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DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

BURDEN OF NEUROPSYCHIATRIC ADVERSE EFFECTS AND CHANGES IN WEIGHT AMONG HIV INFECTED PATIENTS SWITCHED FROM AN EFAVIRENZ BASED TO A DOLUTEGRAVIR BASED FIRST LINE REGIMEN AT THE KENYATTA NATIONAL HOSPITAL.

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any other university. All resources and materials used have been acknowledged by means of reference.

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DEDICATION

I dedicate this work to my parents, without them any of this would not be possible.

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ABREVIATIONS

ABC: Abacavir

ACTG: AIDS clinical trials group

AE: Adverse effect

AIDS: Acquired immunodeficiency syndrome

ART: Antiretroviral therapy

ARV: Antiretroviral

BMI: Body mass index

CCC: Comprehensive care clinic

CNS: Central nervous system

CVD: Cardiovascular disease

DAIDS: Division of AIDS

DM: Diabetes mellitus

DTG: Dolutegravir

EFV: Efavirenz

EVG: Elvitegravir

FTC: Emtricitabine

HIV: Human immunodeficiency virus

HTN: Hypertension

INSTI: Integrase strand transfer inhibitor

LPVr: Lopinavir/ritonavir

MC4R: Melanocortin 4 receptor

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NPAE: Neuropsychiatric adverse effects

NRTI: Nucleoside reverse transcriptase inhibitor

OCT 2: Organic cation transporter

PI: Protease inhibitor

PLHIV: Persons living with HIV

PSQI: Pittsburgh sleep quality index

RAL: Raltegravir

TAF: Tenofovir alafenamide

TDF: Tenofovir disoproxil fumarate

UON: University of Nairobi

VL: Viral load

WHO: World Health Organization

3TC: Lamivudine

DEFINITION OF KEY TERMS

Adverse effects: unwanted harmful effect as a result of medication use.

Integrase strand transfer inhibitors: antiretroviral agents that inhibit the strand transfer step of HIV integration into host DNA.

Body mass index: assessment of a person's weight with respect to their height

ABSTRACT

Background: Current WHO guidelines recommend the use of integrase strand transfer inhibitors (INSTIs) as the first line alternative to efavirenz (EFV). Compared to EFV, INSTIs are associated with fewer adverse effects, less drug interactions and a higher genetic barrier to resistance (2). Several concerns are emerging regarding the adverse effects INSTIs especially their effects on weight and the neuropsychiatric adverse effects (NP-AEs). There is limited data in Kenya on the adverse effects of INSTIs among patients initiated on or switched to dolutegravir (DTG) as a first line alternative to EFV.

Objectives: The main objective of this study was to compare the changes in body weight over a 6 month period and burden of neuropsychiatric adverse effects (NP-AEs) among HIV infected patients switched to a DTG-based regimen versus those on an EFV-based regimen. Some of the factors associated with excess weight gain and NP-AEs were also explored.

Methodology: This was a retrospective cohort study with a cross sectional arm, carried out at the KNH Comprehensive Care Clinic over a period of 3 months. Participants who met the inclusion criteria and gave written informed consent were enrolled into the study. A study proforma was used to obtain socio-demographic and clinical data including the changes in body weight over a period of 6 months. CNS toxicity and insomnia severity index questionnaire were used to establish the presence and severity of the NP-AEs. Data analysis was done using SPSS version 21.0 (Chicago- Illinois). A p value of ≤ 0.05 was interpreted as significant.

Results: 526 participants were included in the study; 272 had been switched to a DTG-based regimen and 254 were on an EFV-based regimen. Participants on DTG gained significantly more weight at 6 months (mean +2.4kg, SD 3.9, 95% CI 1.9-2.9) compared to those on EFV (mean +0.2kg, SD 2.7, 95% CI 0.14-0.5). 18% of the participants on DTG had excess weight gain ($\geq$ 10% increase in body weight or progression to a higher BMI category for those with initially normal BMI) compared to 7.1% among those on EFV (95% CI [1.6- 5.1], $p<0.001$). Being on a DTG-based regimen was the main factor associated with excess weight gain even after adjusting for variables such as age and gender. The burden of NP-AEs was higher among participants on EFV compared to those on DTG (29.5% versus 22.8% respectively, [p=0.079]). There was no significant difference in the burden of insomnia among participants in the two study groups (p=0.381). On multivariate analysis, mean antiretroviral therapy (ART) duration was significantly associated with NP-AEs (OR 1.15, [95% CI 1.07-1.23], $p<0.01$).

Conclusion: Our study showed that patients on DTG-based ART regimen gain significantly more weight compared to those on EFV-based regimens. The prevalence of neuropsychiatric adverse effects and neuropsychiatric toxicity was higher among patients on EFV-based regimen.

CHAPTER ONE

1.0 INTRODUCTION AND PROBLEM STATEMENT

Since the discovery of HIV in 1983, significant progress has been made towards its management using antiretroviral (ARV) agents. Development and approval of newer ARV agents has led to simplification of regimens (fixed drug combinations are now available), safer tolerability profile and improvements in their genetic barrier to resistance (5) (6) (7). Currently, six different ARV classes are available namely: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), INSTIs, fusion and entry inhibitors.

Current WHO recommendations advocate for the use of 2 NRTIs + 1 NNRTI as first-line therapy, with an INSTI as an alternative to the NNRTI (2). INSTIs have fewer side effects, fewer drug interactions and a higher genetic barrier to resistance. Dolutegravir (an INSTI) is available as single tablet regimen co-formulated with TDF/3TC or ABC/3TC and is currently included in most first-line regimens. Kenya has used an efavirenz based regimen (NNRTI) as the preferred first line for patients initiating antiretroviral therapy since 2010. Dolutegravir (DTG) in combination with 2 NRTIs was adopted in 2017 as a first-line ART option for adults with HIV infection and with no contraindications to DTG use. Adult patients who are on an EFV-based first line regimen and are virally suppressed are being switched to a DTG-based regimen (60).

There are emerging concerns regarding adverse effects of DTG that were not apparent in the initial short-term efficacy trials. Recent studies have shown an excess increase in weight among patients who were switched to an INSTI- based regimen with the greatest increase in weight seen with dolutegravir. This effect of INSTIs seems to be more pronounced in women and people of African descent (9). Since PLHIV are at an increased risk of cardiovascular diseases, the possible effect of dolutegravir on weight leading to overweight and obesity needs to be evaluated.

There have also been reports of a higher burden of neuropsychiatric adverse events than what was previously anticipated among patients switched to an INSTI-based regimen. CNS symptoms including dizziness, nervousness, depression, headache, reduced concentration, insomnia and

other sleep problems have been reported (3) (35) (39). There is limited data on neuropsychiatric adverse events of dolutegravir among PLHIV in Kenya and there are no current guidelines on how or when to screen for these adverse effects.

The objective of this study was to determine and compare changes in body weight over a 6 month period, the burden and spectrum of neuropsychiatric adverse effects among HIV infected patients switched to a DTG-based regimen versus those on an EFV-based regimen.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 INTRODUCTION

Approximately 36.9 million people worldwide are living with HIV translating to a global prevalence of 0.9% among adults. Sub- Saharan Africa remains largely affected by this epidemic with 66% of all the PLHIV are from this region (1). ART coverage has increased significantly to 59% globally by the end of 2017. In Kenya, it is estimated that 1.5 million people are living with HIV, with 68% of these on ART (1).

The scale up in ART has had an impact on the profile of HIV patients. The pattern of morbidity among PLHIV has changed with a decrease in the incidence of AIDS related deaths (11) (12) (13). The rates of death have reduced from 1.9 million in 2004 to 940,000 in 2017, a 51% reduction (1). However, there are concerns regarding the role of ART on emergence of cardiovascular, metabolic and central nervous system disorders (14) (15).

2.2 ANTIRETROVIRAL AGENTS AND FIRST LINE THERAPY

Currently, 6 classes of antiretroviral agents are available namely: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase strand transfer inhibitors (INSTI), fusion inhibitors and entry inhibitors. The current WHO recommendations advocate for the use of two NRTIs and one NNRTI as first line therapy, with an INSTI as an alternative to the NNRTI (2). This is because INSTIs have fewer side effects, fewer drug interactions and a high genetic barrier to resistance.

2.3 INTEGRASE STRAND TRANSFER INHIBITORS (INSTIS)

INSTIs prevent integration of HIV DNA by the integrase enzyme into the host DNA. In 2007, the first INSTI (Raltegravir) was approved. Other INSTIs have been approved since then which include elvitegravir (EVG/ELV), dolutegravir (DTG) and bictegravir (BIC). Studies have demonstrated either non-inferiority or superiority with the use of INSTI as part of first line or second line regimens among PLHIV when compared to NNRTI or PI-based regimens (16) (17) (18) (19). RAL and EVG (boosted with cobicistat) have been found to be non-inferior to efavirenz (EFV) when co-administered with tenofovir (TDF) and emtricitabine (FTC) (16) (17).

In the SPRING 1 study (18), DTG was demonstrated to be non-inferior to EFV while in the SINGLE trial (19) where ABC/3TC/DTG was compared to TDF/FTC/EFV, the DTG based regimen offered a superior virologic response compared to the EFV based regimen.

2.4 SAFETY AND TOLERABILITY PROFILE OF INSTIS

The most common adverse effects of INSTIs which are usually self-limiting include nausea, vomiting and headache (20). In recent years however, observational studies have recorded increased prevalence of neuropsychiatric adverse effects and excess weight gain among patients on INSTIs especially those on DTG-based regimens (3) (4). The most commonly observed biochemical alteration among patients on DTG based regimens is elevation of creatinine. This usually occurs in the first week of DTG initiation. Inhibition of the renal transporter OCT 2 has been postulated to be the pathway through which DTG causes creatinine elevation (21). Mild elevations of liver transaminases have also been observed in 5 % of the patients on DTG. Hypersensitivity reactions occur in < 1% of patients on DTG and usually occur immediately after treatment initiation.

2.5 WEIGHT CHANGES AMONG PLHIV ON DTG

2.5.1 Epidemiological transition

In the pre ART era, HIV was largely considered a wasting disease as severe weight loss and wasting was a very common presentation. With the continued use of ART and initiation of treatment in all HIV patients regardless of their WHO clinical stage or CD4 cell count, wasting is now no longer a common presentation of most of the HIV infected patients. Weight gain following ART initiation is a common phenomenon due to suppression of plasma viremia leading to a decrease in basal metabolic rate and improved appetite due to reduction of inflammatory cytokine effects on the hypothalamus (14) (15).

The prevalence of overweight and obesity among HIV infected patients on ART is increasing substantially. A prospective observational study done in the USA among military personnel demonstrated a high prevalence of overweight or obesity (46%) at the time of HIV diagnosis. This prevalence was similar to that of the HIV negative persons within the military (23). Other studies in developing countries demonstrate that the rates of overweight and obesity is now more common than wasting among PLHIV (24).

Sub Saharan Africa is also experiencing a transition with the rates of overweight and obesity among PLHIV increasing rapidly. The Temprano randomized trial conducted in Abidjan found a prevalence of overweight or obesity among HIV positive patients at ART initiation to be 27%. Among female patients the prevalence was 30%, which was similar to the prevalence of overweight and obesity among the general population of women in Abidjan. After 24 months of ART use, the burden of overweight and obesity increased to 32% (38% among women) (25). Similar findings were also demonstrated in studies done in South Africa and Tanzania (26) (27). A study done in Western Kenya found a high prevalence of obesity (22% in females, 10.6% in males) among HIV positive adult patients (28).

2.5.2 INSTIs and weight gain

Excess weight gain has been observed among HIV positive patients who were switched to an INSTI-based regimen. Several studies have tried to evaluate this association. A 2 year retrospective observational study among HIV positive adults assessed weight changes over 18 months in patients switched from TDF/FTC/EFV to an INSTI or a PI versus those who remained on TDF/FTC/EFV. Patients who were switched to an INSTI based regimen gained more weight (2.9 kgs) compared to those who remained on TDF/FTC/EFV (0.9kgs) (4).

Similar findings were also demonstrated in the ACTG 5257 trial where HIV positive patients were randomized to either raltegravir group or PI group with TDF/FTC as backbone NRTI. Patients in the raltegravir group were found to be more likely to become overweight or obese than those in the PI group. The risk of excess weight gain was especially high among black patients (29). A study done in France analyzed weight changes among 462 HIV infected patients on a DTG based regimen for 6 months or more. The mean weight increase was 3 kgs with 20% of the patients having > 10 % increase in their weight. These increases were especially significant for women on ABC/3TC/DTG regimen (9).

Findings from the ADVANCE trial (53) where HIV positive patients were randomized to receive a combination of TDF/TAF with FTC and DTG or the standard regimen of TDF, 3TC and EFV found weight gain to be significantly higher among participants on DTG at week 48 of treatment (+6.4 kg in TAF arm, +3.2 kg in TDF arm and +1.7 kg in the standard group). New

onset obesity was also higher among those on DTG (14% in TAF arm, 7% in TDF arm and 6% in the standard group).

The mechanism of excess weight gain among patients on INSTI based regimens is still poorly understood. In vitro studies have demonstrated that DTG inhibits binding of alpha melanocyte stimulating hormone to the human recombinant melanocortin 4 receptor (MC4R). Deficiency of MC4R has been linked to obesity. However more studies are needed to further evaluate this phenomenon (30).

2.5.3 Implications of overweight and obesity among PLHIV

Overweight and obesity have been associated with serious health, social, physical and psychological consequences to the affected individual. Several studies have reported an increased occurrence of metabolic abnormalities in individuals who are overweight and obese leading to chronic conditions such as HTN, DM and cancer (endometrial, breast, colon etc.) (31)(32). Obesity is an independent risk factor for CVD even after adjustments for other traditional risk factors (33). Obese individuals are two times more likely to experience a cardiovascular disease event compared to normal weight individuals. An increase in all-cause mortality has also been reported in these individuals (34).

Table 1: Classification of overweight and obesity and associated disease risks (WHO)

BMI (kg/m^2)	CLASSIFICATION	RISK OF COMORBIDITIES
<18.5	Underweight	Low (increased risk of other medical problems)
18.5-24.9	Normal	Average
25-29.9	Overweight	Increased
30-34.9	Obese class 1	Moderate
35-39.9	Obese class 2	Severe
40 and above	Obese class 3	Very severe

Overweight and obesity also contribute to poor quality of life and mental health issues such as depression, anxiety and low self-esteem. Among PLHIV who are overweight and obese, these

consequences are challenging especially in their management due to the risk of drug to drug interactions and increased pill burden which may contribute to non-adherence and treatment failure among these patients.

2.5.4 Assessment of body fat and body composition among HIV patients

Several techniques are available for estimating body fat and body composition. Anthropometric measurements are the most commonly used techniques as they are inexpensive and easy to perform. Anthropometry is based on a two component model of body composition. It provides information on fat and fat free mass only. Some of the most commonly used measurements include body mass index (BMI), skin fold thickness and waist- hip ratio.

BMI is widely used to screen for obesity. It's expressed in kg/ m^2 by dividing the weight (kg) of an individual by their height (m^2). Its use is however limited by the fact that BMI cannot differentiate muscle from fat. Individuals who are muscular can therefore be incorrectly classified as obese. Skin fold thickness measurements is based on the fact that a large proportion of total body fat is stored directly underneath the skin. These measurements can be used to estimate the total % body fat. Body fat distribution varies with age, sex, race and athletic activity, which can limit the use of skin fold thickness measurements.

Waist hip ratio is derived from measurement of the waist circumference divided by measurement of the hip circumference. It's often used to determine the coronary artery disease risk associated with obesity. It provides a more reliable risk prediction when used in conjunction with BMI. Other body composition assessment methods include bioelectric impedance analysis (BIA), dual energy x-ray absorptiometry (DEXA), hydrostatic weighing and imaging techniques (such as CT and MRI)

BIA measures body tissues opposition to flow of an alternating current. It is recommended for use in individuals with chronic conditions such as HIV infection. Its use is however limited in our set up due to lack of equipment. DEXA scans can also distinguish body weight into components of fat, muscle and bone. It can also distinguish regional and whole body parameters of body composition. It is however an expensive technique hence not readily available.

In this study, anthropometric measurements of weight and BMI were used to assess the changes in body fat composition among PLHIV who have been switched to a DTG-based regimen compared to those who remain on an EFV-based regimen.

2.6 NEUROPSYCHIATRIC ADVERSE EFFECTS OF DOLUTEGRAVIR

Recent observational studies have raised concerns about the higher rates of NP-AEs among PLHIV on INSTI-based regimens. A retrospective analysis of HIV infected patients on INSTI-based regimens in 2 German outpatient clinics evaluated the rates of discontinuation due to adverse events within 2 years of starting DTG, RAL or ELV/cobicistat. The rate of adverse events was 7.6 % with NP-AEs accounting for 5.6 %. In the DTG arm, rates of discontinuation due to any adverse event and NP-AEs were 7.6 % and 0.7% respectively. This was significantly higher when compared to the other INSTI arms (RAL/ELV). The NP-AEs were more common in those older than 60 years, women and patients on ABC containing regimens who were human leucocyte antigen (HLA)-B*5701-negative (3).

A cohort study done in 2 HIV treatment centers in the Netherlands also evaluated the reasons for discontinuation of DTG based regimens. 13.7 % of patients discontinued DTG due to intolerability. The most common causes of treatment discontinuation included insomnia and sleep disturbances (5.6%), GIT symptoms (4.3%) and other NPAEs i.e. anxiety, psychosis, and depression (4.3 %) (35). In the SINGLE trial, following a 48 week observation period, NP-AEs were found to be more common among patients on EFV based regimens. However the rate of insomnia was higher in the DTG arm (19).

In 2011, a multicenter non-inferiority study was conducted to compare DTG-based treatment regimens versus darunavir (DRV) boosted with ritonavir-based regimens. Adverse events were found to be less frequent for the DTG arm (2 % vs 4 %). The frequency of psychiatric disorders however was higher in the DTG arm (36). In contrast, the rate of NP-AEs was found to be similar in the ARIA study where patients were randomly assigned to DTG-based regimen or atazanavir boosted with ritonavir (ATVr)-based regimen (37).

The most common neuropsychiatric side effect among PLHIV on INSTIs are sleep disturbances especially insomnia. In the SINGLE trial, insomnia was reported in 17% of patients on DTG versus 12% among patients on an EFV based regimen (19). Data from the OPERA (observational pharmacoepidemiology research analysis) database was used to identify and

monitor 11,539 patients on DTG, EFV, RAL, DRV, EVG and rilpivirine (RPV) based regimens for occurrence of any adverse events. The patients who were on a DTG based regimen were more likely to develop insomnia compared to patients on the other regimens ($p < 0.0001$) (38).

A multicenter observational study conducted among the ICONA (Italian cohort naïve antiretroviral) cohort initiated on a DTG based regimen evaluated the risk of DTG discontinuation due to adverse events. NP-AEs were the most common reported adverse events (2%) leading to DTG discontinuation with the commonest NP-AE being insomnia (39). This prevalence was considerably lower compared to the data from the SINGLE trial (19).

The mechanisms leading to sleep disturbances and other neuropsychiatric adverse events among PLHIV on INSTI based regimens remains poorly understood. The drug penetration properties in the CNS are thought to contribute to CNS toxicity and pathology. CNS penetration of these drugs is influenced by several factors which include advanced age, drug interactions, plasma drug concentration and pharmacogenetics. Older patients have a permissive BBB and altered CSF flow which affects CNS absorption of drugs. PLHIV above 60 years on DTG have been reported to be at a higher risk of developing insomnia. The maximum serum drug (DTG) concentration was found to be significantly higher among these older patients and this was associated with poorer scores on the Pittsburgh sleep quality index (PSQI) questionnaire (40). Other factors associated with increased risk of sleep disturbances among PLHIV on an INSTI based regimen include female gender and having an underlying psychiatric condition (3).

2.6.1 Implications of neuropsychiatric adverse effects among PLHIV

a) Sleep disturbance as a risk factor for psychiatric disorders

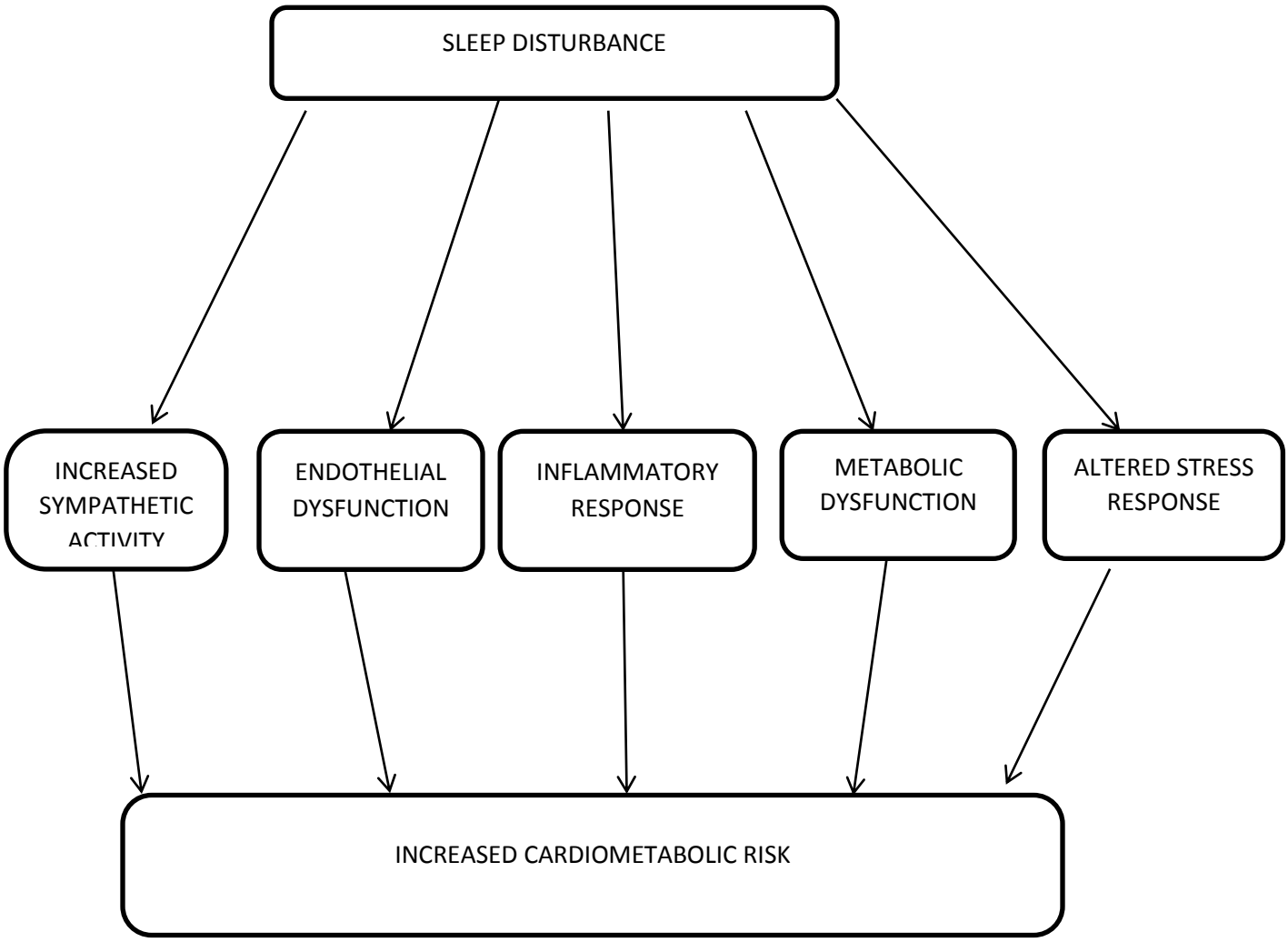
Several studies have shown a link between sleep disturbance and depression. There seems to be a vicious cycle between sleep disorders and depression. Persistent poor sleep is a risk factor for depression and approximately 90% of depressed patients have poor sleep quality (41) (42).

b) Increased cardio- metabolic risk

Regulation of the cardiovascular system varies across the sleep stages. This is due to variations of the autonomic cardiovascular control during the different sleep stages. Sleep disturbances alter this regulation with a shift towards a sympathetic predominance of the

autonomic cardiovascular control, hence leading to an increased cardiometabolic risk (43).

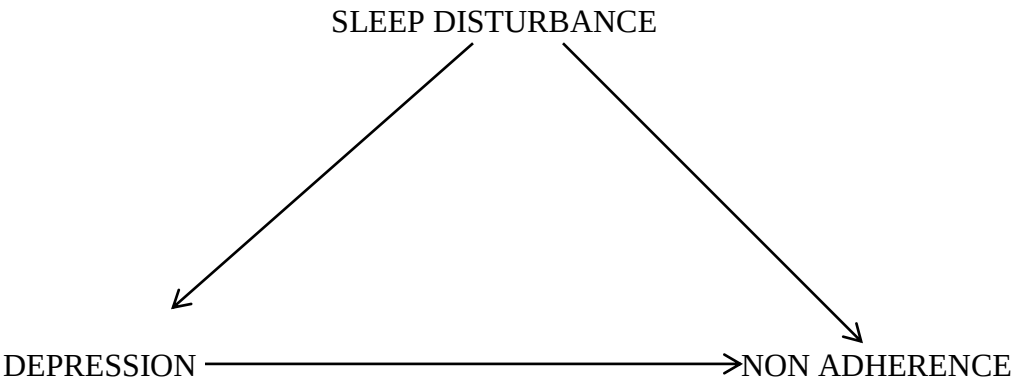
Figure 1: Sleep disturbance and cardiometabolic risk



c) Effect on drug adherence

HIV infected patients with NP-AEs especially sleep disturbances, have been shown to less likely adhere to treatment (44). This has been linked to the comorbid depression that occurs in patients with sleep disorders. Non adherence may lead to selection of mutant HIV strains, treatment failure and HIV disease progression.

Figure 2: Sleep disturbance and non-adherence



c) Impact on quality of life

NP-AEs are associated with poor health related quality of life. They lead to increased daytime fatigue, impaired attention, concentration, memory and daytime sleepiness which all impair health related quality of life (45)**.**

2.6.2 Assessment of neuropsychiatric side effects

Among PLHIV, CNS toxicity questionnaire (based on summary of product characteristics) to evaluate NP-AEs of ART has been used widely. This has especially been applied in several studies evaluating EFV CNS toxicity and the effects of switching to other ART regimens with a safer CNS profile (46) (47). This questionnaire has also been adopted by the WHO implementation tool for monitoring NP-AEs of DTG in countries that have incorporated DTG as an alternative to EFV in first line regimens (48). NP-AEs which are evaluated include: dizziness, depression, insomnia, anxiety, impaired concentration, headache, somnolence, aggressive mood, abnormal dreams and burning/tingling sensation in limbs (Appendix 4). These adverse events are graded using the Division of AIDS (DAIDS) Table (Appendix 5) for Grading the Severity of Adult and Pediatric Adverse Events. The DAIDS grading table gives guidance on severity grading and has been used in clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs (49). The adverse events are graded on a 4 point scale (0= absent, 1= mild, 2= moderate, 3= severe, 4= life threatening). The prevalence of NP-AEs is based on a score of 2 or more for each domain. NP-toxicity is defined as an individual overall score of greater than 12. This is the baseline median score in efavirenz switch studies (46). The insomnia severity index (Appendix 4) is a simple tool used to screen and assess severity of insomnia. Insomnia severity index has been validated as a screening tool in insomnia research

(51) and also among PLHIV (52). It evaluates both night time and day time components of insomnia. It consists of seven items focusing on severity of sleep onset and maintenance abnormalities, satisfaction with sleep patterns, interference with activities of daily living and how noticeable these disturbances are to others. Each item is graded on a 4 point scale (0 to 4) with total score ranging from 0 to 28.

2.7 STUDY JUSTIFICATION

INSTIs are currently recommended by several guidelines as the preferred first line regimen. This recommendation has been based on several clinical trials which have demonstrated that INSTIs have a higher genetic barrier to resistance, fewer adverse effects and fewer drug interactions. However, more recent observational studies have raised concerns regarding NP-AEs and excess weight gain among HIV infected patients on INSTI-based regimen especially DTG-based regimens.

NP-AEs are an important cause of non- adherence, treatment discontinuation and eventually treatment failure. Additionally, given the increased prevalence of overweight and obesity among PLHIV, the excess weight gain attributed to INSTI use can contribute significantly to this burden. This will contribute to increased occurrence of atherosclerotic cardiovascular disease among these patients.

With increased use of DTG-based regimens as the preferred first line in Kenya, it is important to identify these potential adverse effects associated with DTG use. This knowledge will inform the need to screen for these adverse effects and influence need for preventive strategies to mitigate these adverse effects.

To date, there is limited data on weight changes and neuropsychiatric adverse effects of DTG in the Kenyan population and this study aimed to fill this gap.

2.8 SCOPE OF THE STUDY

This study assessed HIV infected patients who had been switched to a DTG- based first line regimen at the KNH CCC and had used it for at least 6 months. It involved administration of the CNS toxicity questionnaire, insomnia severity index and assessment of weight and BMI among consenting participants. These findings were then compared to HIV infected patients who remained on an EFV- based first line regimen from the same clinic. Data on sociodemographic

and clinical characteristics, with retrospective review of patients' medical records to establish weight and BMI of the prior 6 months was also collected during the study.

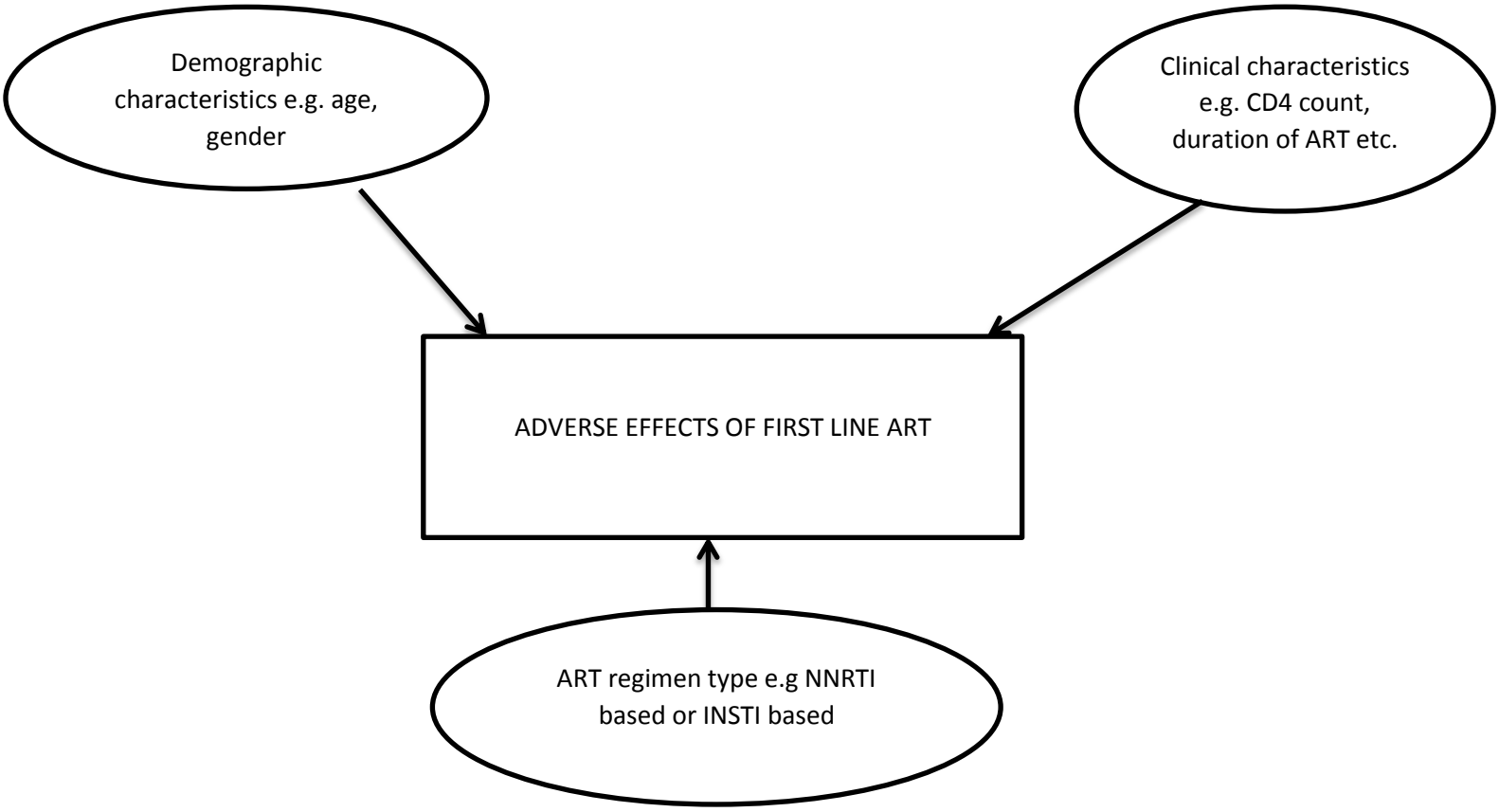
2.9 CONCEPTUAL FRAMEWORK

2.9.1 Narrative

Several factors influence occurrence of adverse events among HIV infected patients on first line ART. The patients' age, gender, race and ART regimen type are among the important factors associated with occurrence of these adverse events. Screening for these adverse events especially following roll out of new ART agents will highlight the burden among our patient population.

2.9.2 Schematic

Figure 3: Factors contributing to ART adverse effects



2.10 RESEARCH QUESTION

Is dolutegravir associated with excess weight gain and neuropsychiatric adverse events among Kenyan HIV infected patients on a DTG-based regimen?

2.11 BROAD OBJECTIVE

To evaluate the changes in weight, neuropsychiatric adverse effect (NP-AE) profile and burden of insomnia among HIV infected patients switched to a DTG-based regimen at the KNH CCC.

2.12 SPECIFIC OBJECTIVES

2.12.1 Primary objectives

1. To determine and compare the changes in weight over a 6 month period among HIV infected patients on DTG-based and EFV-based first line regimen at the KNH CCC.
2. To determine and compare the prevalence of NP-AEs and insomnia among HIV infected patients on DTG-based and EFV-based first line regimen at the KNH CCC.

2.12.2 Secondary objective

1. To identify the factors associated with excess weight gain and NP-AE among these patients.

CHAPTER THREE

3.0 STUDY DESIGN AND METHODOLOGY

3.1 STUDY DESIGN

This was a hospital based retrospective cohort study with a cross sectional arm.

3.2 STUDY SITE

This study was undertaken at the KNH CCC. KNH, the largest teaching and referral hospital in the country, serves as one of the main health facilities for residents of Nairobi and its environs. The hospital also receives several patients from different parts of the country as referrals for specialized care. The CCC is the main outpatient clinic that serves HIV infected patients.

3.3 STUDY POPULATION

The study population consisted of adult HIV positive patients who had been switched to a DTG-based first line regimen at the KNH CCC.

Participants in the comparative group were adult HIV infected patients on an EFV-based first line regimen at the KNH CCC.

3.3.1 Case definition

Adult HIV infected patients who had been switched to a DTG-based first line regimen and had used it for at least 6 months

Comparative group consisted of adult HIV infected patients on an EFV-based first line regimen for at least 6 months.

3.3.2 Inclusion criteria

- HIV infected patients, 18 years and above
- Viral load less than 500 copies/ml taken within the last 6 months (to account for occasional blips in detectable virus) (62) (63)
- Written and informed consent

3.3.3 Exclusion criteria

- Pregnant women and women in the postpartum period
- Patients with known underlying neuropsychiatric disorder before switch to DTG

- Use of any concomitant therapy with known potential to cause NP-AE

3.4 SAMPLE SIZE DETERMINATION

The following formula was used to determine the minimum sample size required for comparison of mean weight gain among HIV infected patients on a DTG based regimen versus those on an EFV based regimen:

$$n = \frac{2\sigma^2(z\beta + z\frac{\alpha}{2})}{d^2}$$

Where

n = Desired sample size for each arm

σ = average SD (+ 2) of the mean weight gain among HIV infected patients on DTG and EFV based regimen based on a retrospective observational study done in the USA (4).

$Z\beta$ =0.84 for the desired power of 80%

$z\frac{\alpha}{2}$ = 1.96 for 95 % confidence interval

d = Difference between the two means (0.5)

$$n\frac{=2(2^2)\ x\ (0.84+1.96)^2}{0.5^2} = 251$$

The minimum sample size required was 251 in each arm.

3.5 SAMPLING TECHNIQUE

Simple random sampling method was used to select patients to participate in the study. On each clinic day, a list of patients on DTG based regimen and EFV based regimen was generated from

the CCC records department. A table of random numbers was used to select patients to take part in the study. A minimum of 5 patients in each group were recruited per day. Those who met the eligibility criteria and gave informed consent were enrolled until the desired sample size was achieved.

3.6 RECRUITMENT PROCEDURE

Recruitment of eligible patients was done from both the consultation and pharmacy waiting bays of the KNH CCC. The eligible patients were taken through the consent process by either the principal investigator or the trained research assistants. Only those who signed an informed consent form were recruited into the study (Appendix 2).

3.7 DATA COLLECTION PROCEDURES

After providing informed consent, a targeted history regarding sociodemographics was obtained directly from patient. The patients' medical records were retrospectively reviewed to obtain information on current treatment regimen, previous regimen, VL, CD4 count and to establish weight and BMI of the patient 6 months prior. Any known comorbidities were also noted. This information was subsequently entered into the study proforma (appendix 3). Thereafter, an interviewer assisted CNS toxicity questionnaire and insomnia severity index questionnaire was administered (appendix 4). The assistance was limited so as not to influence the patients' response.

Anthropometric measurements were then taken to establish the participant's current weight and BMI. Height was measured using a stadiometer and values were recorded to the nearest 0.5 centimeters. Weight was measured using a standard digital weighing scale to the nearest 0.1kgs.

3.8 STUDY INSTRUMENTS

- A study proforma was used to collect targeted history from the patients.
- CNS toxicity questionnaire was used to assess the NP-AEs.
- Insomnia severity index was used to assess insomnia
- A standard digital weighing scale for measurement of weight and a standard stadiometer for measurement of height.

3.9 STUDY VARIABLES

DEPENDENT VARIABLES

- Baseline weight and BMI**:** weight and BMI of the patient 6 months prior
- Current weight and BMI: weight and BMI of patient at time of recruitment into study
- Excess weight gain: defined as ≥10% increase in body weight or progression to a higher BMI category for those with initially normal BMI.
- NP-AEs: Based on CNS toxicity questionnaire score of > 2 for each domain
- NP toxicity- Based on an overall CNS toxicity score > 12
- Insomnia: Based on insomnia severity index score of ≥8

INDEPENDENT VARIABLES

- Age : in years
- Gender : Male or Female
- ART duration: indicated in months from the date of ART initiation
- DTG duration : indicated in months from date of DTG initiation
- CD4 count : the lowest recorded absolute CD4 cell count
- Viral load : current viral load taken within the last 6 months
- WHO stage : current WHO clinical staging
- Comorbidities: documented or on treatment for any comorbidity
- Body mass index: categorized as underweight (less than 18.5 kg/m^2), normal (18.5 -24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2)

3.10 QUALITY ASSURANCE

CNS toxicity questionnaire has been validated and used widely among PLHIV to evaluate NPAE. This has especially been applied in several studies evaluating EFV CNS toxicity and the effects of switching to other ART regimens with a safer CNS profile (46) (47). WHO has also adopted this tool for monitoring NP-AEs of DTG in countries that have adopted the rollout of DTG as an alternative first line agent (48). Insomnia severity index has also been validated as a screening tool in insomnia research (51) and also among PLHIV (52). The questionnaires were translated into Kiswahili for ease of patients understanding.

The research assistants were adequately trained by the PI on the data collection process prior to the onset of the data collection and were well vast with the research tools beforehand. Data verification process was done by the PI at the end of each data collection day to minimize errors.

Weighing scales and stadiometers at the KNH CCC are calibrated monthly using standard calibration techniques hence previous weight and height measurements for these patients were comparable. The same weighing scales and stadiometers were used and properly calibrated using standard calibration techniques.

3.11 ETHICAL CONSIDERATIONS

The study protocol was approved by the Department of Clinical Medicine and Therapeutics as well as the KNH/UON ethics and research committee (approval number P567/07/2019). Participation in the study was voluntary and participants had to give an informed written consent. Patients' confidentiality was maintained by assigning codes to the questionnaires and computerized data. Data collection forms and the signed consent forms were stored in a lockable cabinet accessible only to the principal investigator. The computerized data was stored in a password protected laptop.

The results were communicated to the patient and in case of further intervention; this was communicated to the primary care providers.

The data collected was not used for any other purpose other than meeting the objectives of this study.

3.12 DATA MANAGEMENT AND ANALYSIS

Each study proforma was assigned a unique study serial number to prevent duplication of data. Data forms were kept in a secure cabinet accessible only by the PI. All data from the study proforma were coded, entered and managed in a Microsoft Access (Redmond, Washington, United States) database. Data was entered, cleaned and analyzed using the Statistical Package for Social Science (SPSS; Version 21.0, Chicago Illinois).

The study population was described using sociodemographic and clinical characteristics. Continuous data was analyzed and summarized as mean or medians with corresponding standard deviation and interquartile range, while categorical data was analyzed and presented as

proportions. Weight changes were analyzed and presented as a mean with corresponding standard deviation. The burden and profile of NP-AEs were analyzed and presented as frequencies and proportions. These characteristics were compared between the two groups (DTG vs EFV) using Chi square test for categorical variables and the Student t-test for means. Associations between NP-AEs, excess weight gain and the following factors: age, gender, employment status, ART duration, ART regimen, baseline weight and presence of comorbidities was explored using bivariate and multivariate analysis. All statistical tests were performed at 5% level of significance (95% confidence interval).

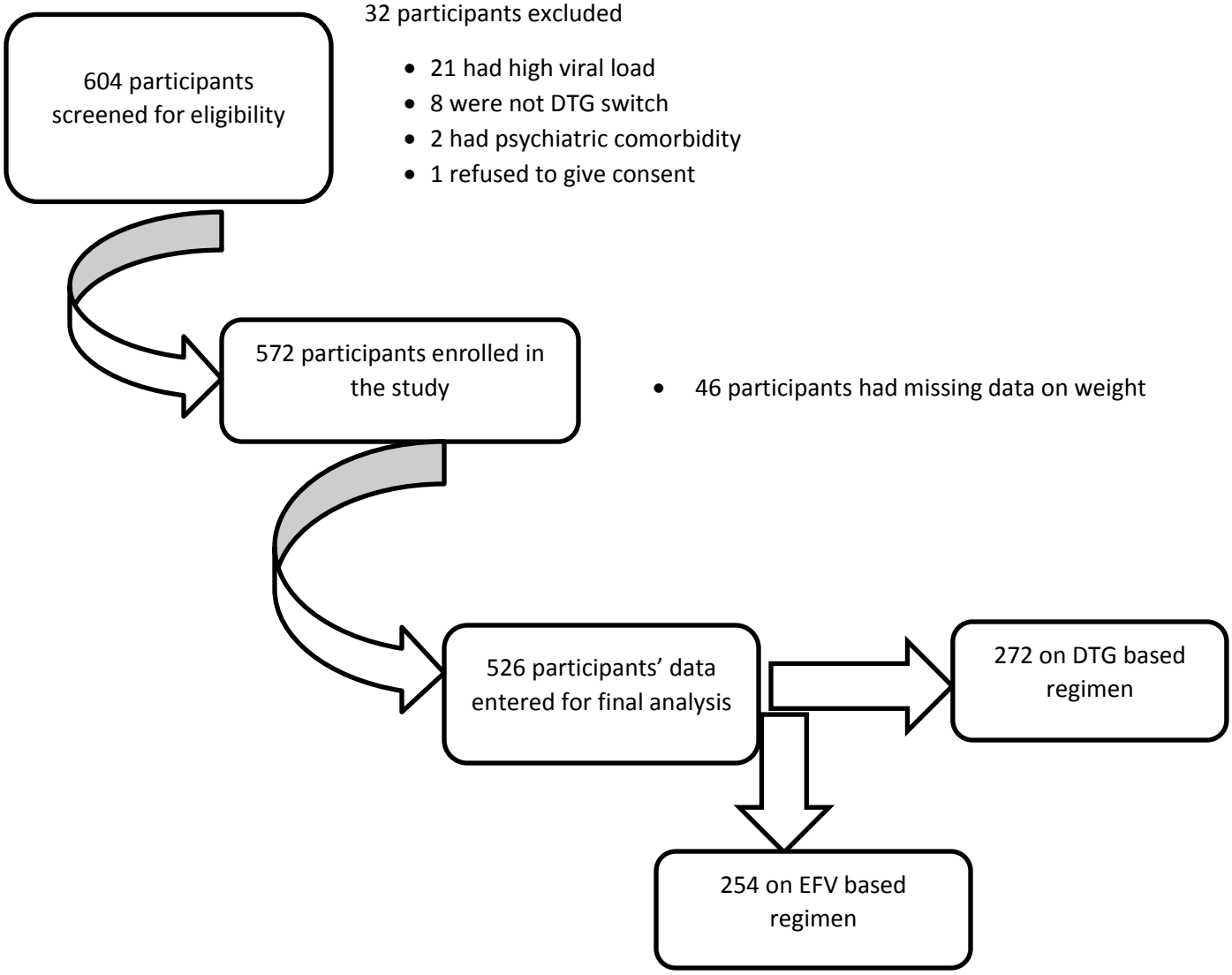
CHAPTER FOUR

4.0 RESULTS

4.1 CHARACTERISTICS OF STUDY PARTICIPANTS

Between October 2019 and January 2020, a total of 604 HIV positive patients on DTG based or EFV based first line regimens were screened for eligibility. 572 participants met the inclusion criteria and were recruited into the study. Final analysis was done on 526 participants, out of which 272 were on a DTG-based regimen while 254 were on an EFV-based regimen.

Figure 4: Flow diagram of patient recruitment



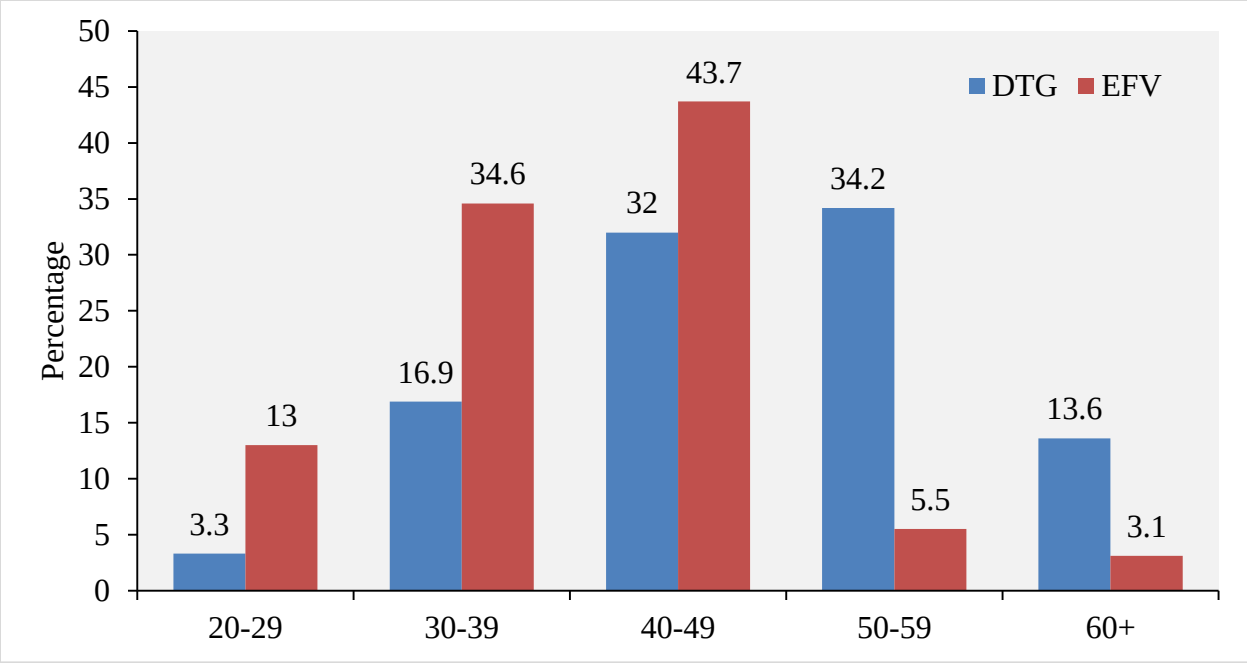
4.1.1 Sociodemographic characteristics of study participants

The mean age of the study participants on DTG-based regimen was 48.0 ± 10.4 years, whereas the mean age for those on an EFV- based regimen was 39.9 ± 8.7 years. Majority of the participants in the DTG group were aged between 40-59 years (66.2%) while most (78.3%) of the participants on EFV-based regimen were aged between 30-49 years. One hundred and thirty seven (50.4%) of participants on DTG were males while one hundred and ninety eight (78%) of the participants on EFV were females. Age, gender and employment status were significantly different between the two study groups. A summary of the socio demographic characteristics is illustrated in table 2 below. Figure 5 illustrates the age distribution of the study participants.

Table 2: Socio demographic characteristics of study participants

Variable	DTG (n= 272)	EFV (n=254)	P value
Mean age (SD)	48.0 (10.4)	39.9 (8.7)	**<0.001**
Gender			
Male	137 (50.4)	56 (22.0)	**<0.001**
Female	135 (49.6)	198 (78.0)	
Education level			
None	8 (2.9)	3 (1.2)	0.170
Primary	72 (26.5)	53 (20.9)	
Secondary	126 (46.3)	124 (48.6)	
University	66 (24.3)	74 (29.1)	
Employment status			
Employed	177 (65.1)	200 (78.7)	**0.001**
Unemployed	95 (34.9)	54 (21.3)	

Figure 5: Age distribution of study participants



4.1.2 Clinical characteristics of study participants

The mean duration on ART was 66 months (SD 37.2) among participants in the DTG group while the mean ART duration for those on an EFV- based regimen was 57.6 months (SD 33.6). For participants who were switched to a DTG-based regimen, the mean duration on DTG was 7.2 months (SD 1.5). TDF/3TC was the NRTI backbone in two hundred and sixty four (97.1%) and two hundred and forty (94.5%) among participants on DTG and EFV respectively. Majority of the participants were in WHO clinical stage 1 accounting for two hundred and five (75.4%) and two hundred and twenty five (88.6%) in the DTG and EFV groups respectively. Sixty four (23.5%) participants on DTG had comorbidities, with hypertension accounting for fifty one (79.7%) of the comorbidities. In the EFV group, thirty four (13.4%) of the participants had comorbidities, hypertension accounting for fifteen (44.1%) of the comorbidities. There was a significant difference in the mean ART duration, WHO clinical stage 2 and presence of comorbidities between the two groups. Table 3 gives a summary of the clinical characteristics of study participants.

Table 3: Clinical characteristics of study participants

Variable	DTG (n= 272)	EFV (n=254)	OR (95% CI)	P value
Mean duration on ART in months (SD)	66 (37.2)	57.6 (33.6)	-	**0.008**
Mean duration on DTG in months (SD)	7.2 (1.5)	-	-	-
Current NNRTI backbone				
TDF/3TC	264 (97.1)	240 (94.5)	1.9 (0.8-4.7)	0.141
ABC/3TC	8 (2.9)	14 (5.5)	1.0	
WHO clinical stage				
1	205 (75.4)	225 (88.6)	1.0	
2	41 (15.1)	17 (6.7)	2.6 (1.5-4.8)	**0.001**
3	8 (2.9)	1 (0.4)	8.8 (1.1-70.8)	0.014
4	18 (6.6)	11 (4.3)	1.8 (0.8-3.9)	0.133
Median nadir CD4 Count (IQR)	378 (241-560)	353 (192-558)	-	0.292
Viral load				
Median (IQR)	0 (0-0)	0 (0-0)	-	0.238
Min-Max	0-379	0-438	-	
Comorbidity				
Yes	64 (23.5)	34 (13.4)	2.0 (1.3-3.1)	**0.003**
No	208 (76.5)	220 (86.6)	1.0	
Comorbidities categories				
Hypertension	51 (79.7)	15 (44.1)	3.7 (2.0-6.7)	**<0.001**
Diabetes	1 (1.6)	2 (5.9)	0.5 (0.0-5.2)	0.523
HTN/DM	2 (3.1)	0	-	0.171
HTN/CKD	5 (7.8)	5 (14.7)	0.9 (0.3-3.3)	0.913
DM/CKD	1 (1.6)	1 (2.9)	0.9 (0.1-15.0)	0.961
HTN/DM/CKD	0	1 (2.9)	-	0.300
CKD	1 (1.6)	5 (14.7)	0.2 (0.0-1.6)	0.084
Others	3 (4.7)	5 (14.7)	0.6 (0.1-2.3)	0.418
Substance use				
Yes	49 (18.0)	48 (18.9)	0.9 (0.6-1.5)	0.794
No	223 (82.0)	206 (81.1)	1.0	

4.2 WEIGHT CHANGES AMONG STUDY PARTICIPANTS

4.2.1 Weight and BMI profile of study participants

The mean weight and mean BMI at baseline was significantly different among participants on DTG (72.8 kg and 26.4 kg/m^2) compared to those on EFV (70.1kg and 26.1 kg/m^2). At month 6, the mean weight and BMI of participants on DTG was 75.2 kg and 27.2 kg/m^2 respectively. For those on EFV, the mean weight and BMI was 70.3 kg and 26.2 kg/m^2 respectively. Table 4 gives a summary of the weight and BMI profile of the study participants.

Table 4: Weight and BMI profile of study participants

Variable	DTG (n= 272)	EFV (n=254)	OR (95% CI)	P value
At baseline				
Mean weight (SD)	72.8 (13.9)	70.1 (14.1)	-	**0.030**
Mean BMI (SD)	26.4 (5.0)	26.1 (5.2)	-	0.598
Category, n (%)				
Underweight	11 (4.0)	6 (2.4)	2.1 (0.7-5.9)	0.159
Normal	105 (38.6)	120 (47.2)	1.0	
Overweight	91 (33.5)	69 (27.2)	1.5 (1.0-2.3)	**0.048**
Obese	65 (23.9)	59 (23.2)	1.3 (0.8-2.0)	0.303
Current (month 6)				
Mean weight (SD)	75.2 (14.5)	70.3 (14.1)	-	**<0.001**
Mean BMI (SD)	27.2 (5.3)	26.2 (5.3)	-	**0.024**
Category, n (%)				
Underweight	8 (2.9)	7 (2.8)	1.4 (0.5-3.9)	0.563
Normal	94 (34.6)	112 (44.1)	1.0	
Overweight	85 (31.3)	73 (28.7)	1.4 (0.9-2.1)	0.122
Obese	85 (31.3)	62 (24.4)	1.6 (1.1-2.5)	**0.024**

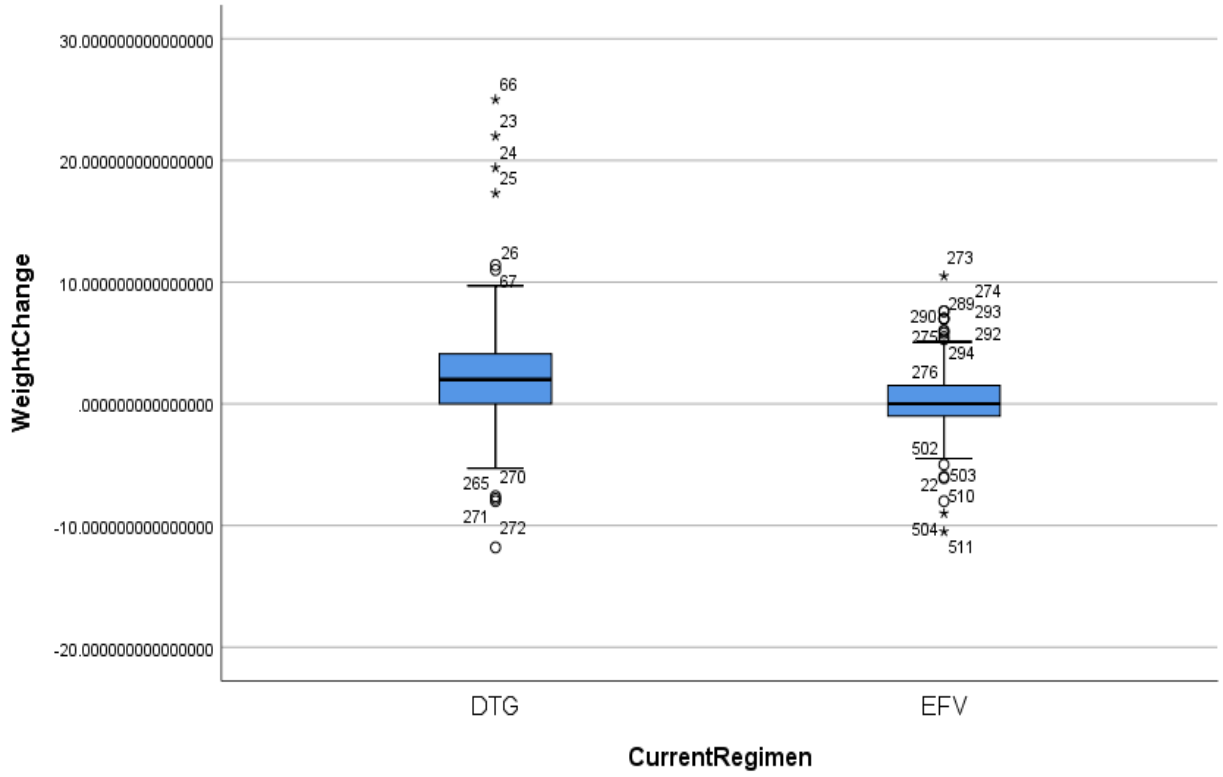
4.2.2 Mean weight change among study participants

Participants who were switched to a DTG-based regimen gained more weight at 6 months compared to those on EFV- based regimen [mean +2.4 kg, SD 3.9 (95% CI 1.9-2.9) vs mean +0.2 kg, SD 2.7, (95% CI 0.14-0.5) respectively]. An independent samples t- test showed the difference in the mean weight change in the two study groups was significant (mean difference 2.2, 95% CI 1.6-2.8, $p < 0.001$). Table 5 gives a summary of the mean weight change while Figure 6 illustrates the weight change distribution in the two study groups.

Table 5: Weight change among study participants from baseline to month 6

	Mean +SE	SD	95%CI
DTG (n=272)	2.4±0.25	3.9	1.9-2.9
EFV (n=254)	0.2±0.17	2.7	0.14-0.5

Figure 6: Distribution of weight change from baseline to month 6 among study participants



4.2.3 Excess weight gain among study participants.

More than 10% increase in weight from baseline was observed among 19 (7%) of participants on DTG, whereas 64 (23.5%) had 5-10 % increase in weight. For those in the EFV group, only 5 (2%) had > 10% increase in weight and 22 (8.7%) had a 5-10% increase in weight from baseline. Excess weight gain was noted among 49 (18%) and 18 (7.1%) of the participants in the DTG and EFV groups respectively, (95% CI 1.6-5.1, p <0.001). Table 6 gives a summary of the above.

Table 6: Excess weight gain among study participants

	DTG (n=272)	**EFV (n=254)**	**OR (95% CI)**	**P value**
Weight change category n (%)				
>10%	19 (7.0)	5 (2)	4.6 (1.7-12.5)	**0.001**
5-10%	64 (23.5)	22 (8.7)	3.5 (2.1-5.9)	**<0.001**
<5%	189 (69.5)	227 (89.4)	1.0	
BMI change category, n (%)				
Overweight to obese	21 (7.7)	5 (2.0)	4.3 (1.6-11.6)	**0.002**
Normal to overweight	18 (6.6)	10 (3.9)	1.8 (0.8-4.1)	0.125
No change	233 (85.7)	239 (94.1)	1.0	
With excess weight gain, n (%)	49 (18%)	18 (7.1%)	2.9 (1.6-5.1)	**<0.001**
Without excess weight gain, n (%)	223 (82%)	236 (92.9%)	1.0	

4.3 PREVALENCE OF NEUROPSYCHIATRIC ADVERSE EFFECTS

The prevalence of neuropsychiatric adverse effects (NP-AEs) was higher among participants on EFV (29.5%) compared to those on DTG (22.8%). Ten (7.3%) of those participants in the EFV group had neuropsychiatric toxicity (NP toxicity) whereas only two (1.6%) had toxicity in the DTG group, (95% CI 0.0-0.9, p=0.026). Table 7 illustrates the prevalence of NPAEs and NP toxicity.

Participants on EFV had a higher burden of insomnia compared to those on DTG (9.1 % vs 7% respectively. Table 8 summarizes the prevalence and severity of insomnia among study participants.

Table 7: Prevalence of NP-AEs and NP toxicity among study participants

Variable	DTG (n= 272)	EFV (n=254)	OR (95% CI)	P value
NP-AEs (overall)				
Yes	62 (22.8)	75 (29.5)	0.7 (0.5-1.0)	0.079
No	210 (77.2)	179 (70.5)	1.0	
NP-AEs				
Dizziness	7 (2.6)	18 (7.1)	0.3 (0.1-0.8)	**0.015**
Low mood/depression	19 (7.0)	21 (8.3)	0.8 (0.4-1.6)	0.579
Insomnia/sleeplessness	10 (3.7)	16 (6.3)	0.6 (0.3-1.3)	0.166
Anxiety/nervousness	6 (2.2)	5 (2.0)	1.1 (0.3-3.7)	0.849
Confusion	3 (1.1)	6 (2.4)	0.5 (0.1-1.9)	0.266
Memory problem	12 (4.4)	26 (10.2)	0.4 (0.2-0.8)	**0.010**
Headache	12 (4.4)	17 (6.7)	0.6 (0.3-1.4)	0.252
Somnolence/daytime sleepiness	11 (4.0)	17 (6.7)	0.6 (0.3-1.3)	0.176
Aggressive mood/behavior	22 (8.1)	25 (9.8)	0.8 (0.4-1.5)	0.481
Abnormal dreams/nightmares	7 (2.6)	13 (5.1)	0.5 (0.2-1.2)	0.127
Burning and tingling sensation in limbs	4 (1.5)	11 (4.3)	0.3 (0.1-1.0)	**0.049**
NP toxicity				
Yes	2 (1.6)	10 (7.3)	0.2 (0.0-0.9)	**0.026**
No	125 (98.4)	127 (92.7)	1.0	

Table 8: Prevalence and severity of insomnia among study participants

Variable	DTG (n= 272)	EFV (n=254)	OR (95% CI)	P value
Insomnia				
Yes	19 (7.0)	23 (9.1)	0.8 (0.4-1.4)	0.381
No	253 (93.0)	231 (90.9)	1.0	
Insomnia severity				
8-14 (sub threshold insomnia)	16 (84.2)	15 (65.2)	2.8 (0.6-12.8)	0.291
15-21 (Clinical insomnia)	3 (15.8)	8 (34.8)	1.0	

4.4: FACTORS ASSOCIATED WITH EXCESS WEIGHT GAIN

Out of all the participants with excess weight gain, 44 (65.7%) were female and 23 (34.3%) were male. However this difference was not statistically significant (P=0.060).There was a significant association between being on a DTG-based regimen and excess weight gain (P <0.001). Table 9 gives a summary of the different associations. After adjusting for other significant variables using multiple logistic regression models, being on a DTG-based regimen was still significantly associated with excess weight gain (95% CI 1.9-7.4, p<0.001). Table 10 gives a summary of the adjusted odds ratio.

Table 9: Factors associated with excess weight gain among study participants

Variable	Excess weight gain		aOR (95% CI)	P value
	Yes	No		
Mean age (SD)	45.4 (11.2)	43.8 (10.3)	-	0.252
Gender				
Male	23 (34.3)	170 (37.0)	1.0	
Female	44 (65.7)	289 (63.0)	1.7 (1.0-3.0)	0.667
Employment status				
Employed	43 (64.2)	334 (72.8)	0.7 (0.4-1.2)	0.145
Unemployed	24 (35.8)	125 (27.2)	1.0	
Baseline BMI, mean (SD)	25.6 (3.8)	26.3 (5.3)	-	0.259
Mean ART duration in months (SD)	54 (37.2)	62.4 (34.8)	-	0.074
Regimen				
DTG-based	49 (73.1)	223 (48.6)	2.9 (1.6-5.1)	**<0.001**
EFV-based	18 (26.9)	236 (51.4)	1.0	
Presence of comorbidities				
Yes	16 (23.9)	82 (17.9)	1.4 (0.8-2.7)	0.237
No	51 (76.1)	377 (82.1)	1.0	

Table 10: Association between DTG use and increased weight change adjusting for other significant variables (multiple logistic regression model)

Variable	Adjusted OR (95% CI)	P value
Age in years	1.09 (1.06-1.11)	<0.001
Gender		
Male	3.9 (2.5-6.2)	<0.001
Female	1.0	
Employment status		
Employed	1.0	
Unemployed	1.7 (1.03-2.7)	0.037
Duration on ART in months	1.04 (0.97-1.12)	0.278
WHO clinical stage		
1	1.0	
2	2.3 (1.2-4.4)	0.017
3	10.7 (1.1-101.8)	0.039
4	1.5 (0.6-3.6)	0.392
Comorbidity		
Yes	1.0 (0.6-1.8)	0.943
No	1.0	
Excess weight gain		
Yes	3.7 (1.9-7.4)	**<0.001**
No	1.0	

4.5 FACTORS ASSOCIATED WITH NEUROPSYCHIATRIC ADVERSE EFFECTS

For the participants with neuropsychiatric adverse effects, 97 (70.8%) were females and 40 (29.2%) were males (P= 0.034). There was a significant association between mean ART duration and prevalence of neuropsychiatric adverse effects (P <0.01). However, upon multivariate analysis, mean ART duration was the only factor identified to be significantly associated with neuropsychiatric adverse effects (P < 0.001). Table 11 gives a summary of the different associations.

Table 11: Factors associated with NP-AEs among study participants

Variable	**NP-AEs**		**OR (95% CI)**	**P value**	Multivariate analysis	
	Yes	**No**			**OR (95% CI)**	**P value**
Mean age (SD)	43.7 (9.6)	44.2 (10.7)	-	0.633	0.99 (0.96-1.01)	0.286
Gender						
Male	40 (29.2)	153 (39.3)	1.0		1.0	
Female	97 (70.8)	236 (60.7)	1.6 (1.03-2.4)	**0.034**	1.5 (0.9-2.3)	0.095
Employment status						
Employed	104 (75.9)	273 (70.2)	1.3 (0.9-2.1)	0.200	1.2 (0.8-2.0)	0.361
Unemployed	33 (24.1)	116 (29.8)	1.0		1.0	
Baseline BMI, mean (SD)	26.8 (5.4)	26.1 (5.0)	-	0.164	1.01 (0.97-1.05)	0.691
Mean ART duration in years (SD)	5.9 (3.0)	4.9 (2.9)	-	**<0.001**	1.15 (1.07-1.23)	**<0.001**
Regimen						
DTG-based	62 (45.3)	210 (54.0)	0.7 (0.5-1.0)	0.079	0.7 (0.5-1.2)	0.213
EFV-based	75 (54.7)	179 (46.0)	1.0		1.0	
Presence of comorbidities						
Yes	31 (22.6)	67 (17.2)	1.4 (0.9-2.3)	0.162	1.7 (1.0-2.8)	0.057
No	106 (77.4)	322 (82.8)	1.0		1.0	

CHAPTER FIVE

5.0 DISCUSSION

This study evaluated the weight changes over a 6 month period and prevalence of neuropsychiatric adverse effects (NPAEs) among HIV infected adults attending KNH CCC, comparing patients on DTG-based to those on EFV-based first line ART. Participants in the EFV group were mainly females (78%) in the reproductive age group, whereas there was a slightly higher proportion of males (50.4%) in the DTG group.

Our study showed that the mean gain in weight over a 6 month period among participants on DTG-based regimen was higher (+2.4 kg) compared to those on EFV-based regimen (+0.2 kg). Progression to a higher BMI class was higher among participants on DTG, with a significant difference in those who progressed from the overweight category to the obese category (7.7% vs 2 % in the DTG and EFV arms respectively). Additionally, excess weight gain was significantly higher among those on DTG compared to those on EFV (18% vs 7.1% respectively). Female patients accounted for 65% of all the participants with excess weight gain. However, the main factor associated with excess weight gain in this study was being on a DTG based regimen, even after adjusting for the significant differences in baseline characteristics.

Findings of excess increase in weight among those on DTG based regimens have been demonstrated in several studies. In the ADVANCE trial (53), the mean weight gain at 48 weeks was significantly higher among participants on DTG compared to those on the standard EFV based regimen (+6.4 kg in TAF/FTC/DTG, 3.2 kg in TDF/FTC/DTG and 1.7 kg in the standard group). New onset obesity was also higher among those on DTG (14% in TAF, 7% in TDF and 6% in the standard group). Weight gain was higher among female patients across all the three study groups, similar to what was demonstrated in our study.

Similar findings were demonstrated in the NAMSAL trial (64) conducted in Cameroon, where participants on DTG gained significantly more weight at 48 weeks compared to those on EFV (+5 kgs and +3 kgs respectively). Female gender and low baseline BMI were associated with weight gain of more than 10% at 48 weeks. Our study did not show any association between baseline BMI and excess weight gain.

Similarly, in a 2 year retrospective observational study done by Norwood et al, those switched to a DTG-based regimen gained significantly more weight compared to those on an EFV-based regimen (+2.9 kgs and +0.9 kgs respectively) at 18 months (4). Excess weight gain was especially significant for those on an ABC/3TC NRTI backbone. In our study only 2.9% of participants on DTG were on an ABC/3TC backbone, hence was likely not powered enough due to the small numbers to show this association.

In contrast to the above study findings, there was no overall increase in weight or BMI following switch to raltegravir or dolutegravir based regimen among 378 individuals in a retrospective analysis of a HIV cohort in the UK (65). Additionally, a prospective cohort study in Italy (66) evaluating factors associated with excess weight gain among participants on DTG demonstrated that female gender was protective against weight gain, while low CD4 counts and a TDF/FTC or TAF/FTC backbone are associated with weight gain of more than 10% from baseline. These differences in the study findings may be attributed to the differences in the study populations (predominantly Caucasian population with few proportion of females compared to predominantly African population in our study, ADVANCE trial and NAMSAL trial) and environmental factors that also play a role in weight changes. Given these findings, one may conclude that there is a greater influence from environmental and genetic factors on weight changes among participants on DTG rather than the effect of the drug itself. In addition, the finding of TDF or TAF backbone being associated with excess increase in weight in the Italian cohort (66) was in contrast to the study done by Norwood et al (4) that demonstrated that ABC/3TC backbone was associated with excess weight gain. These discordant results may be attributed to the different patient populations, environmental and lifestyle factors that are confounders of weight change. Larger multinational trials are therefore needed to determine whether the interactions between the NRTI backbone and INSTIs impact the influence of INSTIs on weight.

The results from our study suggest that being on DTG-based regimen may contribute to excess weight gain among PLHIV. This will contribute significantly to the rising prevalence of overweight and obesity and the consequent increase in cardiovascular and metabolic diseases among these patients, as demonstrated in the ADVANCE and NAMSAL trials where there was an associated increase in truncal fat and glucose levels among those on DTG. With the increased

use of DTG-based regimens as the preferred first line in Kenya, this possible effect of DTG necessitates increased focus on maintenance of normal BMI and lifestyle modification during follow up of these patients, especially in those with a high cardiovascular disease risk.

This study also evaluated the prevalence and spectrum of NP-AEs. The overall prevalence of NP-AEs was 22.8% among participants on DTG and 29.5% among those on EFV (P=0.079). The prevalence in our study was higher when compared to what has been reported in other studies. A study done in 2 German outpatient clinics by Hoffmann et al reported a prevalence of 5.6% for NP-AEs among patients on DTG (3). A cohort study done in the Netherlands evaluated the reasons for DTG discontinuation and NP-AEs accounted for 4.3% (35). These two studies were retrospective and determined the prevalence of NP-AEs based on reports from medical records of the patients whereas we used cross sectional study design to assess the prevalence of NP-AEs. This may have contributed to the lower prevalence when compared to our study due to underreporting or missing data. There may also be a recall bias when answering the CNS toxicity questionnaire contributing to the difference in prevalence rates.

The burden of NP toxicity was significantly higher among participants on EFV-based regimen (P= 0.026) in our study. This is consistent with the well-known NP-AEs associated with EFV, reported in several studies (55) (56).

The prevalence of insomnia in our study higher in the EFV group (9.1%) compared to those on DTG (7%), however this difference was not significant (P=0.381). In the SINGLE trial (19), higher rates of insomnia were reported among participants on DTG compared to those on EFV (17% and 12% respectively), although this difference was not significant. However data from the OPERA database (38), which evaluated occurrence of psychiatric outcomes among patients on DTG based regimens in comparison to other regimens showed no difference in the burden of insomnia across all treatment groups (7% among those on DTG vs 8% among those on EFV). These differences in the burden of insomnia may be attributed to the difficulties in assessment of NP-AEs which is subject to variations and recall bias.

Out of all the participants with NP-AEs (n=137), female patients accounted for 70.8% whereas males were only 29.2%, this difference was statistically significant on bivariate analysis (P=0.034). Hoffmann et al similarly reported a higher burden of NP-AEs among female patients

in a retrospective study done in 2 German outpatient clinics among HIV infected patients on INSTI based regimens (3).

Association between old age (>60yrs) and presence of NP-AEs has been demonstrated in some studies (57) (3). In our study, there was no difference in age among participants with and without NP-AEs. Majority of the participants in our study were below 60 years, hence it was not powered enough to show this association

The strongest factor associated with NP-AEs in this study was the duration on ART. The mean ART duration among participants with NP-AEs was significantly higher compared to those participants without NP-AEs ($P<0.001$). Studies have demonstrated that long term exposure to ART can still contribute to CNS toxicity among PLHIV (58) (59).

These results suggest that neurotoxicity still persists with continued use of ART. Close monitoring for these adverse effects even after viral suppression is therefore important. However, more studies are needed to evaluate the possible mechanisms of ART neurotoxicity among virally suppressed HIV infected patients.

5.1 CONCLUSION

Our study showed that patients on DTG-based ART regimen gain significantly more weight compared to those on EFV-based regimens.

The prevalence of neuropsychiatric adverse effects and neuropsychiatric toxicity was higher among patients on EFV-based regimen, although the difference in the two groups was not significant.

5.2 STUDY STRENGHTS

This is among the first studies done in Kenya that described the changes in weight and neuropsychiatric adverse effects among patients on DTG-based regimens. It can be used as a baseline to generate hypothesis for future studies.

5.3 STUDY LIMITATIONS

1. We could not match for age and sex in the two study groups since the study population was already skewed due to the initial ministry of health directive to switch only males and postmenopausal women to DTG-based regimen.
2. The 6 month follow up period was based on the interval from the date of DTG recommendation as alternative first line in Kenya and the study period; hence weight changes over a longer duration could not be captured.
3. We did not evaluate the effect of the weight changes on other cardiometabolic factors such as lipid profile, HbA1C.

5.4 RECCOMMENDATIONS

On the basis of our study findings, we recommend focused lifestyle interventions with the aim of maintaining a normal BMI should be provided especially for patients on DTG-based ART regimens. Secondly, routine screening for neuropsychiatric adverse effects of ART using simple tools such as the CNS toxicity questionnaire is also needed to identify those with long term toxicities. Thirdly, larger multicenter cohort studies are needed to evaluate the effect of DTG on body fat composition and other cardiometabolic risk factors.

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APPENDICES

APPENDIX 1: SCREENING PROFORMA

Study No.: …….

Age: …….

Date of Birth: ……

Gender: Female ☐ Male ☐

Are you willing to participate in the study to assess burden of adverse effects among HIV infected patients on DTG or EFV based regimens at the KNH CCC?

YES ☐

☐

NO

APPENDIX 2: PARTICIPANT INFORMATION AND CONSENT FORM

BURDEN OF NEUROPSYCHIATRIC ADVERSE EFFECTS AND WEIGHT CHANGES AMONG HIV INFECTED PATIENTS SWITCHED FROM AN EFAVIRENZ BASED TO A DOLUTEGRAVIR BASED FIRST LINE REGIMEN AT THE KENYATTA NATIONAL HOSPITAL.

Principal Investigator

Dr. Abutika Rebecca Ayoti - **UoN**

Co-Investigators

Dr. Loice Achieng - **UoN**

Prof. Titus Munyao - **UoN**

Dr. J.O.Mecha- **UoN**

Introduction:

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

i) Your decision to participate is entirely voluntary

ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities.

We will give you a copy of this form for your records.

May I continue?

YES NO

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No. _____

WHAT IS THIS STUDY ABOUT?

Dolutegravir is a relatively new type of antiretroviral drug that forms part of ARV treatment regimens (in combination with two other drugs). All drugs may have some adverse effects and since Dolutegravir is a relatively new drug, we do not know about its potential side effects. It is therefore important that we talk to patients who have been taking this drug to find out about the side effects they may be experiencing. Since we have used Efavirenz (a different class of antiretroviral) as part of our treatment regimens for longer, patients on Efavirenz will also be included for comparison. Recommendation from the study results can be made to the administration to improve screening and monitoring of these adverse effects.

Your participation in this study is voluntary. Should you accept to participate, this is what the study entails:

Going through your medical records. Your name will not be included in the study proforma.

A brief physical exam to measure your weight and height.

We will also ask you some questions from two questionnaires.

This will take about 30 minutes of your time

Benefits

Knowledge from the study findings could help improve future care of HIV infected patients on DTG based regimens. The findings will be communicated to your primary physician and appropriate referral will be done if there is need. Participants shall not receive any monetary compensation to take part in the study.

Risks

Your participation in this study has minimal risk. You might feel some discomfort when answering questions about personal life**.**

Confidentiality

All the information provided will remain strictly confidential. The filled study proforma, questionnaires and signed consent forms shall be kept in a lockable cabinet which will be accessible to the principal investigator only.

Participation

Participation in this study is on voluntary basis and you are allowed to withdraw at any point or refuse to participate without any victimization.

Questions about the research

If you have any questions on the study kindly contact me (principal investigator) on this telephone number 0706895487.

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 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**

Participant signature / Thumb stamp

Date

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name **Date**

Signature:

Role in the study

Contact information

Dr. Abutika Rebecca Ayoti

Telephone number 0706895487

KIAMBATISHO CHA PILI: FOMU YA HABARI KWA WANAOSHIRIKI NA IDHINI

MZIGO WA ADHARI YA NEUROLOGIA NA MABADILIKO YA UZITO WA MWILI MIONGONI MWA WAGONJWA WANAOTUMIA DAWA YA DOLUTEGRAVIR KATIKA HOSPITALI KUU YA KENYATTA.

Mtafiti mkuu

Dr. Abutika Rebecca Ayoti - **UoN**

Watafiti wenza

Dr. Loice Achieng - **UoN**

Prof. Titus Munyao - **UoN**

Dr. J.O. Mecha - **UoN**

Utangulizi:

Ningependa kukufahamisha kuhusu utafiti huu unaofanywa na watafiti ambao wametajwa hapo juu. Umuhimu wa fomu hii ni kukujulisha yale unatakiwa kujua kabla ya kuamua kushiriki au kutoshiriki katika utafiti huu. Unaweza kuuliza maswali yoyote kuhusu umuhimu wa utafiti huu, faida na hasara zake kama zipo, haki zako ikiwa utajitolea kushiriki na chochote ambacho hujaelewa.

Utakapoelewa utahitajika kutia sahihi kwenye fomu hii.

Unapaswa kuelewa kuwa;

i. Haifai kulazimishwa kushiriki ila kwa uamuzi wako mwenyewe.

ii. Unaweza kujitoa kwenye utafiti huu wakati wowote ule bila kutoa sababu.

iii. Matibabu yako yataendelea kama kawaida hata utakapo kataa kushiriki katika utafiti huu.

Tutakupatia fomu nyingine ili uweze kuiweka.

Je, niendelee?

Ndio La

Utafiti huu umeidhinishwa na KNH-university ya Nairobi ethics &Research committee protocol no. ___

Utafiti huu unahusu nini?

Dolutegravir ni aina mpya ya dawa ya ARV ambayo inatumika (pamoja na dawa mbili tofauti) katika matibabu ya virusi vya ukimwi. Mara kwa mara, madawa huwa na adhari za upande. Kwa kuwa Dolutegravir haijatumika kwa muda, hatufahamu vizuri adhari zake. Ni muhimu basi kufuatilia wagonjwa wanaotumia dawa hii ili kujua ingawa wanaugua adhari zozote kutokana na matumizi ya dawa hii. Kwa sababu tumetumia dawa ya Efavirenz (aina nyingine ya ARV) kwa muda mrefu katika matibabu ya HIV, wagonjwa wanaotumia dawa hii watalinganishwa na wale wanaotumia dawa ya Dolutegravir.Mapendekezo kutokana na utafiti huu yanaweza kutumika na wasimamizi katika kuboresha utoaji wa huduma.

Kushiriki kwako katika utafiti huu ni kwa hiari. Iwapo utakubali kushiriki,haya ndiyo yanahusika na utafiti huu:

Kupitia rekodi zako za matibabu. Jina lako halitatajwa katika profoma ya utafiti.

Mtihani mfupi wa kimwili wa kupima uzito na urefu.

Pia tutakuuliza maswali kidogo kupitia fomu aina mbili.

Haya yote yatachukua muda wa dakika kama thelathini (30).

Faida

Maarifa yatakayotokana na utafititi huu yanaweza kuboresha matibabu ya wagonjwa siku zijazo.Matokeo yatawasilishwa kwa daktari wako na rufaa mwafaka itafanyika iwapo kuna haja.Washiriki hawatapata fidia yoyote ya kifedha kwa kushiriki katika utafiti huu.

Hatari

Ushiriki wako katika utafiti huu una hatari chache.Utaweza kuhisi kwamba unasumbuliwa utakapokua unajibu maswali kuhusu maisha yako ya kibinafsi**.**

Usiri

Habari zote utakazotoa zitabaki kua ni siri. Fomu zitakazotumika kwenya utafiti huu zitahifadhiwa kwenye kabati maalum linaloweza kufikiwa tu na mtafiti mkuu.

Kushiriki

Kushiriki kwa utafiti huu ni kwa hiari na uko na uhuru wa kujitoa katika hatua yoyote ama kukataa kushiriki bila ya maonevu.

Maswali kuhusu utafiti

Kama una maswali yoyote tafadhali wasiliana nami kwa nambari hii ya simu: 0706895487.

Iwapo kuna maswali zaidi kuhusu haki zako kama mshiriki kwenye utafiti huu, wasiliana na karani/mwenyekiti KNH- Chuo kikuu cha Nairobi Ethics &Research committee nambari : Ext 44102.

Fomu ya idhini

Nimesoma fomu hii. Nimepata fursa ya kujadili utafitii huu. Maswali yangu yamejibiwa kwa lugha ninayoielewa. Nimeelewa faida na hatari zinazotokana na utafiti huu. Nimeelewa kuwa kushiriki kwangu sio kwa lazima na ninaweza kujitoa wakati wowote ule.

Nakubali kushiriki kwenye utafiti huu. Naelewa kua juhudi zimewekwa kuhakikishwa habari nitakazozitoa zitakua ni siri.

Kwa kutia sahihi sijapoteza haki zangu kama muhusika.

Nakubali kushiriki katika utafiti huu **Ndio** **La**

Sahihi ya mshirika /alama ya kidole_____

tarehe

Kauli ya utafiti

Mimi niliyetia sahihi kwenye karatasi hii nimeeleza kwa kina mambo yote ambayo mshiriki aliyetajwa hapo juu anapaswa kuelewa na amekubali kushiriki katika utafiti huu bila kulazimishwa.

Jina la mtafiti_____ tarehe_____

Sahihi

Jukumu kwenye utafiti_____

Kwa maelezo zaidi wasiliana na

Dr. Abutika Rebecca Ayoti

Nambari ya simu 0706895487

APPENDIX 3: STUDY PROFORMA

Patient number: _____

Study number: _____

Age (years) _____

Gender

- Male
- Female

Time of first ever ART initiation (year) _____

Nadir CD4 count _____

Current ART regimen (specify) _____

Previous ART regimen (specify) _____

Current viral load (within 6 months) _____copies/ml

Any previous AIDS diagnosis (specify) _____

Known co-morbidity (specify) _____

What is your highest level of education you achieved?

None at all ☐

Primary School ☐

High School ☐

College/ University ☐

What is your marital status?

Single ☐ Divorced ☐ Married ☐ Widowed ☐ Separated ☐

Employment statement: Employed ☐ Not employed ☐

Do you use Alcohol/ cigarettes/ bhang/ miraa/ Injectable drugs? Yes ☐ No ☐

Baseline Weight =

Height =

Baseline BMI =

Current weight =

Current BMI =

APPENDIX 4: CNS TOXICITY QUESTIONNAIRE

Symptom	Did you experience any of the following symptoms over the last 1 month? (Indicate yes or no)	Severity of symptom Mild (grade 1) Moderate (grade 2) Severe (grade 3) Life threatening (grade 4)
Dizziness		
Low mood/depression		
Insomnia/sleeplessness		
Anxiety /nervousness		
Confusion		
Poor concentration/memory problems		
Headache		
Somnolence/daytime sleepiness		
Aggressive mood/ behavior		
Abnormal dreams/nightmares		
Burning and tingling sensation in limbs		

KIAMBATISHO CHA NNE

Dalili	Je, umepata dalili zifuatazo kwa mwezi mmoja uliopoita? (Chagua ndio au la)	Ukali wa dalili Kidogo (1) Kiasi (2) Kuadhirika sana (3) Kuhatarisha maisha (4)
Kizunguzungu		
Huzuni/hali ya chini		
Ukosefu wa usingizi		
Wasiwasi/hofu		
Mkanganyiko		
Matatizo ya kumbukumbu		
Maumivi ya kichwa		
Usingizi wa mchana		
Kiburi		
Ndoto zisizo za kawaida		
Hisia ya kuchoma na kusonga kwenye miguu au mikono		

Insomnia Severity Index

Over the last seven days please rate any sleeping difficulties

	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problem waking up too early	0	1	2	3	4

4. How satisfied/dissatisfied are you with your current sleep pattern:

Very satisfied	Moderately Satisfied	Satisfied	Dissatisfied	Very dissatisfied
0	1	2	3	4

If you have answered 'mild' or above to any of Q 1,2,3 please CONTINUE otherwise STOP.

5. How noticeable to others do you think your sleep problem is, in terms of impairing the quality of your life:

Not at all noticeable	A little	Somewhat	Much	Very much noticeable
0	1	2	3	4

6. How worried/distressed are you about your current sleep problem:

Not at all worried	A little	Somewhat	Much	Very much worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) currently?

Not at all interfering	A little	Somewhat	Much	Very much interfering
0	1	2	3	4

Insomnia Severity Index

Chagua matatizo yoyote ya usingizi uliyopata siku saba zilizopita

	hakuna	kidogo	Kiasi	sana	sana kabisa
1. Ugumu kupata usingizi	0	1	2	3	4
2. Ugumu kukaa usingizini	0	1	2	3	4
3.Tatizo la kuamka mapema sana	0	1	2	3	4

4. Je, umeridhika aje na muundo wako wa usingizi wa sasa:

kuridhika sana	kuridhika kadirifu	kuridhika	kutoridhika	kutoridhika sana
0	1	2	3	4

If you have answered ‘mild’ or above to any of Q 1,2,3 please CONTINUE otherwise STOP.

5.je, kilingana na wengine, tatizo lako la usingizi linathiri aje maisha yako :

haijulikani Kabisa	kidogo	kiasi	sana	inajulikana sana
0	1	2	3	4

6. je, una wasiwasi kuhusu shida yako ya usingizi kwa sasa?

sina wasiwasi	wasiwasi kidogo	wasiwasi kiasi	wasiwasi mingi	wasiwasi sana
0	1	2	3	4

7. je, tatizo lako la usingizi linadhiri aje mienedo yako ya kila siku(kwa mfano uchovu sans mchana,uwezo wa kufanya kazi , na kadhalika)?

halizuii kabisa	linazuia kidogo	linazuia kiasi	linazuia sana	linazuia kabisa
0	1	2	3	4

Total score categories

0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

APPENDIX 5: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS 2017

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death