into the host DNA. The last phase begins with the initiation of transcription and climaxes with the release of the mature virus.

HIV targets dendritic cells, macrophages, lymphocytes and monocytes found in various organs [26]. These cells express the CD4 receptor and chemokine co-receptors CCR5 and CXCR4 that are necessary for the fusion and entry of the virus into cells [21].

The HIV life cycle consists of nine stages [25] as shown in Figure 2.1.

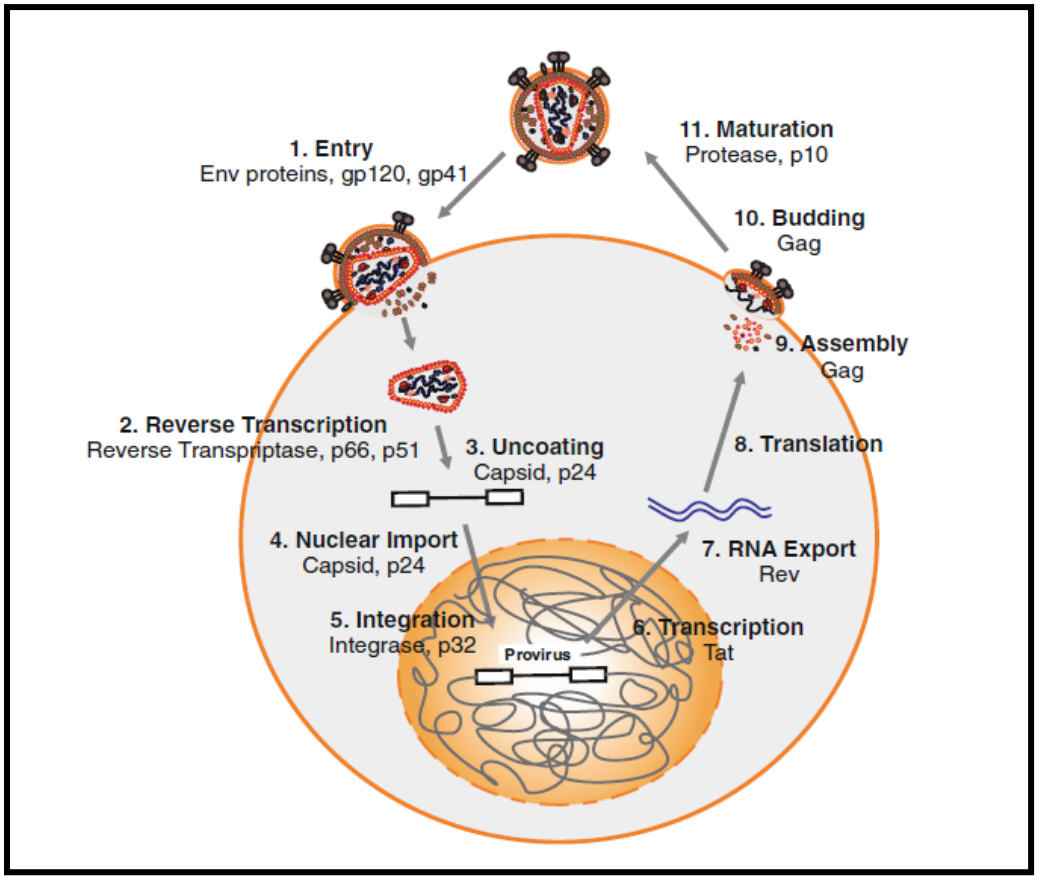

Figure 2.1: Life cycle of HIV (Adapted from the Encyclopedia of AIDS, 2013)[25]

2.2.3 Management of HIV

HIV has no known cure to date [27]. Highly Active Antiretroviral Therapy (HAART) using ARV drugs remains the mainstay treatment for HIV [28]. These drugs stop further replication of the virus by interfering with certain events in the HIV life cycle [29]. Initiation of ARV drugs as soon as possible following diagnosis of HIV is currently recommended for all age groups [30]. Because

early initiation has been linked with better viral suppression, the WHO recommends starting ARV drugs within one week of diagnosis [31].

HIV is a highly adaptable virus with an equally high rate of mutation [25]. This fact allows the virus to develop resistance to ARV drugs rapidly. In order to achieve a high barrier to the development of resistance, HIV treatment regimens currently constitutes combined ART consisting of at least three drugs [25,29].

Six major classes of ARV drugs are currently in use [29,32]. These include Nucleoside and Nucleotide reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Fusion inhibitors, Integrase inhibitors and Entry inhibitors [33]. Table 2.1 shows examples of drugs in the various classes of ARV drugs currently in use.

Table 2.1: Classes of Antiretroviral drugs

Class	Drugs
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine Lamivudine Abacavir Emtricitabine
Nucleotide Reverse Transcriptase Inhibitors	Tenofovir
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine Efavirenz Etravirine
Protease Inhibitors	Lopinavir Atazanavir Ritonavir Darunavir
Integrase Strand Transfer Inhibitors	Dolutegravir Raltegravir Elvitegravir
Entry and Fusion Inhibitors	Maraviroc Enfuvirtide

2.2.3.1 Integrase inhibitors

Integrase inhibitors also known as Integrase strand transfer inhibitors (INSTIs) halt viral replication by stopping the incorporation of HIV DNA into the host DNA [6,29]. Examples of agents in this class are elvitegravir, dolutegravir and raltegravir.

Two reactions are catalysed by the HIV-1 Integrase enzyme. The first reaction involves the cleavage of a dinucleotide at the two 3' ends of the viral DNA. This results in the exposure of hydroxyl groups which are reactive. The second reaction known as strand transfer, involves a nucleophilic attack on host DNA by the hydroxyl groups [34,35]. The INSTIs mainly target the second reaction and only modestly affect the first one [34,36,37].

Dolutegravir is the latest entrant into the INSTI family of drugs and is considered a second generation INSTI [38]. DTG is a polycyclic nitrogen-containing compound with two chiral centres and possesses amide functionality [39]. It is recommended in the most recent Kenyan guidelines as the first line agent to be used in the management of HIV in combination with other drugs [40].

The drug inhibits HIV replication by binding to the active site of the Integrase enzyme thereby blocking the vital strand transfer step of viral DNA integration into the host genome [29,39]. The formulation of DTG that was available in 2018 in Kenya was a 50 mg tablet which is administered orally.Absorption occurs rapidly and in about 2 hours the median maximum plasma concentration is achieved [41].

One major advantage of DTG is its convenient dosing of one tablet taken every 24 hours without a pharmacological booster [42,43]. A number of studies on the pharmacokinetics of DTG detected the drug in the cervicovaginal, cerebrospinal fluid and seminal fluids at higher concentrations than expected [44–46] possibly pointing towards wide distribution of the drug in the body. DTG is highly protein bound with >99% binding to plasma proteins [47].

The major metabolism pathway of DTG is phase II metabolism in the liver via glucuronidation through uridine diphosphate glucurunosyl transferase (UGT) 1A1 [42,48]. Minor pathways involve Cytochrome P450 (CYP450) 3A4 (phase I), UGT1A3 and UGT1A9 (phase II) [48]. DTG is mainly excreted excreted in faeces [48]. Urinary excretion is minimal and therefore the pharmacokinetics of DTG is not affected significantly by impaired renal function [49].

DTG has minimal drug-drug interactions owing to its limited ability to alter enzymes involved in drug metabolism [6]. This makes it compatible with a majority of ARV drug classes. There are no documented interactions between DTG and the NRTIs. A Study investigating the difference in bioequivalence between DTG and Abacavir (ABC)/3TC administered separately and ABC/3TC/DTG formulated as a single tablet found no difference [50]. Another study evaluating potential interaction between TDF and DTG reported no significant interaction [51].

The NNRTIs Nevirapine, Efavirenz and Etravirine lower the levels of DTG significantly [52–54]. One member of this class, rilpivirine, however has no interaction with DTG [55].

Among the PIs, Atazanavir, Lopinavir, Darunavir and Fosamprenavir may be used with DTG with or without Ritonavir boosting [56–58]. An exception is Tipranavir which reduces the levels of DTG [54].

The most important risk factor for TB is HIV and therefore HIV/TB co-infection is common [59]. This means that co-administration of ARV drugs and an anti-TB drug is inevitable. An important interaction exists between the anti-TB drug Rifampicin and DTG. Rifampicin significantly lowers DTG levels and this can be mitigated by either doubling the dose of DTG or substituting Rifampicin with Rifabutin [60].

Outside the realm of ARV and anti-TB drugs, though there are some interactions between DTG and other drugs, they are relatively few in number [6] as illustrated in Table 2.2. Of particular note is the potential increase in plasma levels of metformin by DTG which may require a downward dose adjustment and blood glucose monitoring [40].

Table 2.2: Important drug-drug interactions with Dolutegravir

Drug	Interaction
Efavirenz	Efavirenz decreases levels of DTG.
Etravirine	Etravirine decreases levels of DTG
Metformin	DTG may increase levels of Metformin
Carbamazepine	Carbamazepine decreases levels of DTG
Phenobarbital	Phenobarbital decreases levels of DTG
Phenytoin	Phenytoin decreases levels of DTG
Mineral supplements and antacids containing cations	Decrease the absorption of DTG

2.2.3.2 Non-nucleoside reverse transcriptase inhibitors

NNRTIs inhibit the reverse transcriptase enzyme whose role is to copy the single stranded viral RNA into a double stranded DNA [61]. The drugs bind to the enzyme leading to a conformational change which results in reduced binding affinity of the reverse transcriptase enzyme to its substrates [62]. Drugs in this class include nevirapine, efavirenz, etravirine and rilpivirine.

Nevirapine, a derivative of dipyrido-diazipinone [61], is among the oldest ARV drug. For many years, the drug was widely used in combination with NRTIs in the management of HIV. However, with the discovery of more potent agents with fewer side effects, its use has sharply declined over the years.

The latest Kenya HIV treatment guidelines no longer recommend initiation of ART naive patients on NVP containing regimens [40]. However, NVP in combination with AZT/3TC still remains the first line treatment of choice in newborns up to 4 weeks of age and for infant prophylaxis of HIV in babies born to HIV positive mothers [40].

NVP is available as a 200 mg oral tablet or a 50 mg/mL oral solution. Following oral administration, NVP is rapidly absorbed reaching maximum plasma concentration in approximately 2 hours [63]. About 60% of the drug is protein bound [64,65]. The half life of NVP

after a single dose is long (25 to 30 hours) [66] but diminishes with repeat doses because of auto induction of its metabolism [67,68].

NVP undergoes oxidative metabolism in the liver to form four hydroxyl metabolites and 4-carboxynevirapine [65] which are eliminated in urine mainly as glucuronide conjugates . Enzymes majorly involved in this metabolism are cytochrome 3A4 and 2B6 with 2D6 and 2C9 playing minor roles [69]. It has been shown that genetic variations in the cytochrome 2B6 enzymes influence the steady state plasma levels of NVP in African women [70].

NVP is a potent inducer of cytochrome 3A4 and 2B6 [71] therefore is likely to interact with drugs metabolised by these enzymes. Since cytochrome 3A4 metabolises the PIs, NVP has been shown to reduce the levels of saquinavir and indinavir [66]. Other cytochrome 3A4 substrates whose levels are reduced by NVP include methadone and certain 3-hydroxy-3-methylglutaryl CoA inhibitors (atorvastatin, simvastatin and lovastatin) [72,73].

NVP levels may also be reduced by drugs that induce the cytochrome p450 enzyme such as St. John's Wort and Rifampicin [74,75]. Table 2.3 summarises some key interactions between NVP and other drugs.

Table 2.3: Important drug-drug interactions with Nevirapine

Drug	Interaction
Dolutegravir	NVP decreases levels of DTG
Atazanavir	NVP decreases levels of Atazanavir
Ketoconazole	Ketoconazole increases levels of NVP by 15-30% NVP decreases levels of Ketoconazole by 63%
Rifampicin	Rifampicin decreases levels of NVP by 20%-50%
Clarithromycin	Clarithromycin increases levels of NVP by 26% NVP decreases levels of Clarithromycin by 30%
Ethinyl estradiol	NVP decreases levels of Ethinyl estradiol by about 20%
Methadone	NVP decreases levels of Methadone

2.3 Empirical Literature Review

2.3.1 Viral load suppression as a measure of effectiveness of antiretroviral drugs

The two methods for monitoring response to ART are CD4 cell count and plasma HIV RNA levels commonly known as viral load [76]. For many years CD4 cell count was the recommended method for monitoring treatment response in resource limited settings [77].

Viral load testing offers a number of advantages such as the ability to detect accurately virological failure before immunological and/or clinical deterioration and to predict HIV related deaths. Early detection of treatment failure is useful in guiding resistance genotyping and in enhancing adherence support [78,79]. Cognisant of these advantages, the WHO recommended viral load testing as the routine monitoring method for response to ART [80].

Viral suppression is defined by WHO as viral RNA copies below the lowest detectable levels by a particular assay method (usually less than 50 copies/mL) [80]. In Kenya viral load testing is recommended 6 months after the initiation of ART, then at 12 months and thereafter annually [40].

Non-adherence to medication is the commonest cause of treatment failure [40]. Sustained and consistent adherence to ARV medication is key to achieving and maintaining viral suppression because HIV is capable of establishing a latent reservoir in CD4+ which can be reactivated once ART is halted [81].

Many factors may influence adherence such as the patient's socioeconomic status, characteristics of the drugs prescribed, patient-service provider relationship and the clinical condition of the patient [82]. Other factors that may lead to an unsuppressed viral load include inadequate dosing, drug-drug and drug-food interactions and impaired absorption [40].

2.3.1.1 Viral load suppression of Dolutegravir

Three studies (SPRING-2, FLAMINGO and SINGLE), evaluating the efficacy of DTG among HIV naive patients showed either a higher or a non-inferior viral suppression rate for DTG compared to its comparators [83–85]. SPRING-2 was a blinded randomised controlled trial that compared RAL against DTG with either ABC/3TC or TDF/FTC. About 85% and 88% of patients on RAL and DTG respectively achieved HIV RNA levels <50 copies/mL at 48 weeks [84].

FLAMINGO, an open label study, reported a reduction in the viral load to <50 copies/mL in 90% of patients on DTG compared to 83% for those who were on Darunavir/ritonavir at 48 weeks [85]. The SINGLE study was a randomized placebo controlled one that compared DTG/ABC/3TC against TDF/FTC/EFV. Approximately 88% and 81% of patients on the DTG and the EFV based regimens respectively achieved viral loads of <50 copies/mL at 48 weeks [83].

Similarly, a number of clinical trials found DTG to be effective in inducing viral suppression in ARV treatment experienced patients with resistant strains [86–89].

DTG selects a mutation in the Integrase gene at R263K position leading to a diminished capacity of the virus to replicate and a reduction in the activity of the Integrase enzyme [5]. Other mutations selected both in vivo and in vitro include E138, S153, G118 and F121 [5,90].

The appearance of a primary mutation is often followed by the appearance of secondary and tertiary drug resistance ones in an attempt to compensate for replication [91] by increasing drug resistance and augmenting the replication of the virus. While such mutations have been identified for the NRTIs, NNRTIs and the PIs, none has been documented for DTG [92,93].

2.3.1.2 Viral load suppression of Nevirapine

The efficacy of NVP has dwindled over time with the emergence of resistant strains of HIV which could be attributed in part, to the previous use of single dose NVP for the prevention of mother to child transmission [94,95]. According to the WHO Drug Resistance Report, the prevalence of the Pre-treatment Drug Resistance (PDR) to the NNRTIs has been rising since 2001 [96]. A systematic review of PDR studies on adults from 63 low middle income countries reported that the rise in the resistance was highest in Eastern Africa followed by Southern Africa [96].

WHO PDR survey data obtained from 11 countries between 2014 and 2016 showed that the prevalence of resistance had reached levels >10% in six countries [96]. The overall prevalence of resistance to NNRTIs among people on ART is estimated to range from 5 to 28% and between 50% to above 90% in people failing ART.

One major shortcoming of NVP is its low genetic barrier to mutation which makes it susceptible to drug resistance even with a single mutation in the reverse transcriptase gene [97,98]. Some of the NVP-associated mutations include Y181C, K103N, G190A, Y188C, Y188L and V106A [98].

Cross-resistance among the NNRTIs means that once resistance to NVP occurs, the resistance may also affect other members of the group such as EFV [97].

2.3.2 Adverse drug reactions associated with Nevirapine and Dolutegravir

Adverse drug reactions are a major cause of increased morbidity, deaths and economic burden worldwide [99,100]. The WHO describes an ADR as "*a noxious, unwanted and unintended response to a medicinal product following its use at normal doses in humans*" [101].

One of the biggest barriers to adherence to HIV therapy is ADRs [20]. Adherence simply refers to the degree to which a patient complies to instructions of a healthcare practitioner regarding the use of a certain medicine [102]. ADRs negatively impact on adherence to medication subsequently leading to treatment failure and possibly the development of resistance to certain drugs [103]. Some studies postulate that ADRs impact on adherence by affecting the psychology of patients, lowering self-esteem and heightening self stigma [104,105].

The major adverse effects associated with DTG include insomnia, headache, diarrhoea, nausea, hypersensitivity and hepatotoxicity [40]. A study by Kandel et al on dolutegravir reported an estimated incidence of adverse events of about 90% [6]. This, however, consisted mainly of mild adverse events that by and large subsided with time and whose causality was not definite [6].

Reports from a number of studies listed diarrhoea, nausea and headache as the most frequent adverse events experienced by participants with serious and life threatening events contributing below 1% of cases [106]. Two studies (SINGLE and SPRING 1) comparing the incidence of insomnia in participants on DTG and EFV differed in their findings. The incidence of insomnia was found to be higher among participants on DTG in the SINGLE study with the converse being true in the SPRING 1 study [83,106]. DTG inhibits the renal transporter OCT-2 leading to creatinine elevation with no effect on the glomerular filtration rate [106,107].

Recently, an alert on DTG safety concerns was issued by the WHO and the United States Food and Drug Administration following reports of cases of 4 children with neural tube defects born to mothers taking part in a study [16,17]. Preliminary data from an observational study called the Tsepamo Study showed that 0.9% of newborn babies exposed to DTG had neural tube defects compared 0.1% who were exposed to EFV.

Adverse effects commonly associated with NVP include hypersensitivity reactions mainly in the form of a rash and hepatotoxicity [40]. Hepatotoxicity and life threatening cutaneous reactions (Steven Johnson Syndrome and Toxic Epidermal Necrolysis) are the most serious ADRs associated with NVP [108]. It has been postulated that toxicities due to NVP are due to reactive metabolites of the drug rather than the drug itself [109].

Serious and life threatening cutaneous reactions have been associated in the past with NVP perhaps more than any other ARV [110]. Some evidence point towards an imbalance in the occurrence of NVP reactions between men and women with the latter being at more risk [111]. Chances of these reactions occurring are much higher in treatment naive women with T lymphocyte CD4+ cell counts of 250 cells/mm^3 of blood and men with counts >400 cells/mm^3 [40,111,112].

2.3.3 Risk factors for adverse drug reactions

Identification of risk factors of ADRs may aid in the reduction of their occurrence. The risk factors may be broadly classified into four groups. These include patient related such as gender, age, pregnancy and genetic makeup, drug related such as dose and number of concurrent drugs, disease related such as co morbidities and social factors such as alcohol intake, cigarette smoking and use of herbal medication [113–116].

2.3.3.1 Risk factors for adverse drug reactions relating to the patients

Age is an important risk factor for the development of ADRs with the elderly and children being at a higher risk mainly because of reduced capacity to metabolise and eliminate drugs. Age comes with a myriad of physiological and anatomical changes that combined alter the pharmacokinetics of drugs [114].

Ageing is often accompanied with reduced hepatic and renal function which by extension leads to a diminished ability to metabolise and excrete drugs [117–119]. It has also been documented that the aged have a higher probability of being victims of polypharmacy which further raises their chances of experiencing ADRs [119]. Gender has also been shown to have a bearing on the development of ADRs because of the anatomical, physiological and behavioural differences between men and women. These differences make women more vulnerable to ADRs than their male counterparts [114].

Another important factor that may influence the occurrence of ADRs is pregnancy. Pregnant women undergo numerous changes affecting the cardiovascular, renal and gastrointestinal systems which interfere with the pharmacokinetics of many drugs [114].

Obesity is another risk factor for the occurrence of ADRs. Adipose tissue tends to form a reservoir for fat soluble drugs thereby prolonging their duration of action. This may lead to toxicity especially for those drugs with a narrow therapeutic range.

Individuals who have suffered from an ADR secondary to exposure to an agent tend to have a higher chance of getting an ADR when exposed to the same agent or to a structurally similar one. Genetic variation among individuals especially with regard to enzymes and receptors also leads to differing vulnerabilities to ADRs with slow metabolisers being more prone to ADRs than fast metabolisers.

2.3.3.2 Risk factors for adverse drug reactions relating to drug interactions

The administration and use of many drugs at the same time and in the same patient is a ramapant cause of toxicity and ADRs among the aged [120]. The probability of these toxicities and ADRs occurring is directly proportionally related to the number of drugs involved due to interactions [120,121].

2.3.3.3 Risk factors for adverse drug reactions related to social behaviour

Alcohol intake impacts on the metabolism of drugs in a number of ways. Chronic alcoholism for example eventually leads to liver damage through alcohol induced hepatitis and this impairs drug metabolism in the liver [114]. Alcohol may also directly interact with drugs causing harm to the patient. An example is the potentiation of the effects of sedatives leading to depression of the respiratory system and ataxia.

Cigarettes are potent inducers of the hepatic enzymes CYP1A1, CYP1A2 and CYP2E1 which are heavily involved in the metabolism of drugs[122]. Consequently, a sudden withdrawal of ciggarretes may raise the chances of the development of ADRs secondary to a reduction in hepatic enzyme activity [123,124].

2.3.3.4 Risk factors for adverse drug reactions related to diseases

Any disease affecting any of the organs that play a vital role in the process of metabolising and eliminating drugs are bound to increase the risk of ADR occurrence. Reduced kidney function due to renal failure for example leads to reduced clearance rate of certain drugs and eventual accumulation to toxic levels [125]. Likewise, diseases that affect the liver may lead to a reduction in the ability of the liver to metabolise certain drugs such as the NNRTIs and the PIs thereby raising the probability of hepatic toxicity [126].

2.4 Conceptual framework

Figure 2.2 is a conceptual map that illustrates the relationship between viral load suppression and antiretroviral therapy.

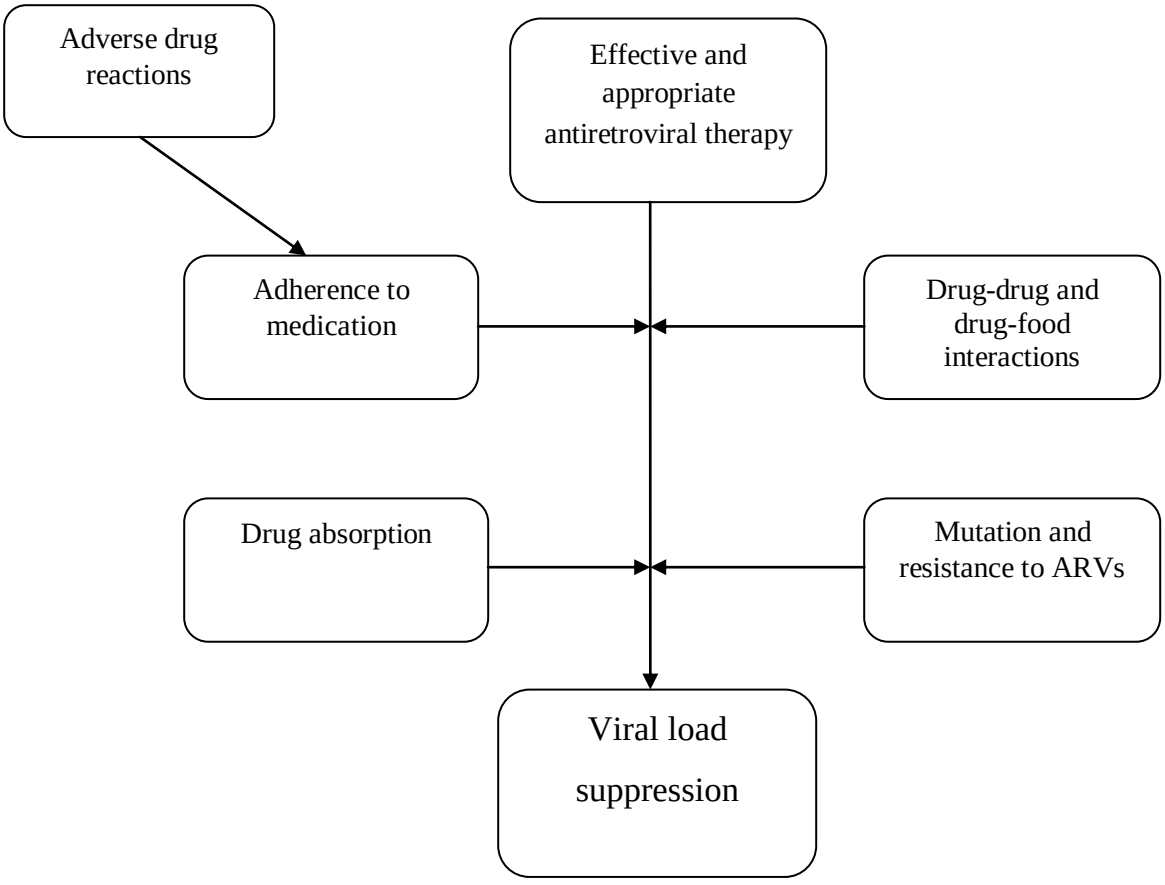

Figure 2.2: Conceptual map showing the relationship between viral load suppression and antiretroviral therapy

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study design

This study adopted a mixture of cross-sectional and historical cohort analytical study designs. The historical cohort study design was used in determining the participants who were using the TDF/3TC/DTG and TDF/3TC/NVP regimens and following them up to find out whether they developed the adverse drug reactions of interest or whether they achieved viral suppression. The follow up was solely based on the patient medical records.

The laboratory component of the study employed the cross-sectional study design whereby blood samples were collected from the participants and two tests were carried out to assess for hyperglycaemia and hepatotoxicity. The tests carried out were random blood sugar (RBS) and Alanine Aminotransferase (ALT).

3.2 Study site

The study was carried out at the comprehensive care centre of KNH which handles all the HIV positive patients in the hospital. KNH is Kenya's largest national teaching and referral hospital, and is one of the Centres of Excellence in the country when it comes to the care and management of HIV infected patients. This fact made it an ideal hospital to undertake this research on behalf of Kenya and its HIV population.

The KNH CCC handles HIV patients drawn from all over the country. In 2018 about 600 of the HIV patients visiting the hospital were on a TDF/3TC/DTG regimen while approximately 400 were on a TDF/3TC/NVP regimen.

3.3 Study and sample population

The study population included all patients on TDF/3TC/NVP and TDF/3TC/DTG attending the CCC clinic at KNH during the study period of June 2017 to June 2019. In order to get the sample population, the exclusion criteria were applied.

3.4 Eligibility criteria

The study included participants of any age or sex who gave voluntary informed consent and who were on either a TDF/3TC/NVP or a TDF/3TC/DTG regimen. The participants must have been on

either of the two regimens for at least 6 months prior to the commencement of the study. In addition, the participants must have had a good medication adherence record for at least 6 months prior to the commencement of the study (medication adherence is monitored and recorded at KNH during each patient visit).

The study excluded participants with missing viral load information for the 6 months prior to the commencement of the study and those who did not give voluntary consent. Also excluded were participants with documented liver disease or active hepatitis confirmed to be due to other causes other than drugs and those with liver disease before the initiation of the current drug regimen

3.5 Sample size estimation

From literature, a head to head comparison of NVP and DTG had never been done. However, a study comparing EFV and DTG found a prevalence of ADRs of 10% and 2% for EFV and DTG respectively [83]. NVP and EFV belong to the same class of ARV drugs. Based on this, the assumed difference between the two drugs in terms of the prevalence of ADRs was set at approximately 10%.

The sample size was estimated using the formula below [127]. This formula was suitable because the study was comparative and the outcomes being measured were binary in nature.

$$n = \frac{[(\alpha + b)^2(p_1q_1) + (p_2q_2)]}{x^2} \quad \text{.....Equation 1}$$

Where: n=sample size in each group

p_1=proportion of subjects with outcome in treatment group 1 (2%)

p_2=proportion of subjects with outcome in treatment group 2 (10%)

$q_1 = (1-p_1)$

$q_2 = (1-p_2)$

α= conventional multiplier for alpha=0.05 (1.96)

b=conventional multiplier for power=0.8 (0.842)

x=difference to be detected (10%)

$$n = \frac{[(1.96 + 0.842)^2 (0.02 \times 0.98)_{+} (0.10 \times 0.9)]}{0.1^2}$$

n = 86 participants

However, the number of patients on TDF/3TC/NVP had greatly declined owing to the decision by the Ministry of Health to expedite the transition of patients from TDF/3TC/NVP to TDF/3TC/DTG. This transition saw the total number of patients on TDF/3TC/NVP drop from about 400 at the beginning of the proposal development to 19 at the end of June. Consequently the achievement of the projected sample size of 86 for that particular arm was impossible. For this reason, the sample size for the TDF/3TC/NVP arm of the study was 25 participants. This was the number of all the remaining eligible participants who were on TDF/3TC/NVP regimen.

3.6 Sampling method

The study adopted the convenient sampling method. The method was suitable for this study because of the relatively few number of patients who were remaining on the TDF/3TC/NVP regimen. Participants included in the study were picked on a daily basis based on the duration of time they had been on either TDF/3TC/NVP or TDF/3TC/DTG. All those who had been on their current regimen for at least 6 months by the end of the study period were included in the study.

3.7 Recruitment of participants and the consenting process

Potential participants were recruited as they came for their medication refill. On the day of the visit, full information about the study was given to the identified patients and only those who signed the voluntary informed consent form (appendix 1, 2, 3 or 4) were enrolled into the study.

In consultation with the enrolled participant, another date was set for the purpose of data collection. As far as possible, the scheduled date coincided with the patient's medication refill appointment date but was not later than three months from the time of enrollment. However, participants who wished to have the interview and the laboratory tests carried out immediately after consenting were given the opportunity to do so.

Because of the rapid transition of patients on TDF/3TC/NVP to the TDF/3TC/DTG regimen, there had been a steep decline in the number of patients on TDF/3TC/NVP. This fact coupled with the short timeline within which to collect data necessitated the use of patient contact information to track and follow up potential study participants.

3.8 Data collection instruments and procedures

Data on definitive diagnosis of all ADRs with special emphasis on hypersensitivity reactions, CNS effects, hyperglycaemia and hepatotoxicity together with viral load test results was extracted from both manual and electronic patient records using a structured Data Collection Form (Appendix 9). Additional data on hypersensitivity reactions and CNS effects were collected using a pre-tested questionnaire (Appendix 10 or 11) that was administered to the patient and filled by the researcher.

Two laboratory tests, random blood sugar (RBS) and Alanine Aminotransferase (ALT), to assess for hyperglycaemia and hepatotoxicity respectively were also carried out. The collection and analysis of blood samples for the tests were carried out by qualified KNH staff at the KNH CCC laboratory and the results were forwarded to the researcher who then recorded them on the Data Collection Form. The approximate volume of blood collected from each participant was 4mL.

3.9 Study variables and definitions

The main outcome variables were the prevalence of hypersensitivity reactions, CNS effects, hyperglycaemia and hepatotoxicity among patients on the two regimens (TDF/3TC/NVP and TDF/3TC/DTG). Another variable was the viral suppression rate achieved by the two regimens. Hyperglycaemia, CNS effects and hepatotoxicity were defined as per the Division of AIDS table for grading the severity of adult and paediatric adverse events, Version 2.0, November 2014 [128]. In that table, hyperglycaemia had been classified based on RBS into four categories namely: Grade 1 (116-160mg/dL), Grade 2 (>160-250mg/dL), Grade 3 (>250-500mg/dL) and Grade 4 (>500mg/dL).

Hepatotoxicity based on ALT, had also been classified into four categories. These were: Grade 1 (1.25 to <2.5 x upper limit of normal (ULN)), Grade 2 (2.5 to <5 x ULN), Grade 3 (5 to <10 x ULN) and Grade 4 (≥10 x ULN). At KNH, the ULN for ALT is 35U/L. Therefore, in this study the four categories of hepatotoxicity were defined as ALT levels ranging from 43.75 to <87.5U/L for Grade 1, from 87.5 to <175U/L for Grade 2, from 175 to <350U/L for Grade 3 and ALT ≥350U/L for Grade 4.

CNS effects assessed included insomnia, headache, suicidal ideation or tendencies, depression and psychosis. These were graded into four categories as shown in Appendix 7.

Hypersensitivity reactions were defined as pruritus and/or the appearance of a rash on the skin that were graded into four categories as shown in Appendix 8.

Effectiveness was evaluated using the viral load test results. Viral suppression was defined as serum HIV RNA numbers of less than 50 copies/mL [101]. Viral suppression rate was obtained by dividing the number of participants in a particular regimen who were virally suppressed by the total number of patients in that regimen.

The predictor variables were the respective regimens. Possible confounding variables included age of the participants, gender, co-morbidities, concurrent medication, alcohol intake, duration of ART and levels of adherence to medication.

3.10 Quality assurance and data management

All the data collection instruments that were used in the study were pretested on five patients and improved based on feedback received.

The data collected was reviewed by the researcher on a daily basis against the source documents to ensure accuracy and completeness. It was then keyed into an electronic database whose access was restricted by a password. The software that was used for this purpose was Epi Info™ Version 7.1.0.6 developed by the Centres for Disease Control and Prevention (CDC). Information contained in the database was backed up on a daily basis onto an external storage device that was kept in a lockable cabinet. Hard copies of the Data Collection Forms, filled questionnaires and laboratory test results were also stored in the same cabinet to restrict access and enhance confidentiality.

At the end of the data collection process, the data underwent a cleaning and a validation process before being exported into STATA software Version 13.0 for analysis.

3.11 Data analysis

The number of patients with ADRs (hepatotoxicity, hyperglycaemia, hypersensitivity and CNS effects) and the number of patients who were virally suppressed across the two groups (TDF/3TC/DTG and TDF/3TC/NVP) was expressed as percentages. A summary of the socio-demographic characteristics showing the frequency distribution of all participants in terms of age, sex, alcohol intake and co-morbidities was also provided.

The Chi-square test was used to assess for any difference in viral suppression and the occurrence of ADRs between the two groups. The influence of other variables such as sex, alcohol intake, age, co-morbidities and concurrent medication was tested by use of multivariable logistic regression.

Odds and odds ratios was calculated to determine the association between the main outcome variables and the predictor variables. The forward step-wise logistic regression method was used to come up with parsimonious models showing the relationship between the outcome and the predictor variables. For all the analyses in this study, the level of significance was set at 0.05.

3.12 Ethical considerations

Before the commencement of the study, approval was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (Appendix 13). In addition to that, the study was registered with the KNH Research and Development Department in accordance with the hospital research guidelines. To implement the study, permission was sought from the relevant hospital management authorities at KNH.

All participants were required to give voluntary written informed consent by signing an Informed Consent Form (Appendix 1 or 2) before taking part in the study. In addition to voluntary consent from their parents or guardians (Appendix 3 or 4), assent was sought from participants below the age of 18 years but above 8 years of age (Appendix 5 or 6). Voluntary informed consent was obtained before administration of the data collection questionnaire. This was done in a consultation room at the CCC department of KNH. During the consenting process, all information about the study was given to the participant as contained in the informed consent information document. Thereafter, if fully satisfied and willing to participate, the participant signed the informed consent form.

Utmost care was taken by the researcher to ensure maximum privacy and confidentiality of the information obtained during the study. Individual participant identifier information was omitted in the data collection tools and instead, codes were used. Electronic data was stored in a password-protected database only accessible to the researcher. The data collection tools and any other materials that were used during the study were kept in a lockable cabinet only accessible to the researcher. At the end of the study, they were handed over to the Department of Pharmacognosy

and Pharmacology, the University of Nairobi for storage for a period of 5 years and thereafter destroyed by shredding.

In the event that there was need to access patient contact information for the purpose of follow up and tracking of potential study participants, the existing mechanism of contacting and following up patients at the KNH CCC was employed. This was done through the community liason and linkage office at the CCC so as to maintain the highest attainable standards of privacy.

All laboratory tests and analyses were carried out by qualified KNH laboratory staff at the KNH laboratory and the results were forwarded to the researcher. Similarly, blood samples for the tests were also obtained by the same staff at the same laboratory. The volume of blood required for the tests was approximately 4mL. Participants found to have laboratory values higher than the upper limit of normal (higher than 35U/L for ALT and 140mg/dL for RBS) were referred to clinicians at the KNH CCC for further evaluation and management.

CHAPTER FOUR: RESULTS

4.1 Introduction

A total of 250 HIV patients were assessed for eligibility. One hundred and thirty nine participants were excluded from the study. Out of the 139 participants, 124 did not meet the inclusion criteria with regard to duration of treatment. Additionally, 3 participants declined to take part in the study while 12 had missing viral load information. Figure 4.1 summarizes participant enrolment and exclusion.

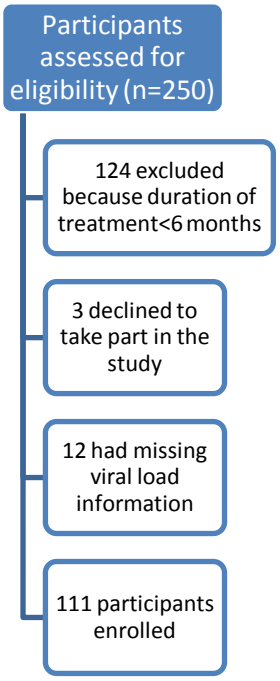

Figure 4.1: Flow of study subjects

A total of 111 participants met the eligibility criteria and were enrolled into the study. Out of these, 86 were on the TDF/3TC/DTG regimen while 25 were on the TDF/3TC/NVP regimen. The projected sample size of 86 participants for each of the regimens was therefore met for the TDF/3TC/DTG arm of the study but not for the TDF/3TC/NVP arm.

Failure to meet the projected sample size for the TDF/3TC/NVP arm was occasioned by the decision of the Ministry of Health to expedite the transition of patients from the TDF/3TC/NVP to

the TDF/3TC/DTG regimen. As a result, all the remaining patients on the TDF/3TC/NVP regimen who met the eligibility criteria were incorporated into the study.

4.2 Characterisitics of the participants

Overall, the study had more females (69) than males (42) corresponding to about 62% and 38% of the participants respectively. In the TDF/3TC/DTG arm of the study, the number of female participants was 48 (56%) while that of males was 38 (44%). Contrastingly in the TDF/3TC/NVP arm, there were 21 female participants constituting about 84% of the total number of participants in that arm and 4 male ones (16%). A summary of the distribution of the two genders across the regimens is shown in Table 4.1.

The median age of the participants was 50 years (inter-quartile range [IQR] 42, 55). The youngest participant was 14 years old while the eldest had 69 years. All the 86 participants in the TDF/3TC/DTG regimen and most of those in the TDF/3TC/NVP arm of the study (24) were above 15 years of age. Only one participant (4%) on the TDF/3TC/NVP regimen was below 15 years of age. There was however no statistically significant difference in the distribution of the age groups across the regimens (p=0.23).

The mean Body Mass Index (BMI) was 26.13 kg/m^2 with a standard deviation of ±4.28 kg/m^2. The BMI ranged from 17.05 to 35.82 kg/m^2.

Table 4.1: Demographic characteristics of HIV patients at Kenyatta National Hospital (n=111)

Characterisitic		TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	TOTAL n	p-value
Age	>15 years	86 (100)	24 (96)	110	**0.23**
	<15 years	0 (0)	1 (4)	1	
	Total	86	25	111	
Sex	Male	38 (44)	4 (16)	42	**0.01***
	Female	48 (56)	21 (84)	69	
	Total	86	25	111	

** Statistically significant*

4.3 Medical history of the participants

Information on existing allergies, history of mental illness, WHO HIV staging and history of ADRs was collected and recorded.

4.3.1 Most recent WHO HIV staging of the participants

Nearly all the participants were on WHO HIV stage I (Table 4.2). The total number of participants in this stage was 96 representing about 87.3% of all participants. Stage II comprised of 8 participants (7.3%) while Stages III and IV each had 3 participants (2.7%).

The stratification of the stages by regimen revealed that 72 participants (75%) and 24 participants (25%) on TDF/3TC/DTG and TDF/3TC/NVP regimens respectively were in Stage I. All the participants in the latter three stages belonged to the TDF/3TC/DTG arm of the study. The difference in the distribution of the participants into the various stages between the groups was not statistically significant (p=0.377).

Table 4.2: WHO HIV staging of the participants according to regimen (n=111)

WHO Staging	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	Total n (%)
I	72 (75)	24 (25)	96 (100)
II	3 (100)	0 (0)	3 (100)
III	8 (100)	0 (0)	8 (100)
IV	3 (100)	0 (0)	3 (100)

4.3.2 History of drug allergies of participants

Most of the participants did not have any known drug allergies (Table 4.3). Out of the 111 participants who took part in the study, 92 (82.9%) did not have a history of drug allergies. The TDF/3TC/DTG arm of the study had 14 participants (73.7%) with a history of allergic drug reactions while the TDF/3TC/NVP arm had 5 participants (26.32%). The difference between the two groups with regard to a history of allergic drug reactions was not statistically significant (p=0.664).

Table 4.3: History of allergic drug reactions by regimen

Allergy	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	Total	P-value
Yes	14 (73.68)	5 (26.32)	19 (100)	**0.664**
No	72 (78.3)	20 (21.7)	92 (100)	

The most implicated agents were sulphur containing drugs (63.2%) followed by Isoniazid (15.8%). Other agents included Azithromycin, Zidovudine and quinine each contributing about 5.3%. Figure 4.2 illustrates the various agents implicated for the allergies.

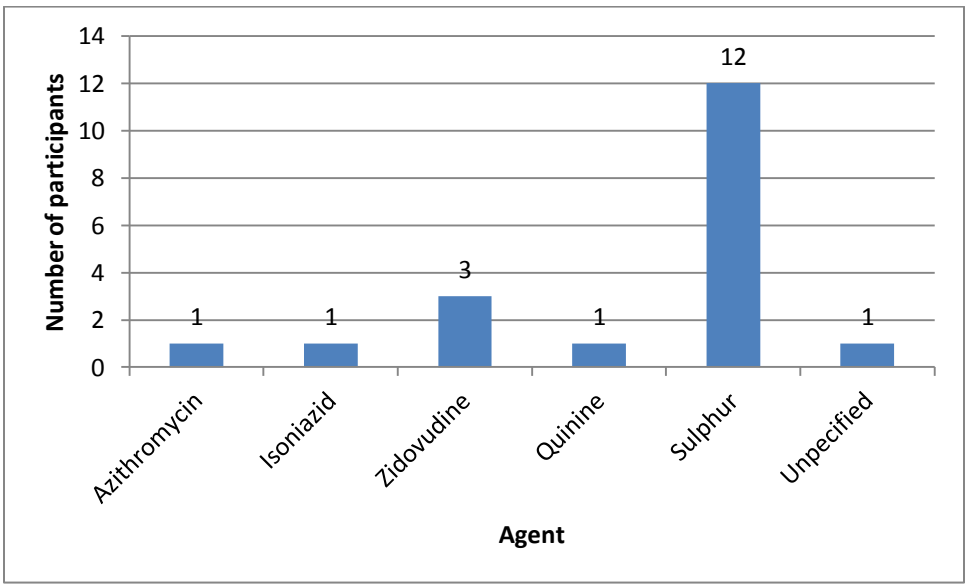

Figure 4.2: Agents implicated for allergic reactions among the participants (n=19)

4.3.3 History of mental illnesses among the participants

There were relatively few participants (5) with documented history of mental illnesses. This constituted about 4.5% of all the participants. The five were distributed relatively equally across the two regimens with 3 (60%) of them on TDF/3TC/DTG and 2 (40%) on TDF/3TC/NVP.

The mental illness cited in all the cases was depression. The Fischer's exact chi square test did not find any statistically significant difference in the existence of a history of mental illnesses across the regimens (p=0.314).

4.3.4 History of occurrence of adverse drug reactions in participants

The total number of participants with documented history of ADRs due to drugs other than the ones under study was 14 corresponding to approximately 12.6% of all participants. About 78.6% of them (11 participants) were on TDF/3TC/DTG while 3 (21.4%) were on TDF/3TC/NVP. The difference between the two groups was not statistically significant (p=1.0).

4.4 Co-morbidities of participants

The most common co-morbidity was hypertension followed by diabetes. About 26 participants (23%) were hypertensive while about 5 (5%) were diabetic. Asthma, deep venous thrombosis (DVT), epilepsy and ulcers were each present in 2 participants (2%). Other co-morbidities namely cervical cancer, bipolar disorder, chronic bronchitis, hyperthyroidism and chronic back pain were present in one participant each. Collectively, these other co-morbidities affected around 5% of the participants.

All the 5 participants who had diabetes were in the TDF/3TC/DTG arm of the study. Out of the 26 participants who were hypertensive, 21 (80.8%) of them were on the TDF/3TC/DTG regimen while 5 (19.2%) were on the TDF/3TC/NVP regimen.

Asthma, DVT and ulcers were individually present in 2 participants each. All of these participants belonged to the TDF/3TC/DTG arm of the study. Nevertheless, there was no statistically significant difference in the distribution of the various co-morbidities across the two groups as shown in Table 4.4.

Table 4.4: Co-morbidities in HIV patients at Kenyatta National Hospital (n=111)

Disease		TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	TOTAL n	P-value
Diabetes	Yes	5 (100)	0 (0)	5	**0.586**
	No	81 (76.4)	25 (23.4)	106	
Hypertension	Yes	21 (80.8)	5 (19.2)	26	
	No	65 (76.5)	20 (23.5)	85	**0.646**
Asthma	Yes	2 (100)	0 (0)	2	**1.000**
	No	84 (77.1)	25 (22.9)	109	
Deep Venous Thrombosis (DVT)	Yes	2 (100)	0 (0)	2	
	No	84 (77.1)	25 (22.9)	109	**1.000**
Ulcers	Yes	2 (100)	0 (0)	2	**1.000**
	No	84 (77.1)	25 (22.9)	109	
Epilepsy	Yes	1 (50)	1 (50)	2	**0.401**
	No	85 (78)	24 (22)	109	
Others	Yes	4 (80)	1 (20)	5	**1.000**
	No	82 (77.4)	24 (22.6)	106	

4.5 Duration of antiretroviral therapy

The duration of time that had elapsed since a participant was first initiated on ART was recorded. Similarly, the duration of time that had elapsed since the start of the current ART regimen was also recorded for those whose regimens had been switched during the course of therapy. The median duration of time

4.5.1 Duration of treatment since initiation of ART

Generally, participants on the DTG based regimen had been on ART for a shorter duration of time than those on the NVP based regimen. The median duration of time since initiation of ART for the two groups was 10 and 11 years respectively.

4.5.2 Duration of treatment since initiation of the current ART regimen

Overall, participants on the TDF/3TC/NVP regimen had been on that regimen for a longer duration of time compared to those who were on the TDF/3TC/DTG regimen. The median duration of time since initiation of the current ART regimen was about 10 years for the TDF/3TC/NVP group and 1 year for the TDF/3TC/DTG group.

4.6 Previous ART regimen of the participants

The previous regimens used by the study participants are summarized in Table 4.5. A large portion of participants in the TDF/3TC/DTG arm of the study were previously on TDF/3TC/NVP (60.5%) and TDF/3TC/EFV (30.2%). About 2.3% (2 participants) in this arm of the study had not been on any other regimen.

Table 4.5: Previous regimens of the participants (n=111)

Previous regimen	**Current regimen**	
	TDF/3TC/DTG	TDF/3TC/NVP
	n (%)	n (%)
TDF/3TC/NVP	52 (60.5)	0 (0)
TDF/3TC/EFV	26 (30.2)	1 (4)
AZT/3TC/NVP	3 (3.5)	3 (12)
No previous regimen	2 (2.3)	19 (76)
AZT/3TC/ATV/r	1 (1.2)	0 (0)
TDF/3TC/ATV/r	1 (1.2)	0 (0)
AZT/3TC/RAL	1 (1.2)	0 (0)
D4T/3TC/NVP	0 (0)	1 (4)
TDF/3TC/DTG	0 (0)	1 (4)
Total	86	25

Nearly all the participants (19) on the TDF/3TC/NVP group had not been on any previous regimen constituting about 76% of all the participants in that group.

4.7 Use of herbal medicine and substances of abuse (alcohol, cigarettes and others) by participants

Overall, about 20 participants (18%) and 2 participants (2%) took alcohol and smoked cigarettes respectively. Among those who took alcohol, 18 (21%) were on the TDF/3TC/DTG regimen while 2 (8%) were on the TDF/3TC/NVP regimen. This difference in those who took alcohol between the two regimens was not statistically significant (p=0.24). The two participants who smoked cigarettes both belonged to the TDF/3TC/DTG arm of the study. Similarly, there was no statistically significant difference between the two regimens with regard to cigarette smoking (p=1.0).

The use of Miraa/Khat and herbal medication was also assessed. Nearly none of the participants partook of these substances. Among all the participants, only 2 (1.8%) and 1 (0.9%) used herbal medication and chewed Miraa respectively. All the 3 belonged to the TDF/3TC/DTG group. The Fischer's Exact Chi-square test did not show any statistically significant difference in the use of these two substances across the regimens (p=1.0).

4.8 Concurrent medication used by participants

Most of the participants 81 (73%) were not on any other medication other than ARV agents and cotrimoxazole. Among those who were on concurrent medication, a large number (24) were on the TDF/3TC/DTG regimen (Table 4.6). This translated to about 80% of all those who were on concurrent medication. About 6 participants (20%) were on TDF/3TC/NVP. There was no statistically significant difference in the use of concurrent medication between the regimens (p=0.699).

Table 4.6: Concurrent medication use among HIV patients at Kenyatta National Hospital (n=111)

Concurrent medication	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	Total	P-value
Yes	24 (80)	6 (20)	30 (100)	**0.699**
No	62 (76.5)	19 (23.5)	81 (100)	
Total	86	25	111	

The most commonly used drugs were antihypertensive agents with about 21 (18.9%) partitcipants using them followed by antidiabetic agents with 6 (5.4%) participants. Warfarin, Salbutamol inhaler, Isoniazid and pyridoxine (IPT) were each being used by 2 participants (1.8%). Other drugs including Phenytoin, Lamotrigine, Fluoxetine, Atorvastatin, Pregabalin, Acetylsalicylic acid and Folic acid each had one patient on them (Figure 4.3).

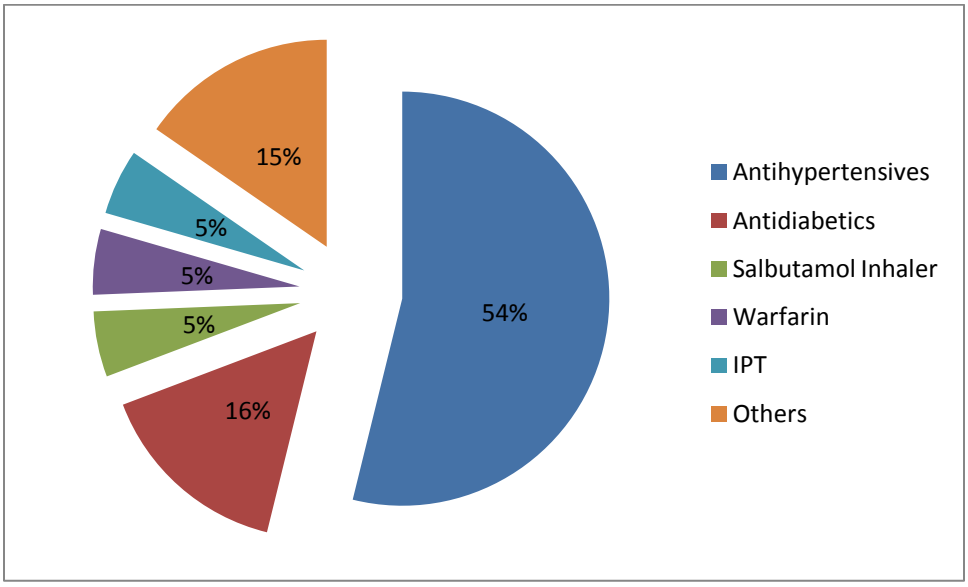

Figure 4.3: Distribution of concurrent medications in HIV patients at Kenyatta National Hospital (n=39)

4.9 Comparative effectiveness in viral load suppression

The viral load suppression rate was obtained by calculating the percentage of participants who were virally suppressed in a particular regimen. One was considered to have achieved viral

suppression using two criteria. The first criterion was the WHO one which defined viral suppression as a viral load less than 50 copies/mL. The second criterion was derived from the Kenyan HIV treatment guidelines which set the viral suppression ceiling at a viral load of less than 1000 copies/mL.

4.9.1 Participants attaining a viral load <50 copies/mL

Overall, about 93 participants (84.6%) had a viral load <50 copies/mL while 17 participants (15.4%) had a viral load >50 copies/mL. Among 85 participants on the TDF/3TC/DTG regimen, 79 (92.9%) achieved viral suppression. In the TDF/3TC/NVP arm, 14 participants (56%) achieved viral suppression. The difference in the viral suppression rate between the two regimens was statistically significant (Table 4.7).

Table 4.7: Viral load suppression rate based on the WHO criteria (n=110)

Viral load	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
<50 copies/mL	79 (92.9)	14 (56)	**<0.001***
>50 copies/mL	6 (7.1)	11 (44)	**<0.001***
Total	**85 (100)**	**25 (100)**	

** Statistically significant*

4.9.2 Participants attaining a viral load <1000 copies/mL

Nearly all the participants had a viral load <1000 copies/mL. Out of 110 participants, 105 (95.5%) achieved viral suppression. According to this criterion, all the participants (85) who were on TDF/3TC/DTG were virally suppressed. In the TDF/3TC/NVP group of participants, 20 (80%) were virally suppressed as illustrated in Table 4.8. The differences in the viral load suppression rate between the two groups was statistically significant ($p<0.001$).

Table 4.8: Viral load suppression rate based on the Kenya HIV treatment guidelines (n=110)

Viral load	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
<1000 copies/mL	85 (100)	20 (80)	**<0.001***
>1000 copies/mL	0 (0)	5 (20)	**<0.001***
Total	**85 (100)**	**25 (100)**	

** Statistically significant*

4.10 Prevalence of hyperglycaemia

The overall prevalence of hyperglycaemia was 8.7%. Grade I (mild) hyperglycaemia was the most prevalent (5.8%) followed by Grades II (moderate) and III (severe) with prevalences of 2% and 1% respectively.

In both regimens over 90% of participants had normal blood sugar levels. In the TDF/3TC/DTG arm, the prevalence of Grades I, II and III hyperglycaemia was about 6.2%, 2.5% and 1.2% respectively. No participant in this arm had Grade IV (potentially life threatening) hyperglycaemia.

Among the participants on the TDF/3TC/NVP regimen, the prevalence of Grade I hyperglycaemia was 5%. None of the participants on this regimen had Grades II, III or IV hyperglycaemia (Table 4.9). There was no statistically significant difference in the prevalence of the various grades of hyperglycaemia across the two groups (p=1.0).

Table 4.9: Prevalence of hyperglycaemia by severity and regimen (n=103; p=1.0)

Severity of hyperglycaemia	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	73 (90.1)	21 (95.5)
Grade I	5 (6.2)	1 (5)
Grade II	2 (2.5)	0 (0)
Grade III	1 (1.2)	0 (0)
Grade IV	0 (0)	0 (0)
Total	**81 (100)**	**22 (100)**

The participants were further divided into two sub-groups: those with diabetes and those without diabetes. All the 5 participants who had diabetes were on the TDF/3TC/DTG regimen. These participants already had diabetes at the time of initiation of therapy. The prevalence of hyperglycaemia in this sub-group was 20% for Grades I, II and III hyperglycaemia (Table 4.10). There were no cases of Grade IV hyperglycaemia.

Table 4.10: Prevalence of hyperglycaemia by severity and regimen among the diabetic participants (n=5)

Severity of hyperglycaemia	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	2 (40)	0 (0)
Grade I	1 (20)	0 (0)
Grade II	1 (20)	0 (0)
Grade III	1 (20)	0 (0)
Grade IV	0 (0)	0 (0)
Total	**5 (100)**	**0 (0)**

Among the participants who did not suffer from diabetes, the TDF/3TC/DTG regimen had a slightly higher prevalence of Grade I hyperglycaemia (5.3%) than the TDF/3TC/NVP regimen (4.6%) as shown in Table 4.11. A similar scenario was seen with Grade II hyperglycaemia where the TDF/3TC/DTG regimen had a prevalence of 1.3% while the comparator had a prevalence of 0%. No cases of Grade IV hyperglycaemia were encountered.

Table 4.11: Prevalence of hyperglycaemia by severity and regimen among the non-diabetic participants (n=98; p=1.0)

Severity of hyperglycaemia	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	71 (93.4)	21 (95.4)
Grade I	4 (5.3)	1 (4.6)
Grade II	1 (1.3)	0 (0)
Grade III	0 (0)	0 (0)
Grade IV	0 (0)	0 (0)
Total	**76 (100)**	**22 (100)**

Bivariable logistic regression was done to test the association between hyperglycaemia and five predictor variables: diabetes status, BMI, age, time from last meal taken and the current ART regimen. The results are shown in Table 4.12.

Table 4.12: Findings of a bivariate logistic regression analysis of risk factors for hyperglycaemia among HIV patients at KNH

Variable	Odds ratio (95% CI)	P-value
Diabetes status	23 (3.206-165.022)	**0.002***
BMI	1.128 (0.958-1.328)	**0.150**
Age	1.027 (0.953-1.107)	**0.481**
Time from last meal taken	0.418 (0.107-1.629)	**0.209**
Current ART regimen	0.435 (0.051-3.674)	**0.444**

**Statistically significant*

The participants' diabetes status had a statisitically significant influence on hyperglycaemia (p=0.002). With a crude odds ratio of 23 (95% confidence interval [CI], 3.206-165.022), patients with diabetes were 23 times as likely as those without diabetes to be hyperglycaemic. BMI, age, time from last meal taken and the current ART regimen did not have any statistically significant association with hyperglycaemia.

4.11 Prevalence of hepatotoxicity

The most prevalent grade of hepatotoxicity was Grade I followed by Grade II with 13(12.2%) and 3 (2.8%) participants respectively. There were no cases of Grades III and IV hepatotoxicity.

In the TDF/3TC/DTG arm of the study, 9 (10.8%) participants had Grade I hepatotoxicity while 3 (3.6%) had Grade II. The TDF/3TC/NVP group had no cases of Grade II hepatotoxicity. However, the prevalence of Grade I hepatotoxicity in this group was slightly higher than in the TDF/3TC/DTG group with 4 (16.7%) participants as shown in Table 4.13. The difference in the prevalence of hepatotoxicity between the two regimens was not statistically significant (p=0.549).

Table 4.13: Prevalence of hepatotoxicity by severity and regimen (n=107; p=0.549)

Severity of hepatotoxicity	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	71 (85.5)	20 (83.3)
Grade I	9 (10.8)	4 (16.7)
Grade II	3 (3.6)	0 (0)
Grade III	0 (0)	0 (0)
Grade IV	0 (0)	0 (0)
Total	**83 (100)**	**24 (100)**

Bivariable logistic regression to test the association between hepatotoxicity and five predictor variables yielded the results shown in Table 4.14. The five variables were age, alcohol intake, current ART regimen, sex and time since initiation of ART.

Alcohol intake (p=0.666), current ART regimen (p=0.445) and sex (p=0.075) were not statistically significant predictors of hepatotoxicity. Age was the most statistically significant (p=0.001) predictor of hepatotoxicity (OR=1.105 (95% CI, 1.041-1.172).

Table 4.14: Findings of a bivariate logistic regression analysis of risk factors for hepatotoxicity among HIV patients at KNH

Variable	Odds ratio (95% CI)	P-value
Age	1.105 (1.041-1.172)	**0.001***
Alcohol intake	0.736 (0.183-2.964)	**0.666**
Current ART regimen	0.608 (0.170-2.181)	**0.445**
Sex	2.958 (0.895-9.770)	**0.075**
Time since initiation of ART	1.502 (1.103-2.046)	**0.01***

**Statistically significant*

Time since initiation of ART was also a statistically significant predictor of hepatotoxicity (p=0.01). On average, participants who had been on ART longer were 1.502 times as likely as those who had been on ART for a shorter time to have hepatotoxicity (OR=1.502 (95% CI, 1.103-2.046).

4.12 Prevalence of CNS effects

Five parameters were identified and graded under CNS effects. These parameters included insomnia, headaches, suicidal ideation/tendencies, depression and psychosis.

4.12.1 Prevalence of insomnia

Generally, the prevalence of insomnia was about 17%. Grade I insomnia was the most prevalent (7.2%) followed by Grades II and III with prevalences of 6.3% and 3.6% respectively (Table 4.15). The prevalence of Grade I insomnia was higher in the TDF/3TC/NVP arm of the study (16%) compared to the TDF/3TC/DTG arm (4.7%). Similarly, the prevalence of Grade II insomnia was also higher among participants on the TDF/3TC/NVP regimen (12%) than those on TDF/3TC/DTG (4.7%).

Table 4.15: Prevalence of insomnia by severity and regimen (n=111; p=0.072)

Severity of insomnia	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	74 (86.1)	18 (72)
Grade I	4 (4.7)	4 (16)
Grade II	4 (4.7)	3 (12)
Grade III	4 (4.7)	0 (0)
Total	**86 (100)**	**25 (100)**

In contrast, the prevalence of Grade III insomnia was approximately 4.7% in those on the TDF/3TC/DTG regimen and 0% in those on TDF/3TC/NVP. The differences in the prevalence of insomnia between the two groups were however not statistically significant (p=0.072).

Bivariable logistic regression was carried out to find out if there was any association between insomnia and a number of variables. The results are as shown in Table 4.16.

Table 4.16: Findings of a bivariate logistic regression analysis of risk factors for insomia among HIV patients at KNH

Variable	Odds ratio (95% CI)	P-value
Age	1.009 (0.962-1.058)	**0.713**
Current ART regimen	2.398 (0.827-6.957)	**0.107**
Sex	3.925 (1.069-14.409)	**0.039***

**Statistically significant*

Sex was the only variable with a statisitically significant association with insomnia (p=0.039). Female participants were about 4 times as likely as the male ones to have insomnia.

4.12.2 Prevalence of headaches

Overally the prevalence of headaches across the two groups was nearly 10% with Grade I headaches having the highest prevalence (7.2%) followed by Grade II (2.7%). There was no encounter of Grades III and IV headaches.

The prevalence of Grade I headaches was slightly higher in the TDF/3TC/NVP arm (8%) than that in the TDF/3TC/DTG arm (7%). Whereas there was no encounter of Grade II headaches in the TDF/3TC/DTG arm, the prevalence of those headaches was about 12% in the TDF/3TC/NVP arm (Table 4.17). The difference in the prevalence of headaches between the two groups was statistically significant (p=0.01).

Table 4.17: Prevalence of headaches by severity and regimen (n=111; p=0.01*)

Severity of headaches	**TDF/3TC/DTG**	**TDF/3TC/NVP**
	n (%)	**n (%)**
Normal	80 (93)	20 (80)
Grade I	6 (7)	2 (8)
Grade II	0 (0)	3 (12)
Grade III	0 (0)	0 (0)
Grade IV	0 (0)	0 (0)
Total	**86 (100)**	**25 (100)**

** Statistically significant*

4.12.3 Prevalence of suicidal ideation/tendencies

The prevalence of suicidal ideation/tendencies among all the participants was about 6.3%. Grade III suicidal ideation/tendency was the most prevalent (2.7%) followed by Grades I and II with a prevalence of 1.8% each.

Stratification of the prevalence of suicidal ideation/tendencies by regimen revealed that the prevalence of Grade I was 8% in the TDF/3TC/NVP arm and 0% in the TDF/3TC/DTG arm (Table 4.18). Additionally, the stratification showed that the prevalence of Grade II suicidal

ideation/tendencies was about 2.3% in those on the TDF/3TC/DTG regimen and 0% in the comparator regimen.

The TDF/3TC/NVP group had a slightly higher prevalence of Grade III suicidal ideation/tendencies (4%) than that in the TDF/3TC/DTG group (2.3%). The differences in the prevalence of suicidal tendencies/ideation across the regimens was not statistically significant (p=0.076).

Table 4.18: Prevalence of suicidal ideation by severity and regimen (n=111; p=0.076)

Severity of suicidal ideation	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)
Normal	82 (95.4)	22 (88)
Grade I	0 (0)	2 (8)
Grade II	2 (2.3)	0 (0)
Grade III	2 (2.3)	1 (4)
Grade IV	0 (0)	0 (0)
Total	**86 (100)**	**25 (100)**

Results of a bivariate regression analysis of suicidal ideation/tendencies against possible predictor variables did not find statistically significant association between suicidal ideation/tendencies and age (p=0.192), current regimen (p=0.199), sex (0.604) and history of mental illness (p=0.544). However, history of ADRs was significantly associated with suicidal ideation/tendencies (p=0.002). Participants who had experienced an ADR previously had 12 times the probability of those with no history of ADRs of having suicidal ideation/tendencies (OR=12.533, 95% CI, 2.449-64.145). These results are summarized in Table 4.19.

Table 4.19: Findings of a bivariate logistic regression analysis of risk factors for suicidal ideation/tendencies among HIV patients at KNH

Variable	Odds ratio (95% CI)	P-value
Age	0.958 (0.899-1.022)	**0.192**
History of ADR	12.533 (2.449-64.145)	**0.002***
Current ART regimen	2.795 (0.582-13.426)	**0.199**
Sex	1.563 (0.289-8.440)	**0.604**
History of mental illness	2 (0.214-18.721)	**0.544**

**Statistically significant*

4.12.4 Prevalence of depression

The study found no cases of depression among all the participants across the two regimens.

4.13 Prevalence of hypersensitivity reactions

In this study, two parameters of hypersensitivity reactions were identified and graded. These parameters included pruritus and the appearance of a rash.

4.13.1 Prevalence of pruritus

The overall prevalence of pruritus was about 10% in all the participants. Grade I pruritus was the most prevalent (8.1%) followed by Grade II (1.8%). There was a higher prevalence of Grade I pruritus in the TDF/3TC/NVP regimen (16%) than in the TDF/3TC/DTG regimen (5.8%).

Similarly, the prevalence of Grade II pruritus was also higher among the participants on TDF/3TC/NVP (8%) than those on TDF/3TC/DTG (0%). The study found no instances of Grade III pruritus as illustrated in Table 4.20. The difference in the prevalence of pruritus between the two groups was statistically significant (p=0.008).

Table 4.20: Prevalence of pruritus by severity and regimen (n=111; p=0.008*)

Severity of pruritus	**TDF/3TC/DTG**	**TDF/3TC/NVP**
	n (%)	**n (%)**
Normal	81 (94.2)	19 (76)
Grade I	5 (5.8)	4 (16)
Grade II	0 (0)	2 (8)
Grade III	0 (0)	0 (0)
Total	**86 (100)**	**25 (100)**

** Statistically significant*

4.13.2 Prevalence of rash

Generally, the prevalence of rash was very low (0.9%) across the two regimens. There were no reports of rash in the TDF/3TC/DTG regimen. The prevalence of Grade III rash in the TDF/3TC/NVP regimen was however 4%. There was no statistically significant difference in the prevalence of rash between the two regimens (p=0.225)

4.14 Other reported ADRs associated with the TDF/3TC/DTG regimen

Reports of ADRs by participants on the TDF/3TC/DTG regimen together with those in their medical records were obtained and recorded. This excluded all the ADRs that were part of the second objective of this study.

4.14.1 Participant-reported ADRs

Apart from dizziness and neuropathy which had frequencies of 3 and 2 respectively, these were mainly isolated cases whose causality and temporal sequence in some cases was difficult to establish. Table 4.21 contains a summary of the reported ADRs.

Table 4.21: Patient-reported ADRs when on TDF/3TC/DTG therapy (n=86)

ADR	Frequency	Period after start of medication	Concurrent drugs	Co-morbidity
Dizziness	3	Immediately	None	None
		2 – 3 days	Cotrimoxazole	None
		8 months	Cotrimoxazole	None
Loss of hair in two patches	1	1 month	None	None
Abdominal pain	1	2 – 3 days	Cotrimoxazole	None
Somnolence	1	2 – 3 days	Cotrimoxazole	None
Weight loss	1	3 months	None	None
Low blood pressure	1	3 months	None	None
Vivid dreams	1	2 days	None	None
Neuropathy	2	5 months	Glibenclamide 5mg, sitagliptin 50mg	Diabetes
		6 months	Metformin 500mg, Glibenclamide 5mg	Diabetes
Palpitation	1	5 months	Glibenclamide 5mg, sitagliptin 50 mg	Diabetes

The ADRs were reported to have occurred within a week of initiating therapy with TDF/3TC/DTG in slightly less than half of the cases (41.7%) and between 1 to 8months in about 58% of the reported ADRs.

In approximately 58% of the cases reported, the participants were on other drugs in addition to ARV drugs. The other 42% were not on any other drug concurrently. About 25% of the participants reportedly suffered from diabetes at the time of ADR occurrence.

4.14.2 Reports of ADRs extracted from medical records

The study found one isolated report of a case of acute psychosis which warranted a change in regimen from TDF/3TC/DTG to TDF/3TC/NVP. The psychotic symptoms resolved thereafter. There were no other reports.

4.15 Parsimonious models for the most important predictors

Multivariable logistic regression was done for three outcomes which had shown a statistically significant difference across the two regimens. The three outcomes were the viral load suppression rate, the prevalence of pruritus and the prevalence of headaches.

4.15.1 Parsimonious model for the most important predictors of viral load suppression rate

The four most important predictors of the viral load suppression rate were the current regimen, sex, time since initiation of ARV and the history of ADR of the patient (Table 4.22).

Table 4.22: Findings of logistic regression analysis for most important predictors of viral load suppression among HIV patients at KNH

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Current regimen	10.35 (3.29 – 32.53)	14.40 (3.41 – 60.84)	**<0.0001***
Gender	0.083 (0.011 – 0.651)	0.135 (0.015 – 1.185)	**0.071**
Time since initiation of ARV	1.270 (0.933 – 1.731)	1.547 (1.029 – 2.326)	**0.036***
History of ADR	0.257 (0.074 – 0.897)	0.241 (0.049 – 1.171)	**0.078**

**Statistically significant*

The most powerful predictor of viral load suppression with an odds ratio (OR) of 10.35 was the current regimen in which the participants were on (p=<0.0001). This meant that participants who were on the TDF/3TC/NVP regimen were 10 times as likely as those on TDF/3TC/DTG to be virally suppressed.

4.15.2 Parsimonius model for the most important predictors of the prevalence of pruritus

The results of a multivariate logisitic regression revealed that the four most important predictors of the prevalence of pruritus were time since initiation of current regimen, time since initiation of ARV, BMI and alcohol intake (Table 4.23).

Table 4.23: Findings of logistic regression analysis for most important predictors of the prevalence of pruritus among HIV patients at KNH

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Time since initiation of current regimen	1.556 (1.129 – 2.144)	2.018 (1.262 – 3.228)	**0.003***
Time since initiation of ARV	0.782 (0.555 – 1.103)	0.540 (0.328 – 0.890)	**0.016***
BMI	1.120 (0.966 – 1.299)	1.109 (0.945 – 1.301)	**0.206**
Alcohol intake	1.012 (0.201 – 5.089)	3.093 (0.398 – 24.055)	**0.281**

**Statistically significant*

Time since initiation of current regimen was the most powerful predictor of the prevalence of pruritus with an OR of 1.556 (p=0.003).

4.15.3 Parsimonius model for the most important predictors of the prevalence of headaches

Time since initiation of current regimen, history of ADR, concurrent medication and BMI were the four most important predictors of the prevalence of headaches as shown in Table 4.24.

Table 4.24: Findings of logistic regression analysis for most important predictors of the prevalence of headaches among HIV patients at KNH

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Time since initiation of current regimen	1.361 (0.985 – 1.881)	1.480 (1.032 – 2.123)	**0.033***
History of ADR	3.034 (0.699 – 13.161)	4.981 (0.973 – 25.507)	**0.054**
Concurrent medication	2.5 (0.702 – 8.904)	3.074 (0.738 – 12.804)	**0.123**
BMI	1.139 (0.981 – 1.323)	1.114 (0.945 – 1.313)	**0.198**

**Statistically significant*

Time since initiation of current regimen was the most powerful predictor of the prevalence of headaches with an OR of 1.361 (p=0.033).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study sought to compare DTG and NVP based regimens among HIV positive patients at KNH with regard to effectiveness and safety. Four aspects of safety were assessed consisting of hyperglycaemia, hepatotoxicity, CNS effects and hypersensitivity. Viral suppression was used as a measure of effectiveness.

5.1.1 Viral load suppression rate

In terms of the viral load suppression rate, the two regimens had a statistically significant difference ($p<0.001$). The TDF/3TC/DTG regimen was superior to the TDF/3TC/NVP in viral load suppression using both the WHO criterion and the Kenya HIV treatment guidelines. Using the WHO criterion, the TDF/3TC/DTG regimen had a viral load suppression rate of about 93% while the TDF/3TC/NVP had a viral load suppression rate of 56%.

Although there was no evidence in literature of a head to head comparison of the two regimens, the superior effectiveness of DTG over drugs in the NNRTI class was previously demonstrated in two studies christened the SINGLE and SPRING-1 studies. The SINGLE study was a randomized placebo controlled study. In that study, DTG/ABC/3TC was compared to TDF/FTC/EFV. At 48 weeks, 88% of patients on the DTG based regimen had achieved viral loads of <50 copies/mL compared to 81% of those who were on the EFV based regimen [83].

The SPRING-1study on the other hand was a randomized partially blinded study in which treatment naïve participants received three doses of DTG (10, 25 and 50mg) or EFV 600mg with a backbone of either ABC/3TC or TDF/FTC. At 96 weeks, 88% of the participants on the DTG 50mg based regimen had achieved viral suppression while 72% of those on the EFV based regimen were virally suppressed [129].

The lower efficacy of NVP could be attributed to the previous use of single dose NVP in the prevention of mother to child transmission which could have induced resistant mutations in both mothers and their offspring [94,95]. Moreover, NVP has been in use for a very long time and this coupled with the fact that the drug has a very low genetic barrier to mutation [97,98,110] may have led to the development of resistance. The dwindling effectiveness of NVP based regimens

has been shown before by Berg-Wolf et al in a study that compared long term treatment outcomes between NVP and EFV based regimens. AT 12 months, only 55% of participants in the NVP arm were virally suppressed [130].

The impact that the two regimens had on viral suppression was emphasised by the results obtained from the multivariable logistic regression analysis. The current regimen the participants were on had the most statistically significant association (p=<0.0001) with viral suppression. An adjusted odds ratio (AOR) of 14.4 (95% confidence interval [CI], 3.41-60.84) meant that participants on the TDF/3TC/NVP regimen were 14 times as likely as those on the TDF/3TC/DTG regimen to be virally suppressed.

Another variable with a statistically significant influence on viral suppression was the time since initiation of the current regimen (AOR 1.547(95% CI, 1.029-2.326; p=0.036). Our study found that participants who had been on ART longer were more likely to be virally suppressed. The distribution of the participants in the two regimens based on the time since initiation of the current regimen differed significantly (p=<0.001) with a majority of those on TDF/3TC/NVP (76%) having been initiated more than 3 years back. In contrast with this, all the participants in the TDF/3TC/DTG regimen had been on that regimen for less than 3 years. This fact notwithstanding, the TDF/3TC/DTG regimen still had a larger number of virally suppressed partiticipants and this further demonstrated its superior effectiveness.

5.1.2 Prevalence of hyperglycaemia

As expected, diabetes appeared to have statistically significant association with hyperglycaemia in this study (p=0.002). Diabetics were 23 times as likely as the non-diabetics to have hyperglycaemia (OR=23 (95% CI, 3.206-165.022). This could partially explain the higher prevalence of hyperglycaemia among the participants who had diabetes. In that sub-group, the TDF/3TC/DTG regimen had prevalences of 20% each of Grades I, II and III hyperglycaemia. Given that all the diabetics were on the TDF/3TC/DTG regimen and that the study did not assess the adherence of these participants to their diabetes medication, it was difficult to establish whether the high prevalence was due to uncontrolled diabetes or was due to an aggravation by the ARV drugs.

Whereas there have been some reports of an increasing occurrence of hyperglycaemia in patients using DTG based regimens [131,132], the study found no statisitically significant difference in the occurrence of hyperglycaemia among patients without diabetes across the two regimens (p=1.0). In this sub-group, the prevalence of Grade I hyperglycaemia was marginally higher in the TDF/3TC/DTG arm of the study (5.3%) than the TDF/3TC/NVP one (4.6%). Except for a prevalence of 1.3% of Grade II hyperglycaemia in the TDF/3TC/DTG regimen, there were no other reports of hyperglycaemia in this sub-group. This finding differs from that of the SAILING study that found a prevalence of 1% of Grades III to IV hyperglycaemia [86] and the SINGLE study that reported a prevalence of 7% of Grade I hyperglycaemia [83]. The difference could be attributed to the short duration of treatment of the participants in this study. There was no evidence in literature that linked NVP with hyperglycaemia.

5.1.3 Prevalence of hepatotoxicity

In both regimens, Grade I hepatototoxicity was the most prevalent. The TDF/3TC/NVP regimen had a higher prevalence of Grade I hepatotoxicity (16.7%) than the TDF/3TC/DTG regimen (10.8%). Contrastingly, the TDF/3TC/NVP regimen had no cases of Grade II hepatotoxicity whereas the TDF/3TC/DTG regimen had a prevalence of 3.6% of Grade II hepatotoxicity. These differences however, were not statistically significant.

A review of the clinical effectiveness of Dolutegravir by Taha et al found a similar trend. The prevalence of Grades II – IV hepatotoxicity was between 2% and 3% [41]. The SAILING study also found the prevalence of Grades III and IV hepatotoxicity to be 3%. The SAILING study was a randomized double blind non-inferiority study that compared DTG and RAL based regimens. A similar picture was seen in the SINGLE study that compared a DTG with an EFV based regimen. That study reported an incidence of Grades II to IV hepatotoxicity of 2% [83].

Whereas this study found no instances of Grade III and IV hepatotoxicity with the NVP based regimen, evidence from literature seemed to suggest higher prevalences of these two grades. A case in hand is the NNRTI sub-study of the FIRST study that reported prevalences of 15% and 8.5% of Grades III and IV hepatotoxicity respectively [130]. Nearly the same result was seen in a study by Schouten et al that assessed the safety and efficacy of NVP substitution. The study found a prevalence of 14% of Grades III and IV hepatotoxicity [133]

In our study, neither alcohol intake (p=0.666) nor the current ART regimen (p=0.445) were significant predictors of hepatotoxicity. Statistically significant preditors included the age of participants (p=0.001) and time since initiation of ART (p=0.01). The risk of hepatotoxicity seemed to increase significantly with the time that one was on ART (OR=1.502, 95% CI, 1.103-2.046) and very marginally with age (OR=1.105, 95% CI, 1.103-1.172).

5.1.4 Prevalence of CNS effects

Four parameters were investigated in this study: insomnia, headaches, suicidal ideation/tendencies and depression/psychosis. No cases of depression were reported. There were no statistically significant differences in the prevalence of insomnia (p=0.072) and suicidal ideation/tendencies (p=0.076).

Interestingly, the prevalence of insomnia was higher in the TDF/3TC/NVP arm of the study than in the TDF/3TC/DTG for Grades I and II. The TDF/3TC/DTG regimen had prevalences of 4.7% for Grades I, II and III insomnia while the TDF/3TC/NVP one had prevalences of 16% and 12% of Grades I and II insomnia. Whereas there were no statistically significant differences in the prevalence of insomnia between the two regimens as mentioned earlier, a prevalence of 4.7% of severe (Grade III) insomnia in the DTG arm may have clinical significance.The prevalence of insomonia among participants on TDF/3TC/DTG in this study was similar to that observed in the SINGLE study where the prevalence of Grades II-IV insomnia was about 4% at 48 weeks but different from that observed in the SPRING-2 study (<1%) [83,84].

The higher prevalence of insomnia for NVP based regimens is unprecedented in literature and could be related to the sex of the participants rather than the ART regimen. This assumption was strengthened by the results of a bivariate logistic regression analysis that found no statistically significant association between the current ART regimen (p=0.107) and insomnia. The analysis however did suggest that sex was significantly associated with insomnia (p=0.039). Female participants had about 4 times the probability of male participants of having insomnia (OR=3.925, 95% CI, 1.069-14.409). In this study, the TDF/3TC/NVP regimen had a significantly higher number of women (84%) than the TDF/3TC/DTG regimen (56%).

The study did not find significant differences in the prevalence of suicidal ideation/tendencies between the two regimens (p=0.072). The TDF/3TC/DTG regimen had prevalences of 2.3% each

of Grades II and III suicidal tendencies/ideation while the TDF/3TC/NVP had prevalences of 8% and 4% of Grades I and III suicidal ideation/tendencies. History of ADRs showed the greatest association with suicidal ideation/tendencies (p=0.002). Participants who had experienced an ADR previously were about 13 times as likely as those who had no history of ADRs of having suicidal ideation/tendencies (OR=12.533, 95% CI 2.449-64.145).

With regard to headaches, the TDF/3TC/NVP regimen had statistically significant higher prevalences of both Grades I and II headaches (p=0.01). The headaches appeared to be statistically significantly associated with the duration of time that one had been on their current ART regimen (p=0.033). Averagely, participants who had been on their current ART regimen longer had about 1.5 times the probability of those who had been on their current regimen for a shorter time of having headaches. Participants in the two regimens differed significantly in terms of how long they had been on their current ART regimen (p=<0.001) with those in the TDF/3TC/NVP regimen having been on their current regimen for a longer time. This could partially explain the higher prevalence of headaches among participants in that regimen. About 2 (8%) and 3 (12%) of participants in that regimen had Grades I and II headache respectively. This mirrors the finding of a review by Pollard et al that assessed the safety profile of NVP based on data from clinical trials [134]. The prevalence of mild to moderate headache in that study was about 7%.

The prevalence of headaches for the DTG based regimen in this study was 7% for Grade I headaches and 0% for Grades II, III and IV. This was lower than what had been reported in previous studies. The SPRING-2 study for example reported prevalences of 12% and14% at week 48 and 96 respectively for all grades of headache [84,135]. The prevalence of Grades III and IV headaches in that study however was less than 1%. Yet another study dubbed 'the SINGLE study' found a prevalence of 3% of Grades II to IV headaches [83]. A similar scenario was seen in the SAILING study which was a randomized, double blind, non-inferiority study that compared DTG and RAL in ART-experienced adults. The prevalence of headaches in that study was 9% at week 48 [86].

5.1.5 Prevalence of hypersensitivity reactions

This study assessed two parameters of hypersensitivity: pruritus and the appearance of a rash. There were significant differences in the prevalence of Grades I and II pruritus across the two

regimens (p=0.008) with the TDF/3TC/NVP regimen scoring higher in both. Most of the cases were mild in nature (Grade I) with prevalences of 16% for the TDF/3TC/NVP regimen and 5.8% for the TDF/3TC/DTG regimen. Whereas the TDF/3TC/DTG regimen had no cases of moderate (Grade II) pruritus, the TDF/3TC/NVP regimen had a prevalence of about 8%.

The occurrence of pruritus was significantly associated with the time since initiation of the current ART regimen (p=0.003). Participants who had been on their current ART regimen longer were about 1.5 times as likely as those who had been on theirs for a shorter time to have pruritus.

The prevalence of rash was generally low across the two regimens (0.9%) with no statistically significant difference across the two regimens (p=0.225). The TDF/3TC/NVP regimen had one case of severe rash (Grade III) representing a prevalence of about 4% while the TDF/3TC/DTG regimen had no reports of rash of any grade. Evidence from literature seemed to corroborate the rare encounters of rash with DTG based regimens with a study carried out in North America, Europe and Australia reporting an incidence of 1% [83]. However, the SAILING study reported a higher prevalence of about 5% [86].

The prevalence of rash reported in this study for the NVP based regimen was also significantly lower than that in literature. The FIRST study, a randomized comparative study of different ARV combinations for initial ART treatment, found a 16% prevalence of Grade III and IV rash.

5.1.6 Other reported ADRs associated with the TDF/3TC/DTG regimen

The study sought to find out other ADRs that may have been experienced by the participants from their medical records and from interviews. A total of 9 ADRs were reported by the participants while one was obtained from patient records. They included dizziness, abdominal pain, somnolence, weight loss, low blood pressure, vivid dreams, acute psychosis, palpitation, neuropathy and loss of hair in two patches.

Dizziness associated with the use of DTG based regimens has been reported in literature albeit with very low incidences. SINGLE, a phase III randomized double blind study, reported an incidence of Grades II to IV dizziness of less than 1% [83]. A similar incidence (<1%) was also reported in the SPRING-2 study that compared DTG and RAL combined with either ABC/3TC of TDF/FTC in a cohort of 822 subjects.

Cases of abdominal pain are also not new to DTG based regimens and were reported in a multicentre phase 3 randomised, double blind study. That study found a prevalence of 5% of upper abdominal pain [86]. Somnolence and abnormal dreams have been reported in five clinical trials with incidences ranging between 0 to 2% and 0 to 6% respectively [106].

The study found an isolated case of acute psychosis that led to treatment discontinuation. The case involved a 40 year old woman with a previous history of depression who had been switched from TDF/3TC/NVP to TDF/3TC/DTG. It is possible that the psychosis was related to the drug because the symptoms resolved when the participant was put back on the NVP based regimen. Evidence from literature shows that neuropsychiatric adverse events including psychosis are the most reported DTG related adverse events [136,137].

Additionally, study found one case each of weight loss and hair loss. There was no evidence in literature to suggest a causal relationship between these two symptoms and DTG containing regimens. Weight loss and hair loss have been listed among the 20 common symptoms associated with HIV disease or treatment [138].

Two cases of neuropathy and palpitations were reported by two participants in this study. While there is no evidence in literature associating DTG with either palpitations or neuropathy, some studies have linked the use of DTG based regimens to paraesthesia which is closely related to neuropathy [38,139]. It is however worth noting that the two participants also suffered from diabetes which has been associated with similar symptoms.

5.2 Conclusion

In conclusion, this first Kenyan study comparing DTG with NVP based regimens confirmed the superior effectiveness of the former in viral suppression. The study also found significantly higher prevalences of headaches and pruritus in the NVP based regimen than the DTG based regimen. There were no significant differences in the prevalences of hyperglycaemia, hepatotoxicity, insomnia, suicidal ideation/tendencies and rash. Other documented adverse effects associated with the TDF/3TC/DTG regimen in this study included dizziness, abdominal pain, somnolence, abnormal dreams and psychosis. Although more research needs to be done to assess the safety of

DTG especially with regard to undocumented patient reported adverse effects, the finding of this study paves way for the wider use of DTG in the country.

5.3 Recommendations

Given the superiority of TDF/3TC/DTG in regard to viral suppression and a relatively better safety profile, the study supports the Kenyan Government's decision to transition patients from NVP based regimens to DTG based ones and recommends its countrywide implementation.

The study also recommends further investigation on the effect of DTG on blood sugar control among HIV patients suffering from diabetes using a larger cohort of participants.

5.4 Study limitations

There were a number of limitations in this study. First, the study used a smaller sample size than had been projected and this may have had an impact on its statistical power. However, this only affected the NVP arm of the study but not the DTG one. Second, some aspects of the study relied on patient reports hence a risk of recall bias. This risk was minimized by using information obtained from participants' medical records in addition to participants' reports. Third, the study was observational in nature and therefore it was difficult to establish temporal sequence and by extension causality for some of the adverse events.

5.5 Study delimitations

Whereas there exists numerous backbone ART regimens that are used in combination with NVP and DTG, this study only focused on a common backbone ART regimen of TDF/3TC. This was because apart from being the recommended backbone regimen for both first and second line ART in the Kenya HIV treatment guidelines, this regimen also formed part of the ART regimen for a vast majority of HIV patients being managed at KNH at the time of the study.

Additionally, comparison of the safety of the two regimens only focused on four parameters based on reports from literature of their high frequency of occurrence and severity. The four included hepatotoxicity, hyperglycaemia, CNS effects and hypersensitivity reactions. The study did not assess the effect of the two regimens on other body systems such as the cardiovascular and the renal systems.

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APPENDICES

Appendix 1: Adult participant information and consent form

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

Introduction

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

May I continue? YES/NO

This study has been approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No……and approval reference No……

What is this research study about?

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

There will be approximately 200 participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

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

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

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

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

Are there any risks to my participation in this study?

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

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

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

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

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

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

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

What are my rights as a research study participant?

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

Who can I talk to if I have questions?

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

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

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

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

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

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

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

Participant name: _____

Participant signature/Thumb stamp _____Date_____

Researcher's Agreement

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

Researcher's signature _____

Date_____

You can contact the following researcher at;

Kevin Awere
School of Pharmacy, University of Nairobi
kevinawere@yahoo.com
0777 810 932

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

Kulinganisha usalama na ufanisi wa Nevirapine na Dolutegravir miongoni mwa wagonjwa wa virusi vya ukimwi katika Hospitali Kuu ya Kenyatta (Kenya)

Utangulizi

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

Naweza kuendelea? NDIO LA

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

Utafiti huu ni wa nini?

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

Kutakuwa na washiriki wapatao 200 waliochaguliwa kwa nasibu katika utafiti huu. Tunaomba ridhaa yako ili ushiriki katika utafiti huu.

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

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

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

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

Je, kuna hatari yoyote itakayonikumba nikishiriki katika utafiti huu?

Hatari moja ya kuwa katika utafiti ni uwezekano wa kupoteza faragha. Tutaweka mikakati kuweka maelezo yote utakayotupa siri. Njia moja ya kutekeleza wajibu huu itakuwa ni kutoandika jina lako katika vyombo vyetu vya ukusanyaji data. Badala ya jina, utapewa nambari ya kipekee itakayotumika kukutambua kwenye hifadhidata yetu itakayohifadhiwa na nenosiri. Kumbukumbu zote zitahifadhiwa katika kabati kitakachofungwa wakati wote kwa kufuli ili kuhakikisha ya kwamba ni mimi tu ndiye nitakayeweza kuzifikia au kuzitumia. Matokeo ya utafiti huu yanaweza kuchapishwa au kupelekwa kwenye mikutano ya kitaaluma lakini jina lako halitatumiwa au kuhusishwa na matokeo.

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

Huenda pia ukasikia uchungu kidogo wakati sampuli ya damu yako itakapochukuliwa lakini hatutarajii majeraha yoyote au matatizo kutokana na shughuli hiyo.

Kuna faida yoyote kwangu ikiwa nitaamua kushiriki katika utafiti huu?

Unaweza kunufaika kwa kupata vipimo viwili vya maabara bila ya kulipa, yaani kipimo cha kiwango cha sukari katika damu yako na kipimo cha kuangalia kama ini lako linafanya kazi vizuri. Tutakuelekeza kwa madaktari katika kliniki hii kwa ajili ya huduma na msaada zaidi ikiwa kutakuwa na sababu. Pia, maelezo utakayoyatoa yatatusaidia kuelewa vizuri faida na madhara ya dawa unazozitumia. Maelezo hayo vilevile yatachangia maarifa ya kisayansi na yanaweza kusaidia kufanya maamuzi ya baadaye juu ya uchaguzi wa dawa za kupunguza makali ya virusi vya ukimwi.

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

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

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

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

Ninaweza kuwasiliana na nani ikiwa nina maswali?

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

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

FOMU YA RIDHAA (TAARIFA YA RIDHAA)

Taarifa ya Mshiriki

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

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

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

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

Jina la mshiriki : _____

Sahihi / Alama ya kidole _____Tarehe _____

Mkataba wa Mtafiti

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

Sahihi ya Mtafiti _____

Tarehe_____

Unaweza kuwasiliana na mtafiti afuatayo ;

Kevin Awere

Shule ya Famasia ya Chuo Kikuu cha Nairobi

kevinawere@yahoo.com

0777 810 932

Appendix 3: Parental participant information and consent form for participants who are children

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

Introduction

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

May I continue? YES/NO

This study has been approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No……and approval No……

For children below 18 years of age we give information about the study to parents or guardians. We will go over this information with you and you need to give permission in order for your child to participate in this study. We will give you a copy of this form for your records. If the child is at an age that he/she can appreciate what is being done then he/she will also be required to agree to participate in the study after being fully informed.

What is this research study about?

The researcher listed above is interviewing individuals who are taking antiretroviral drugs. The purpose of the interview is to find out if the medication they are taking is working and whether they have experienced or are experiencing any side effects from their medication. Participants in

this research study will be asked questions about their experience with the antiretroviral drugs they are taking, whether they are on any other medication or have any other medical problems. Participants will also have the choice to undergo two tests to measure their blood sugar levels and to check if their liver is working well.

There will be approximately 200 participants in this study randomly chosen. We are asking for your consent to consider your child participating in this study.

What will happen if you decide you want your child to participate in this research study?
If you agree for your child to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 10 minutes. The interview will mainly focus on the medication your child is taking.

After the interview has finished, you will proceed to the hospital laboratory where a sample of your child's blood will be taken to test his/her blood sugar level and his/her liver function.

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

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

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

Your child may also feel some slight pain when his/her blood is being drawn but we do not anticipate any injury or complications arising from this.

Are there any benefits being in the study?

Your child may benefit by receiving free blood sugar and liver function testing. We will refer your child to doctors at this clinic for care and support where necessary. Also, the information you provide will help us better understand the benefits and harms of the medication your child is taking. This information is a contribution to science and may help in making future decisions on the choice of antiretroviral drugs.

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

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

What are your other choices?

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits. Just inform the study staff and the participation of your child in the study will be stopped. You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities

Who can I talk to if I have questions?

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

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

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study staff. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw it any time.

I understand that all efforts will be made to keep information regarding me and my child's personal identity confidential.

By signing this consent form, I have not given up my child's legal rights as a participant in this research study.

I voluntarily agree to my child's participation in this research study:

	Yes	**No**
I agree to have my child undergo liver function and blood sugar testing:	Yes	No
I agree to provide contact information for follow-up:	Yes	No

Parent/Guardian signature /Thumb stamp: _____ Date _____

Parent/Guardian printed name: _____

Researcher's Agreement

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

Researcher's signature _____

Date_____

You can contact the following researcher at;

Kevin Awere
School of Pharmacy, University of Nairobi
kevinawere@yahoo.com
0777 810 932

Appendix 4: Maelezo na fomu ya ridhaa ya wazazi wa washiriki ambao ni watoto

Kulinganisha usalama na ufanisi wa Nevirapine na Dolutegravir miongoni mwa wagonjwa wa virusi vya ukimwi katika Hospitali Kuu ya Kenyatta (Kenya)

Utangulizi

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

Naweza kuendelea? NDIO LA

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

Kwa watoto walio chini ya umri ya miaka 18, tunatoa maelezo juu ya utafiti kwa wazazi au walezi. Tutakupa hayo maelezo kisha utahitajika kutoa idhini yako kwanza ili mtoto wako ashiriki katika utafiti huu. Nitakupa nakala ya fomu hii kwa rekodi yako. Ikiwa mtoto wako amefika umri ambao anaweza kuelewa kitakachofanyika, naye pia atahitajika kutoa idhini yake baada ya kupewa maelezo yote kuhusu utafiti huu.

Utafiti huu ni wa nini?

Mtafiti aliyeorodheshwa hapo juu anahoji watu ambao wanatumia dawa za kupunguza makali ya virusi vya ukimwi. Lengo la mahojiano haya ni kujua kama dawa wanazozitumia zinafanya kazi

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

Kutakuwa na washiriki wapatao 200 waliochaguliwa kwa nasibu katika utafiti huu. Tunaomba ridhaa yako ili mtoto wako ashiriki katika utafiti huu.

Je, ni nini kitakachofuata ikiwa nitaamua mtoto wangu ashiriki katika utafiti huu?

Ikiwa utakubali mtoto wako ashiriki katika utafiti huu, mambo yafuatayo yatatokea: Utahojiwa na mtafiti katika eneo la faragha ambako utajisikia huru kujibu maswali. Mahojiano yatachukua kama dakika kumi na yatazingatia dawa ambazo mtoto wako anazitumia.

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

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

Je, kuna hatari yoyote itakayokumba mtoto wangu akishiriki katika utafiti huu?

Hatari moja ya kuwa katika utafiti ni uwezekano wa kupoteza faragha. Tutaweka mikakati kuweka maelezo yote utakayotupa siri. Njia moja ya kutekeleza wajibu huu itakuwa ni kutoandika jina la mtoto wako katika vyombo vyetu vya ukusanyaji data. Badala ya jina, mtoto wako atapewa nambari ya kipekee itakayotumika kumtambua kwenye hifadhidata yetu itakayohifadhiwa na nenosiri. Kumbukumbu zote zitahifadhiwa katika kabati kitakachofungwa wakati wote kwa kufuli ili kuhakikisha ya kwamba ni mimi tu ndiye nitakayeweza kuzifikia au kuzitumia. Matokeo ya utafiti huu yanaweza kuchapishwa au kupelekwa kwenye mikutano ya kitaaluma lakini jina la mtoto wako halitatumiwa au kuhusishwa na matokeo.

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

Huenda pia mtoto wako akasikia uchungu kidogo wakati sampuli ya damu yake itakapochukuliwa lakini hatutarajii majeraha yoyote au matatizo kutokana na shughuli hiyo.

Kuna faida yoyote kwangu ikiwa nitaamua mtoto wangu ashiriki katika utafiti huu?

Mtoto wako anaweza kunufaika kwa kupata vipimo viwili vya maabara bila ya kulipa, yaani kipimo cha kiwango cha sukari katika damu yake na kipimo cha kuangalia kama ini lake linafanya kazi vizuri. Tutaelekeza mtoto wako kwa madaktari katika kliniki hii kwa ajili ya huduma na msaada zaidi ikiwa kutakuwa na sababu. Pia, maelezo utakayoyatoa yatatusaidia kuelewa vizuri faida na madhara ya dawa mtoto wako anazozitumia. Maelezo hayo vilevile yatachangia maarifa ya kisayansi na yanaweza kusaidia kufanya maamuzi ya baadaye juu ya uchaguzi wa dawa za kupunguza makali ya virusi vya ukimwi.

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

Hakutakuwa na gharama kwako mtoto wako akishiriki katika utafiti huu. Hutapata fedha au aina yoyote ya fidia mtoto wako akishiriki katika utafiti huu.

Je, uko na chaguo gani zingine?

Uamuzi wako wa kukubali mtoto wako ashiriki katika utafiti huu ni kwa hiari. Uko huru kukataa mtoto wako asishiriki au kumwondoa wakati wowote kutoka kwa utafiti huu bila ya kudhulumiwa au kuadhibiwa kwa njia yoyote. Utahitajika tu kuambia mfanyi kazi yeyote wa utafiti kuwa ungependa kuondoa mtoto wako na ataondolewa kutoka kwa utafiti. Vilevile, sio lazima utoe sababu yoyote ya kumwondoa mtoto wako ikiwa hutaki kufanya hivyo. Kuondoa mtoto wako kutoka kwa utafiti hautaathiri kwa namna yoyote huduma ambazo ana haki ya kupokea katika hospitali hii au hospitali ingine yoyote, sasa na siku za usoni.

Ninaweza kuwasiliana na nani ikiwa nina maswali?

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

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

FOMU YA RIDHAA (TAARIFA YA RIDHAA)

Mtu anayeombwa kushiriki katika utafiti huu hawezi toa idhini kwa niaba yake mwenyewe kwa sababu ni mtoto aliye na umri chini ya miaka 18. Unaombwa kutoa idhini ili mtoto wako ajumuishwe katika utafiti huu.

Taarifa ya Mshiriki

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

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

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

Nakubali mtoto wangu ashiriki katika utafiti huu:	**Ndiyo**	**Hapana**
Nakubali kutoa maelezo ya mawasiliano kwa ufuatiliaji:	Ndiyo	Hapana

Nakubali mtoto wangu afanyiwe vipimo vya maabara vya kupima kiwango cha sukari na kupima ikiwa ini lake linafanya kazi vizuri: Ndiyo Hapana

Jina la mzazi/mlezi : _____

Sahihi / Alama ya kidole _____Tarehe _____

Mkataba wa Mtafiti

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

Sahihi ya Mtafiti _____

Tarehe_____

Unaweza kuwasiliana na mtafiti afuatayo ;

Kevin Awere

Shule ya Famasia ya Chuo Kikuu cha Nairobi

kevinawere@yahoo.com

0777 810 932

Appendix 5: Child assent form

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

Introduction

My name is Kevin Awere. We are doing a research study to find out if the medication you are taking is working and whether you have experienced or are experiencing any side effects from your medication.

Permission has been granted to undertake this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC Protocol No..... and approval No.....)

This research study is a way to learn more about people. At least 10 children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be asked some questions about your medicines. You will also have the choice to undergo two tests to measure your blood sugar levels and to check if your liver is working well.

There are some things about this study you should know. First, we will keep everything you tell us here a secret and no one else will know what you tell us. To make sure this happens, we will hide your real name and give you a secret number.

Second, you do not have to answer any question that you do not like or feel uncomfortable answering.

Third, you may feel some little pain when a blood sample is being taken from you for the laboratory tests. Apart from that we do not expect any other problem.

Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. We think these benefits might be making sure that your medicine is working and is safe.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

_____ _____

(Signature/Thumb stamp) (Date)

Appendix 6: Fomu ya Idhini ya watoto

Kulinganisha usalama na ufanisi wa Nevirapine na Dolutegravir miongoni mwa wagonjwa wa virusi vya ukimwi katika Hospitali Kuu ya Kenyatta (Kenya)

Utangulizi

Jina langu ni Kevin Awere. Tunafanya utafiti ili kujua kama dawa unazozitumia zinafanya kazi vizuri na ikiwa umewahi pata au unapata madhara yoyote kutokana na dawa zako.

Utafiti huu umeidhinishwa na kamati ya Maadili na Utafiti ya Hospitali Kuu ya Kenyatta-Chuo Kikuu cha Nairobi. Nambari ya usajili.....na nambari ya kuidhinishwa.....
Utafiti huu ni njia ya kujua mengi kuhusu watu. Angalau watoto 10 watashiriki katika utafiti huu na wewe.

Ikiwa utaamua kuwa unataka kushiriki katika utafiti huu, utaulizwa maswali kadhaa kuhusu dawa zako. Utakuwa pia na chaguo la kufanyiwa vipimo viwili vya maabara; moja ya kupima kiwango cha sukari kwa damu yako na kingine cha kuangalia kama ini lako linafanya kazi vizuri.

Kuna baadhi ya mambo kuhusu utafiti huu ambayo unapaswa kujua. Kwanza, tutaweka kila kitu utakachotuambia hapa siri na hakuna mtu mwingine atajua ulichotuambia. Kuhakikisha kwamba hii inafanyika, tutaficha jina lako halisi na kukupa nambari ya siri.

Pili, si lazima ujibu swali lolote ambalo hulipendi au ambalo hutaki kulijibu.

Tatu, huenda ukasikia uchungu kidogo wakati sampuli ya damu itachukuliwa kutoka kwako kwa ajili ya vipimo vya maabara. Mbali na hiyo hatutarajii shida nyingine yoyote.

Si kila mtu anayeshiriki katika utafiti huu atafaidika. Faida ina maana kwamba kitu kizuri kitatokea kwako. Faida ambayo tunatarajia ni kuhakikisha kuwa dawa zako zinafanya kazi vizuri na ni salama.

Tutakapomaliza utafiti huu tutaandika ripoti kuhusu kile tulichojifunza. Ripoti hii haitajumuisha jina lako au kuashiria ya kwamba ulikuwa katika utafiti.

Si lazima ushiriki katika utafiti huu ikiwa hutaki. Hakuna shida pia ukiamua kujiondoa kutoka kwa utafiti baada ya kuingia na kuanza. Wazazi wako wanajua kuhusu huu utafiti pia.

Ikiwa umeamua unataka kuwa katika utafiti huu, tafadhali andika jina lako.

Mimi,_____, nataka kuwa katika utafiti huu.

_____ _____

(Sahihi / Alama ya kidole) (Tarehe)

Appendix 7: Grading of CNS effects

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

PARAMETER	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (POTENTIALLY LIFE THREATENING)
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	Not applicable
Psychiatric disorders (Depression or Psychosis)	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or attempt	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted
Headaches	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Source: Division of AIDS table for grading the severity of adult and paediatric adverse events [128]

Appendix 8: Grading of Hypersensitivity

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

PARAMETER	**GRADE 1 (MILD)**	**GRADE 2 (MODERATE)**	**GRADE 3 (SEVERE)**	**GRADE 4 (POTENTIALLY LIFE THREATENING)**
Pruritus	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	Not applicable
Rash	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Source: Division of AIDS table for grading the severity of adult and paediatric adverse events [128]

Appendix 9: Data Collection Form

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

DATA COLLECTION FORM

Patient Biodata

Participant Unique Number.....	Sex.....
Age (years).....	Weight (Kg).....
Height (cm).....	BMI.....

Social History

Cigarette smoker: Yes ☐	Takes alcohol: Yes ☐
No. of cigarettes per day.....	No. of bottles per day.....
No ☐	No ☐

Current regimen: TDF/3TC/DTG ☐ Date started:.....

TDF/3TC/NVP ☐

Previous regimen:..... Date changed:.....

Reason for change: ☐ Virological treatment failure

☐ Clinical treatment failure

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

☐ Other (Specify).....

☐ Unspecified

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

Drug allergies ☐ Yes (Specify).....

☐ No

Food allergies ☐ Yes (Specify).....

☐ No

Lab results before and after initiation of current therapy

Test	Value	Date
Viral load (copies/mL)		
Random blood sugar (mmol/L)		
Alanine Aminotransferase (U/L)		
CD4 (cells/mm^3)		

Medical History

Active Tuberculosis ☐ Yes

☐ No

History of mental illness ☐ Yes

☐ No

WHO HIV Staging at initiation of therapy: ☐ Stage I

☐ Stage II

☐ Stage III

☐ Stage IV

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

Appendix 10: Data Collection Questionnaire

Comparison of the safety and effectiveness of Nevirapine and Dolutegravir in HIV patients at the Kenyatta National Hospital

DATA COLLECTION QUESTIONNAIRE

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

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

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

1. a) Which drug regimen are you currently on? ☐TDF/3TC/DTG
   ☐ TDF/3TC/NVP

   b) Approximately how long have you been on your current regimen?.....

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

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

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

   ☐ After

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

   ☐ Never

   ☐ Once in a while

   ☐ Sometimes

   ☐ Usually

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

   ☐ No

   If answer to 1(g) is NO then jump to question 2.

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

   .....

   .....

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

.....

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

.....

k) Were you on any other drugs at the time? ☐ Yes ☐ No

l) If yes in (k), which drugs?.....

.....

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

2. Do you have any allergies? ☐ Yes (specify).....

☐ No

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

A – No difficulty
B – Mild difficulty
C – Moderate difficulty
D – Severe difficulty

a) Do you get any difficulty falling asleep? A B C D
b) Do you get any difficulty staying asleep? A B C D
c) Do you get any difficulty waking up early? A B C D

4. a) Have you ever been diagnosed with a mental illness? ☐ Yes
☐ No

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

b) If yes in (a), which one? ☐ Depression ☐ Mania ☐ Psychosis
☐ Don't know ☐ Other

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

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

e) What action was taken? ☐ No action ☐ Hospitalisation ☐ Medication

☐ Other (Specify)

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

A - No or minimal interference with usual social & functional activities
B - Greater than minimal interference with usual social & functional activities
C - Inability to perform usual social & functional activities
D - Inability to perform basic self-care functions

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

g) Did you harm or threaten to harm yourself or others? ☐ Yes ☐ No

5. a) Have you ever had headaches after taking your medication? ☐Yes ☐ No

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

b) Have you ever been hospitalised for the headaches? ☐ Yes ☐ No

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

A - No or minimal interference with usual social & functional activities
B - Greater than minimal interference with usual social & functional activities
C - Inability to perform usual social & functional activities
D - Inability to perform basic self-care functions

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

6. a) Do you suffer from any other illness? ☐ Yes ☐ No

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

.....

7. Are you on any other medications other than the antiretrovirals and cotrimoxazole?.....

.....

.....

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

☐ Alcohol ☐ Cigarette ☐ Miraa (Khat) ☐ Other (Specify).....

☐ Herbal medication

9. a) Have you ever felt itchy after taking your medication? ☐ Yes ☐ No

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

A - No or minimal interference with usual social & functional activities
B - Greater than minimal interference with usual social & functional activities
C - Inability to perform usual social & functional activities

b) If yes in (a) to what extent did the itchiness affect your day to day activities?
A B C

10. a) Have you ever had a skin reaction because of your medication? ☐ Yes ☐ No

b) If yes in (a), what type of reaction was it? ☐ Rash in one part of the body

☐ Rash all over the body

☐ Rash all over the body and vesicles

☐ Other (Specify).....

.....

c) Were you hospitalised because of the reaction? ☐ Yes ☐ No

11. a) Have you ever found yourself thinking about death a lot? ☐ Yes ☐ No

b) Have you ever thought of taking your own life? ☐ Yes ☐ No

c) Have you ever made plans to take your own life? ☐ Yes ☐ No

d) Have you ever been hospitalised because of thinking or planning to take your own life? ☐ Yes ☐ No

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

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

Appendix 11: Maswali ya ukusanyaji data

Kulinganisha usalama na ufanisi wa Nevirapine na Dolutegravir miongoni mwa wagonjwa wa virusi vya ukimwi katika Hospitali Kuu ya Kenyatta (Kenya)

MASWALI YA UKUSANYAJI DATA

Nambari ya kipekee:..... Tarehe ya mahojiano.....

Jinsia: ☐ Mume ☐ Kike Tarehe ya kuzaliwa..... Miaka.....

Kwa maswali yaliyo na chaguo zaidi ya moja, chagua jibu MOJA lililo sahihi zaidi.

1. a) Ni dawa gani unazozitumia kwa sasa? ☐ TDF/3TC/DTG
   ☐ TDF/3TC/NVP

   b) Umetumia dawa hizo kwa takriban muda gani?.....

   c) Kwa kawaida huwa unameza dawa zako saa ngapi?.....

   d) Huwa unameza tembe ngapi kwa siku?.....

   e) Huwa unameza dawa kabla au baada ya kula? ☐ Kabla

   ☐ Baada

   f) Kumeza dawa si rahisi. Je, wakati mwingine huwa unasahau kumeza dawa zako?

   ☐ Kamwe

   ☐ Mara moja moja

   ☐ Mara nyingine

   ☐ Kila mara

   g) Dawa zako zimewahi kukudhuru kwa njia yeyote? ☐ Ndio

   ☐ La

   Ikiwa jibu la 1(g) ni LA ruka hadi swali namba 2.

   h) Dawa hizo zilikudhuru kwa njia gani?.....

   .....

   .....

i) Ulikuwa umetumia dawa zako kwa mda gani kabla ya madhara kutokea?.....

.....

j) Ni hatua gani ilichukuliwa?.....

.....

k) Kuna dawa zingine ulikuwa unatumia wakati huo? ☐ Ndio ☐ La

l) Ikiwa jibu la (k) ni ndio, dawa gani?.....

.....

m) Dawa ulizoziorodhesha (l) zilikuwa za nini?.....

2. Je, uko na allergies zozote? ☐ Ndio (fafanua).....

☐ La

3. Kwa maswali yanayofuata, chagua herufi iliyo na jibu sahihi zaidi kulingana na jedwali ifuatayo.

A – Hakuna ugumu
B – Ugumu mdogo
C – Ugumu wa wastani
D – Ugumu mwingi

d)	Je, unapata ugumu wowote kupata usingizi?	A	B	C	D
e)	Je, unapata shida yoyote kubakia usingizini?	A	B	C	D
f)	Je, unapata ugumu wowote kuamka mapema?	A	B	C	D

4. a) Je, umewahi kuwa na ugonjwa wa kiakili? ☐ Ndio
☐ La

Ikiwa jibu la 4(a) ni La ruka hadi swali namba 5.

b) Ikiwa jibu la (a) ni Ndio, ugonjwa gani? ☐ Depression ☐ Mania ☐ Psychosis
☐ Sijui ☐ Ingine

c) Ulipatakana na ugonjwa huo lini?.....

d) Je, ulikuwa na dalili gani?.....
.....

e) Ni hatua gani iliyochukuliwa? ☐ Hakuna ☐ Lazwa hospitalini ☐ Madawa

☐ Nyingine (fafanua).....

Kwa swali 4(f) tumia jedwali ifuatayo kuchagua jibu lililo sahihi zaidi

A - Haikuathiri au iliathiri kwa kiwango kidogo shughuli za kawaida za kijamii na kazi

B - Iliathiri kwa kiwango zaidi ya kidogo shughuli za kawaida za kijamii na kazi

C – Sikuweza kufanya shughuli za kawaida za kijamii na kazi

D – Sikuweza kufanya kazi za msingi za kujitegemea

f) Je, ugonjwa huo uliathiri shughuli zako za kila siku vipi? A B C D

g) Je, ulijidhuru au kutishia kujidhuru wewe au wengine? ☐ Ndio ☐ La

5. a) Je, umewahi kuumwa na kichwa baada ya kumeza dawa zako? ☐ Ndio ☐ La

Ikiwa jibu la 5(a) ni La ruka hadi swali namba 6.

b) Umewahi lazwa hospitalini juu ya kuumwa na kichwa? ☐ Ndio ☐ La

Kwa swali 5(c) tumia jedwali ifuatayo kuchagua jibu lililo sahihi zaidi

A - Haikuathiri au iliathiri kwa kiwango kidogo shughuli za kawaida za kijamii na kazi

B - Iliathiri kwa kiwango zaidi ya kidogo shughuli za kawaida za kijamii na kazi

C – Sikuweza kufanya shughuli za kawaida za kijamii na kazi

D – Sikuweza kufanya kazi za msingi za kujitegemea

c) Je, kuumwa na kichwa iliathiri shughuli zako za kila siku vipi? A B C D

6. a) Je, uko na magonjwa mengine yoyote? ☐ Ndio ☐ La

b) Ikiwa jibu la (a) ni ndio, magonjwa gani?.....

.....

7. Kando na dawa za kupunguza makali ya virusi vya ukimwi na cotrimoxazole, unatumia dawa zingine zozote ?.....

.....

8. Je, wewe hutumia yafuatayo? (Jibu zaidi ya moja imekubalika)

☐ Pombe ☐ Sigara ☐ Miraa (Khat) ☐ Nyingine (fafanua).....

☐ Madawa ya kienyeji

9. a) Je, umewahi hisi kujikuna baada ya kumeza dawa zako? ☐ Ndio ☐ La

Kwa swali 9(b) tumia jedwali ifuatayo kuchagua jibu lililo sahihi zaidi

A - Haikuathiri au iliathiri kwa kiwango kidogo shughuli za kawaida za kijamii na kazi

B - Iliathiri kwa kiwango zaidi ya kidogo shughuli za kawaida za kijamii na kazi

C – Sikuweza kufanya shughuli za kawaida za kijamii na kazi

b) Ikiwa jibu la (a) ni ndio, kujikuna iliathiri shughuli zako za kila siku vipi?

A B C

10. a) Je, umewahi pata shida yoyote ya ngozi kutokana na dawa zako? ☐ Ndio ☐ La

b) Ikiwa jibu la (a) ni ndio, ilikuwa shida gani?

☐ Vipele kwenye sehemu moja ya mwili

☐ Vipele kila sehemu ya mwili

☐ Vipele na vilengelenge (majipu) kila sehemu ya mwili

☐ Nyingine (fafanua).....

c) Je, ulilazwa hospitalini kwa sababu ya shida hiyo ya ngozi? ☐ Ndio ☐ La

11. a) Je, umewahi jipata ukifikiria kuhusu kifo sana? ☐ Ndio ☐ La

b) Je, umewahi kuwa na mafikira ya kujitoa uhai? ☐ Ndio ☐ La

c) Je, umewahi kuwa na mipango ya kujitoa uhai? ☐ Ndio ☐ La

d) Je, umewahi lazwa hospitalini kwa sababu ya mafikira au mipango ya kujitoa uhai?

☐ Ndio ☐ La

12. Je, ulikula mwisho leo saa ngapi?

☐ Chini ya saa 1 iliyopita ☐ Kati ya masaa 1-2 iliyopita ☐ Zaidi ya masaa 2 iliyopita

Appendix 12: Dummy tables

Table 1: Participant baseline characteristics

Variable		TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	TOTAL n (%)	p-value
Age	>15 years				
	<15 years				
	Total				
Sex	Male				
	Female				
	Total				
Alcohol intake					
Cigarette Smoking					
Diabetes					
Renal disease					
Concurrent medication					

Table 2: Prevalence of CNS effects

Adverse Drug Reaction		TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
Insomnia	Grade 1			
	Grade 2			
	Grade 3			
	Total			
Psychosis	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			
Depression	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			
Suicidal ideation/attempt	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			
Headaches	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			

Table 3: Prevalence of hypersensitivity reactions

Adverse Drug Reaction		TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
Pruritus	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			
Rash	Grade 1			
	Grade 2			
	Grade 3			
	Grade 4			
	Total			

Table 4: Prevalence of hyperglycaemia

Severity of hyperglycaemia	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Total			

Table 5: Prevalence of hepatotoxicity

Severity of hepatotoxicity	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Total			

Table 6: Number of patients achieving viral suppression

Viral load	TDF/3TC/DTG n (%)	TDF/3TC/NVP n (%)	P-value
<50 copies/mL			
<1000copies/mL			

Table 7: Output for logistic regression analysis showing the relationship between selected predictor variables and the occurrence of ADRs

Variable	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	P-Value
Age			
Sex			
Alcohol intake			
Cigarette smoking			
Diabetes			
Renal disease			
Concurrent medication			

Appendix 13: Ethical approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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05 MAR 2019

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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/79

5th March, 2019

Awere Kevin Okech
Reg. No.U51/7549/2017
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Kevin

RESEARCH PROPOSAL: COMPARISON OF THE SAFETY AND EFFECTIVENESS OF NEVIRAPINE AND DOLUTEGRAVIR BASED REGIMENS IN HIV PATIENTS AT THE KENYATTA NATIONAL HOSPITAL(KENYA) (P872/12/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 5th March 2019 – 4th March 2020.

This approval is subject to compliance with the following requirements:

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

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July 31 2019

Dr. Kevin Okech Awere
Reg. No.U51/7549/2017
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Awere

Re: Approval of modifications– study titled 'Comparison of the safety and effectiveness of Nevirapine and Dolutegravir based regimens in HIV patients at the Kenyatta National Hospital (Kenya) (P872/12/2018)

Refer your communication dated 9th July 2019.

Upon review, the KNH-UoN ERC has **approved** downward adjustment of sample size due to reduced number of available patient population. This is probably due to the recent policy shift. This is a justifiable request.

These changes are reflected in the revised document.

Yours sincerely

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

c.c. The Principal, College of Health Sciences, UoN
The Director CS, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UON
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