UPTAKE OF DOLUTEGRAVIRBASED ART IN CHILDREN AND ADOLESCENTS LIVING WITH HIV AT KENYATTA NATIONAL HOSPITAL

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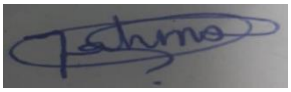
2023

DECLARATION

I declare that this dissertation is my work and has not been published or presented for a degree in any other institution

Dr Fahmo Mohamed. Yusuf

Signature:  **Date** :17//07/2023

SUPERVISORS APPROVAL

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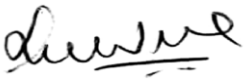
Signature:  **Date:** 17/07/2023

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LIST OF ABBREVIATIONS

2DR: 2-drug regimens

3TC: Lamivudine

ABC: Abacavir

AIDS: Acquired Immunodeficiency syndrome

ART: Antiretroviral Therapy

ARV: antiretroviral drugs

CCC: Comprehensive Care Centre

CLHIV: Children living with HIV

DHIS: District Health Information Software

DTG: Dolutegravir

EFV: Efavirenz

FDC: Fixed Drug Combination

HIV: Human Immunodeficiency virus

INSTI: integrase strand transfer inhibitor

KNH: Kenyatta National Hospital

LMIC: Low- and Middle-Income Country

LPV/r: Lopinavir/ritonavir

NASCOP: National AIDS and STIs Control Programme

NNRTIs: Non-nucleoside reverse transcriptase inhibitors

NRTIs: Nucleoside/Nucleotide reverse transcriptase inhibitors

NVP: Nevirapine

PAWG: Paediatric Antiretroviral Working Group

PIs: protease inhibitors

PLHIV: People living with HIV

RAL: Raltegravir

SPSS: Statistical Package for Social Sciences

TB: Tuberculosis

UON: University of Nairobi

VLS: Viral load suppression

WHO: World Health Organization

DEFINITION OF TERMS

Dolutegravir: is a prescription medicine in the class of Integrase strand transfer inhibitors approved for the treatment of HIV infection.

Adverse effects: An effect, whether therapeutic or adverse, that is secondary to the one intended

Uptake: The action of taking up or making use of something.

ABSTRACT

Background: The World Health Organization (WHO) in 2018 recommended the use of dolutegravir (DTG) containing antiretroviral regimens in all populations including children. DTG has been a major component of Antiretroviral Therapy (ART) treatment for adults in low-resource settings. However, its application in children and experiences of switching to DTG-based ART have not been fully investigated.

Objectives: The primary objective was to evaluate the level of viral suppression following a switch to DTG-containing ART regimens at Kenyatta National Hospital. The secondary objectives were to determine the proportion of children and adolescents living with Human Immunodeficiency Virus (CALHIV) who switched from non-DTG to DTG- containing ART regimens over the past 12 months and short-term caregiver experiences.

Methods: This was a mixed-method study conducted at the Kenyatta National Hospital. A census approach was used to recruit patients who met the inclusion criteria. An interviewer-administered questionnaire was used to collect data on patients' experiences after being initiated on DTG-based ART. The responses were written down by the principal investigator and the research assistant.

Data analysis and presentation: Data analysis was done using R version 4.1.2. Categorical variables e.g., gender and adverse effects were analysed using frequencies and proportions and presented in graphs and charts. Continuous data e.g., age was analysed using Median and Interquartile ranges (IQR) and presented using density plots. The inferential analysis utilized McNemar's test for correlated categorical data to compare differences in viral load before and after initiation of DTG. Tests were interpreted at 5% significance level and p-values less than 0.05 were considered significant.

Results: Of the 495 children from the CCC records, 52.8% (258 out of 495) were males. Before the switch to DTG-based ART, 41%, 19%, 33% and 7% of the children were in WHO stage 1,2,3 and 4 respectively. After the switch to DTG-based ART, there was a shift in WHO stages with 98.7%, 0.2%, 0.9% and 0.2% in WHO stages 1,2,3 and 4 respectively. The proportion of children with viral load < 500 copies/ml increased from 54% before switch to 85% after switch to DTG.

Four hundred and seventy five of the 495 children switched from 1st line non-DTG to DTG containing regimens over the period of study (96% (95% CI 93.7%, 97.4%).

We used McNemar's test for correlated categorical data to compare viral load suppression before and after initiation of DTG-based ART which showed a significant change in viral suppression one year after starting the DTG-based ART regimen ($p < 0.001$).

Experiences from caregivers revealed that appetite had improved and there was an increase in weight for those who previously had challenges with low weight. Scheduling of the drug was reported as a difficulty since it was supposed to be taken at a specific time thus interfering with school. Reduction of episodes of illness, admissions and improvement in health were also reported. There was a reduction of adverse effects compared to previous regimen, others reported no adverse effects while others reported abdominal pain and nausea.

Conclusion: Uptake of DTG optimisation/based ART was high with 96% of participants switching to DTG during the five-year period. Viral suppression improved from 54% to 85% due to switch to DTG in the five-year period under study. Dolutegravir-based ART regimen was associated with fewer adverse effects, there was improvement in appetite and, a reduction in episodes of sickness and admissions.

Utility: The findings of this study will play a critical role in the use of dolutegravir. The results have demonstrated that dolutegravir is an effective drug in viral suppression after its initiation. This study, therefore, supports the WHO recommendations of using dolutegravir as a first-line drug in combination with other drugs to prevent the progression of HIV to AIDS.

CHAPTER ONE: INTRODUCTION

Background

Antiretroviral therapy (ART) optimization is the harmonization of global efforts to accelerate access to simpler, safer and more affordable Human Immunodeficiency virus (HIV) treatment. To meet the needs of people in low- and middle-income countries, HIV treatment must be effective, safe, well-tolerated and affordable (1). Human Immunodeficiency virus (HIV)-acquired immunodeficiency syndrome (HIV-AIDS) is the sixth leading cause of mortality in the world and the top cause of death in Sub-Saharan Africa. In 2019, World Health Organization (W.H.O) estimated that 38.0 million people were living with HIV globally. Actually, 0.7% of adults aged 15-49 years worldwide are living with HIV. During the same year, 2019, 690,000 people are estimated to have died of HIV-related illness worldwide (2).

In 2018, 1.3 million people were living with HIV in Kenya, with an incidence rate of 0.14% of adults (15-64 years) annually. The prevalence among adults aged 15-49 years was 4.9%. The prevalence of HIV among children is 0.7% accounting for about 139,000 children aged between 0-14 years (3). Antiretroviral drugs are currently in use for the management of HIV. The adherence rate to antiretroviral medication should be >95% to achieve the third 90% of the 90-90-90 strategy, that 90% of People Living with Human Immunodeficiency Virus (PLHIV) on treatment achieve an undetectable viral load (4). W.H.O defines adherence as the process by which patients take their medicines as prescribed including, the right dose and right time (2). In Kenya, the levels of adherence to ART among children and adolescents are much lower than the WHO set target.

To improve health and save lives, children living with HIV must have access to timely diagnosis and effective, child-friendly, antiretroviral (ARV) treatment and care that will ensure continuous viral suppression. In 2019, fewer than 55% of the estimated 1.8 million children living with HIV (CLHIV) received life-saving antiretroviral therapy (ART) Children in low- and middle-income countries (LMIC) continue to have limited access to optimal paediatric, and viral load suppression (VLS) rates among children remain unacceptably low (5). To achieve the UNAIDS 95-95-95 benchmarks for all ages by 2030.

World Health Organization (WHO) guidelines recommend immediate ART for all adults and children living with HIV. Although there has been substantial recent improvement in coverage of antiretroviral therapy (ART), only half of the children in need have access to

ART, with the majority (> 80%) living in Sub-Saharan Africa. DTG has been considered child friendly and efficacious although the switch to this regimen has been limited as a result of varied factors such as access.

The prevalence of HIV in Kenya is high, ranking the country fifth in the world (6). In 2018, the prevalence of HIV in Kenya was 4.9%. Women had twice the prevalence compared to men at 6.6% and 3.1% respectively (7). The government of Kenya has initiated free Comprehensive Care Centre (CCC) services around the country to mitigate the HIV problem, and also offers free Anti-Retroviral Therapy (ART) as well as maintains a District Health Information Software (DHIS) database to monitor HIV and manage the drugs used for therapy. Despite the availability of free medicines, HIV remains poorly controlled among children and adolescents (0-18 years) with Viral Load Suppression achieved in only 48.3% of them, which is way below the 90% target (6).

Despite the scarcity of data on the pharmacokinetic properties of drugs in children and infants, the Paediatric Antiretroviral Working Group (PAWG) strives to consolidate registration trial data and recommends suitable formulations for paediatric use. In 2018, PAWG recommended the use of dolutegravir (DTG) in the 20-24 kg weight band. Raltegravir (RAL) is currently in use in the form of granules for neonates. RAL has also been formulated as chewable/dispersible tablets for older children (8).

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI). It has a high genetic barrier for resistance compared to NVP and EFV. It has also been found to have a high level of tolerability in clinical trials and can also be used concurrently with TB treatment. The adverse effects are not severe including insomnia and an increase in body mass index. However, there is limited information on the switch to DTG among children in Sub-Saharan Africa despite the high prevalence of HIV in the region. There are also anecdotal reports of excessive weight gain following the introduction of DTG which warrant evaluation. Thus, this study seeks to determine the proportion of children who switched to DTG-containing ART, short-term experiences and comparison of HIV-1 viral suppression in those who have switched compared to those who have not yet switched.

CHAPTER TWO: LITERATURE REVIEW

2.1.Dolutegravir (DTG) based ART Therapy

Antiretroviral therapy (ART) optimization is essential to attain high-quality care and management of the needs and well-being of children with HIV. The WHO recommends the HIV medication dolutegravir (DTG)-containing ART regimens as the optimal first-line and second-line treatment for all populations based on new evidence weighing benefits and hazards. DTG has been shown in trials to be more effective, easier to use, and has fewer adverse effects than currently available alternatives. DTG also has a high genetic barrier to drug resistance, which is critical given the rising trend of Efavirenz (EFV) and nevirapine-based regimen resistance. It is therefore appropriate for use in both ART-naïve and experienced children. In 2019, WHO revealed that pre-treatment medication resistance levels of Non-nucleoside reverse transcriptase inhibitors (NNRTIs) which have been the backbone of ART regimens in the past two decades in 12 of the 18 countries surveyed were higher than the recommended threshold of 10% (9). The threshold of 10% is significant in that above this it is not optimal to use such a molecule as the first-line regimen.

Paediatric dolutegravir 10 mg dispersible, scored tablets (pDTG) have recently been introduced and this is a valuable addition to the previously available formulation of 50mg tablets. This paediatric formulation of ART has been tested and found to be effective and safe for children LHIV) at least one month of age and weigh at least 3 kg and up to 20 kg. This formulation can readily be used together with ABC/3TC dispersible in a convenient once–daily dosing which makes it highly tolerable and easily fits into the schedule of caregivers.

The introduction of a DTG dispersible pill is a huge step forward in CLHIV treatment. DTG's efficacy is superior to both protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) based on data extrapolated from adult studies (NNRTIs). The introduction of DTG directly targets CLHIV medication resistance before treatment as well as acquired drug resistance following the failure of NNRTI or PI-based regimens (10). DTG can also be utilized as an anchor medication alongside an optimized NRTI backbone throughout childhood and adulthood due to a high genetic barrier to resistance. This is especially important in low- and middle-income countries, where genotypic drug resistance testing is scarce (11).

The current National guidelines for ART treatment recommend that children between 3kg and less than 20kg be either started on (ART –naïve) or switched (ART-experienced) to DTG-containing ART. Figure 1 shows the current recommendation to transition children

Paediatric DTG in the current once-daily dispersible tablet that can be dissolved and provided

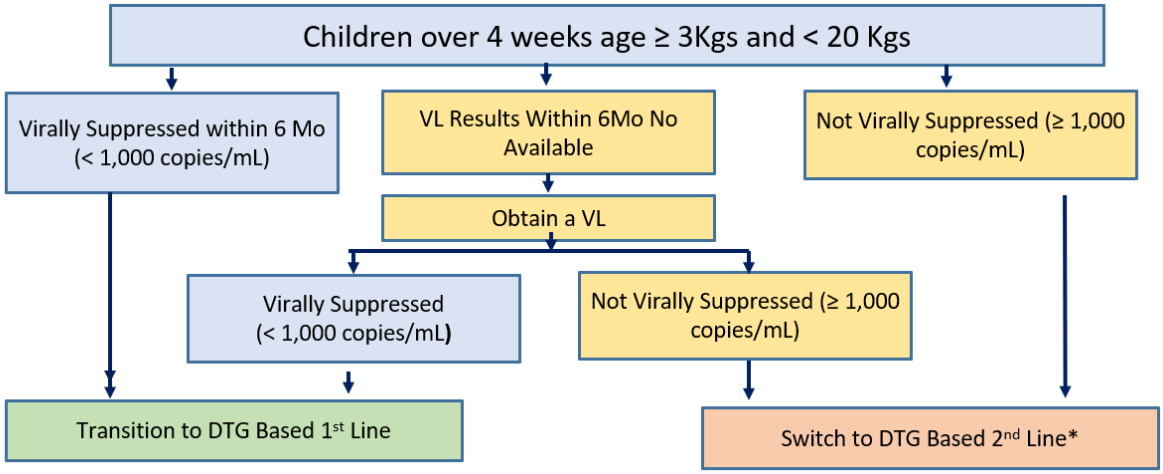

Figure 1: Recommended schedule on DTG-10 optimization in children

alongside dispersible Abacavir/ Lamivudine (ABC/3TC) formulations is more convenient than taking Lopinavir/ritonavir (LPV/r) twice a day and lowers pill burden. LPV/r granules and pellets require additional training to ensure appropriate adherence; LPV/r oral solution has poor palatability and requires a consistent cold chain until dispensed; and the LPV/r heat-stable tablet cannot be cut, crushed, chewed, or dissolved, preventing its use in young CLHIV patients (12).

2.2.Uptake of dolutegravir in children

Early studies on the use of DTG in children primarily included small numbers of ART-experienced children. A case study was conducted in Italy to investigate DTG efficacy among six cases of HIV-infected children. Patients were started on a DTG-based ART regimen due to low-level adherence to previous regimens, multiple drug resistance mutations and adverse effects. The study reported a complete viral suppression and an increase in CD4+ cell count within 4-8 weeks of starting DTG treatment. After two years of follow-up, four patients demonstrated durable viral suppression. The patient who had been enrolled due to severe dyslipidaemia and hyper-transaminase demonstrated a complete normalization of test values one month after starting DTG. There were no adverse events recorded during follow-up (median 24 months, range 9-24 months) and most patients showed strong adherence to medication (1).

Rolando et al. in 2020 conducted a multicentre open-label cohort study of DTG in children. The study showed that 16 of the 23 enrolled teenagers remained on treatment for at least 144 weeks, with a median follow-up of 153 weeks (range, 55-193 weeks). Dolutegravir was well tolerated, with 5 subjects reporting grade 3 clinical adverse events, 3 reporting grade 3 laboratory abnormalities, and 1 reporting grade 4 laboratory abnormalities. None of the adverse events or abnormalities were deemed treatment-related. In an intent-to-treat analysis, 43 percent (10 of 23 patients; 95% C.I 23.2%-65.5 %) had an HIV-1 Ribonucleic acid (RNA) level of 400 copies/mL at week 144, while 35% (8 of 23; 95% C.I 16.4 -57.3 %) had an HIV-1 RNA level of 50 copies/mL (13)

Another study conducted by Bruzzese et al. revealed that DTG-based treatments demonstrated efficacy and good safety profile in adolescents. All patients demonstrated a rapid virologic and immunological response within 4–8 weeks, with good adherence and absence of adverse effects.

In a large open-label, randomized, non-inferiority trial involving 707 participants comparing three-drug ART based on the dolutegravir (DTG) with standard care (efavirenz-based ART) in children and adolescents starting first- or second-line ART, DTG-based ART was superior to standard care. By 96 weeks, 47 participants in the DTG group and 75 in the standard care group had treatment failure (estimated probability, 0.14 vs. 0.22, p = 0.004) (14).

Adverse effects of dolutegravir

Dolutegravir has been significantly associated with a higher degree of success although there are adverse effects which have been identified in patients who have utilized DTG-based ART. Thivalapill et al. in a retrospective study conducted in 2021 investigating the effect of DTG on body mass index (BMI). The findings from the study revealed that, before the DTG transition, adolescents' BMI increased at a rate of 0.3 kg/m2 per year, increasing to 1.2 kg/m2 per year following the DTG transition. The link between DTG and rate of BMI change was influenced by the adolescent's gender: females' BMI rate of change following DTG transition was raised by 1.1 kg/m2 per year, while boys' BMI rate of change was increased by 0.6 kg/m2 per year (14). Thus, it has been noted that transitioning to DTG is linked to a faster rate of BMI change in virally suppressed adolescents (ages 10–19 years). Female adolescents may go through more changes than male adolescents. More research is needed to explain the mechanism that underpins these findings and to determine how DTG affects BMI in adolescents during extended treatment periods.

A multi-centre study conducted by Viani et al. revealed that out of the 23 participants, 39% discontinued study treatment before 144 weeks, but none because of adverse events or drug intolerance. All participants with sustained virologic control had excellent adherence; most who experienced virologic failure had adherence levels <90%. HIV-1 genotypic drug resistance testing was available at the time of failure from 6 participants; 1 had an evolution in integrase resistance with E138T, S147G, and R263K mutations at week 192 and phenotypic dolutegravir resistance of a 5.1-fold change (13). Dolutegravir plus an optimized background regimen seemed safe, well tolerated, and efficacious in this cohort of treatment-experienced HIV-1-infected adolescents. Adherence remains problematic in this population.

Another cohort study conducted by Waznia et al in investigating the impact of DTG found that DTG plus optimized background regimen (OBR) in children was found to be safe, well tolerated and provided virologic efficacy through week 48 in HIV-infected children 6-12 years of age(15)

According to the ODYSSEY trial, a multi-country randomised trial, DTG-based ART was superior to SOC (predominantly protease inhibitor-based ART) in young children starting first or second-line therapy, judged on treatment failure by 96 weeks. The treatment benefit for DTG in the <14kg cohort was consistent with that observed in children enrolled ≥14kg. There were no safety concerns on DTG. At 96 weeks, 76% of children in the DTG arm had VL< 50 copies/mL compared with 50% in SOC; corresponding proportions with VL< 400 copies/mL were 91% vs. 71%.

2.3.Experiences following the switch to dolutegravir-containing ART regimens

Ward et al. in a retrospective study investigating the switch to DTG-based ART therapy and found that DTG was most commonly paired with darunavir (55%) or rilpivirine (27%). The most common physician-reported reasons for initiating DTG 2DR were treatment

simplification/streamlining (30%) and avoidance of potential long-term toxicities (20%). Before starting DTG-2-drug regimens (2DR), 42% of patients were virologically suppressed; of those, 95% maintained suppression while on DTG 2DR. Of the 50% of patients with detectable viral load before DTG 2DR, 79% achieved and maintained virologic suppression on DTG 2-drug regimens (2DR) during follow-up. there was no virologic data for 8% of patients before starting DTG 2DR (16).

A qualitative study conducted in Uganda by Twimukye et al. investigating the experiences of switching from Efavirenz to DTG-based ART revealed that participants reported accepting

provider recommendations to switch to DTG mainly because they anticipated that swallowing a smaller pill once a day would be more convenient. While most participants initially felt uncertain about drug switching, their providers' offer of frequent appointments and a toll-free number to call in the event of adverse effects allayed their anxiety. In addition, participants said they felt rushed to switch to the new ART regimen considering that they had been on their previous regimen(s) for several years and the switch to DTG happened during a routine visit when they had expected their regular prescription. Some participants felt unprepared for new adverse events associated with DTG and for the abrupt change in treatment schedule. Most participants said they needed additional support from their health providers before and after switching to DTG (17). However, the response and experiences among children and adults vary significantly which might provide different results from those obtained in this study.

2.4.Conceptual framework

The conceptual framework as defined in this case investigates the switch to a DTG-based ART regimen. Independent variables focus on child demographic characteristics and HIV-specific characteristics. The child characteristics investigated in this case include gender, age, presence of underlying condition and BMI. HIV-specific factors that have been investigated include viral load, WHO classification, duration since diagnosis, change of ART regimen history, high viral load, advanced disease (viral neurotoxicity/inflammation), long duration of illness (chronic inflammation) and adverse effects of ARVs.

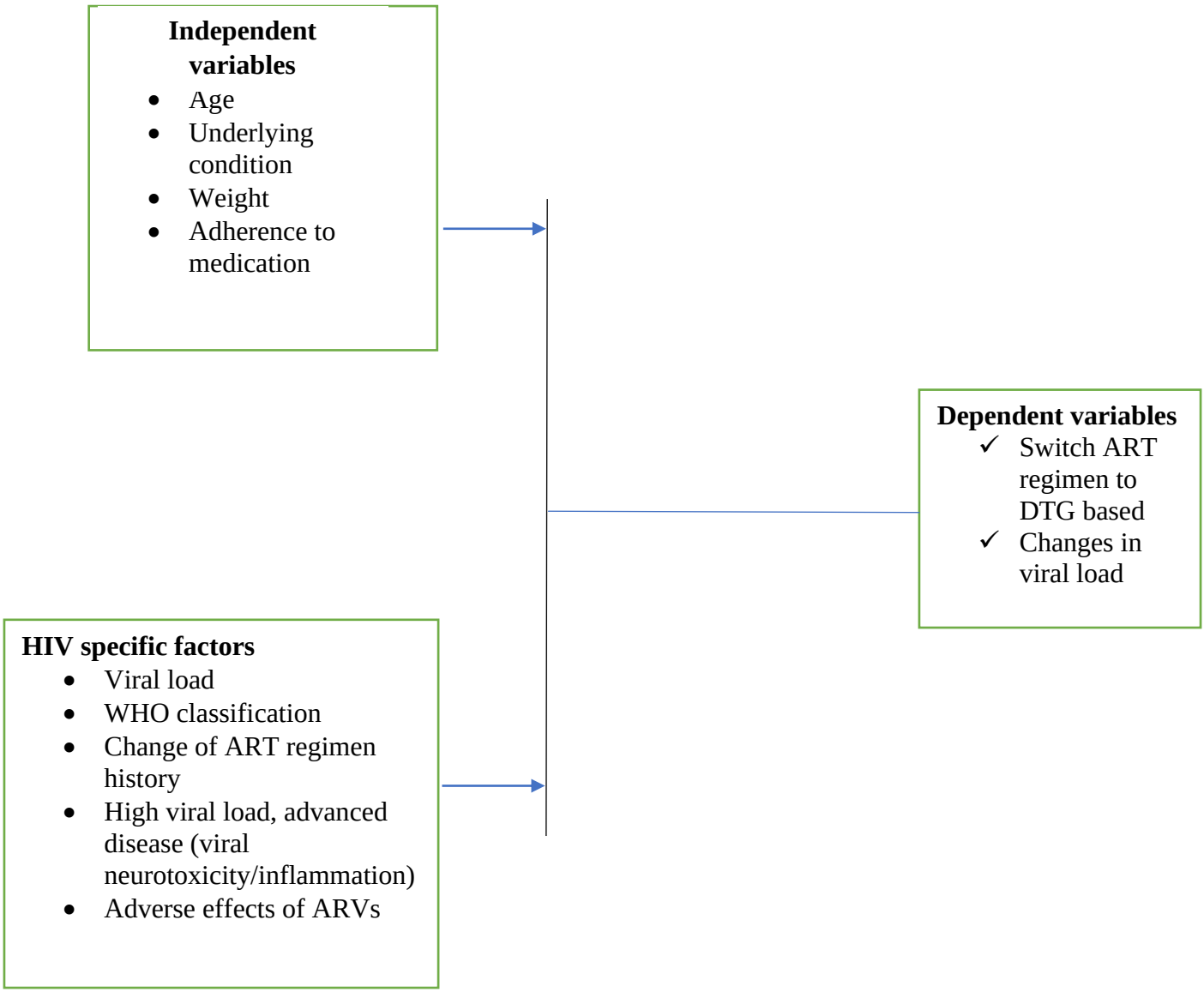

Figure 2: Conceptual Framework

2.5.Justification of the study

Significant efforts are being undertaken to end or reduce HIV significantly. However, achieving significant success in this context requires the adoption of more efficacious ART regimens. Children have always suffered lower rates of adherence and poor viral suppression in comparison to adults and this problem is especially magnified in adolescents. The World Health Organization has recommended the use of DTG-based ART regimens as a result of successful trials which have shown better tolerance, higher adherence and more effective viral suppression. Thus, following the WHO recommendation, Kenya's Treatment guidelines for children living with HIV have included DTG. However, there is no published data on the uptake of DTG-based regimens among children and adolescents. This forms the basis of the study. DTG uptake is likely to result in higher viral suppression rates and easier

administration. On the other hand, concerns have been raised including adverse effects such as a rapid increase in BMI which can affect optimization and need to be evaluated. This study is an opportunity to review uptake and short-term experiences following optimization in a large tertiary centre.

2.6.Research question

What is the uptake and patient/caregiver experience following DTG optimization for children and adolescents < 18 years?

2.7.Objectives

Primary objectives

1. To determine the proportion of children and adolescents living with Human Immunodeficiency Virus (CALHIV) who switched from non-DTG to DTG-containing ART regimens over the past 12 months at Kenyatta National Hospital.
2. To evaluate the level of viral suppression following a switch to DTG-containing ART regimens at Kenyatta National Hospital.

Secondary objective

3. To determine the short-term patient/caregiver experiences (ease of administration, convenience with daily schedule, adverse effects) following a switch to DTG-containing ART regimens at Kenyatta National Hospital.

CHAPTER THREE: METHODOLOGY

3.1.Research design

For the primary objective (To evaluate the level of viral suppression following a switch to DTG-containing ART regimens) and first secondary objectives we utilized retrospective design based on hospital records from January 2018 to June 2022 and a qualitative component (in-depth interviews) conducted on selected participants. The data was acquired from the CCC database where all the observations that met the inclusion criteria were included in the study.

For the second secondary objective cross sectional design was used. Qualitative data was collected from parents of children aged less than 15 years and living with HIV. Children living with HIV and aged more than 15 years responded to the interview questions in person. The qualitative approach of this study was exploratory in nature.

3.2 Study setting

The study was conducted in the CCC at Kenyatta National Hospital, Nairobi County, Kibra sub-county, Woodley/Kenyatta Golf course ward. Kenyatta National Hospital is a level six hospital and the largest hospital in Kenya with a bed capacity of 1800. The facility serves as a teaching and referral hospital for the University of Nairobi making it a suitable site. The facility has about 60 theatres (16 specialized), 50 wards, 22 outpatient clinics as well as an Accident and Emergency department. It offers a wide range of services including the Comprehensive Care Centre (CCC) where People Living with HIV-AIDS access healthcare. The services offered at the CCC include; testing and counselling, pharmaceutical care, nutritional support, laboratory services as well as Prevention of Mother to Child Transmission (PMTCT).

3.3 Study Population

The target population was children and adolescents living with HIV (CALHIV) less than 18 years old in Kenya. Adolescents were included as they are still legally minors and dependent on caregivers for their healthcare. The number of CAHIV enrolled at the KNH CCC at the time of this study was 562. Caregivers of CALHIV were enrolled to provide information on experiences after their children were switched to DTG-based ART.

3.4 Eligibility criteria for the retrospective cohort

Inclusion Criteria

- Children and adolescents living with HIV aged < 18 years attending the CCC clinic

- Attended the CCC for at least 18 months with complete hospital records

Exclusion criteria

- Patients who don't have complete records in the CCC database

3.5 Sample size determination

The study included all children and adolescents LHIV < 18 years who had received ART treatment at CCC for more than 18 months.

3.6 Sampling technique

This study adopted a census approach where all children and adolescents LHIV< 18 years who had received ART treatment at CCC over 18 months were included. Eligibility for in-depth interviews.

Inclusion Criteria

-Children and adolescents living with HIV aged < 18 years attending the CCC clinic

- They must have switched to DTG in the past 12 months

-Those who give consent or assent to participate

Exclusion criteria

- Lack for consent

3.7 The sample size for experiences after the switch to dolutegravir-based ART

This included a sample of 20 participants as initially indicated in the protocol. Data collection was interviewer-guided using a semi-structured questionnaire. Data saturation dictated the sample size for in-depth interviews and was achieved at 20 participants.

3.8 Sampling technique for in-depth interviews

Purposive sampling was used to recruit participants for the interviews on experiences after the switch to DTG-based ART. Majority of the children encountered in the clinic were less than 15 years and we decided that they make the majority of the sample. We intended to do 50% each for females and males but the proportion of gender varied due to the understanding of the topic and consent to participate leading to a slight difference in gender. The initial treatment was not accounted for in sampling.

3.9 Data collection tools

The quantitative data for the retrospective component of the study was mainly secondary data from the CCC database. The data was abstracted from the CCC database based on the inclusion criteria and study variables. Data collection for patients' experiences after switching

to DTG-based ART was interviewer-guided. A semi-structured questionnaire was used to collect data for this purpose.

Pre-test

The questionnaire was pretested using 10% of the sample at Kenyatta National Hospital comprehensive care centre. The tool was mainly pretested to determine the internal validity and reliability of the questionnaire.

3.10 Data quality control

To avoid duplicate findings, the questionnaires was assigned serial numbers. Following collection, the data was reviewed to ensure completeness.

3.11 Ethics

The request to get the data was made formally after the study had been approved by KNH-UoN ERC and permission to conduct the study had been given by the KNH research and programs department.

The data included:

a. Socio-demographic characteristics
b. Clinical status including WHO stages
c. Current ART regimens
d. History of ART including any switches. Specifically, whether the patient switched to DTG in the past year.
e. Viral loads – the latest level before the switch and the first viral load available after the switch.
f. Any adverse effects experienced in the past 12 months.

Collection of data from caregivers and patients' on dolutegravir experiences through interviews

This data was collected to gain insights into patients' experiences after being switched to DTG-based ART. This data was collected from caregivers for children who could not respond to questions and adolescents who could respond to questions. The data collected in this section included adverse effects, improvements from the previous regimens and challenges of taking DTG-based ART. The verbal responses from study participants were recorded in the questionnaire by the principal investigator and research assistants. The interviews were conducted in both English and Swahili. The Kiswahili responses were translated when recording them in the questionnaire.

Study flowchart

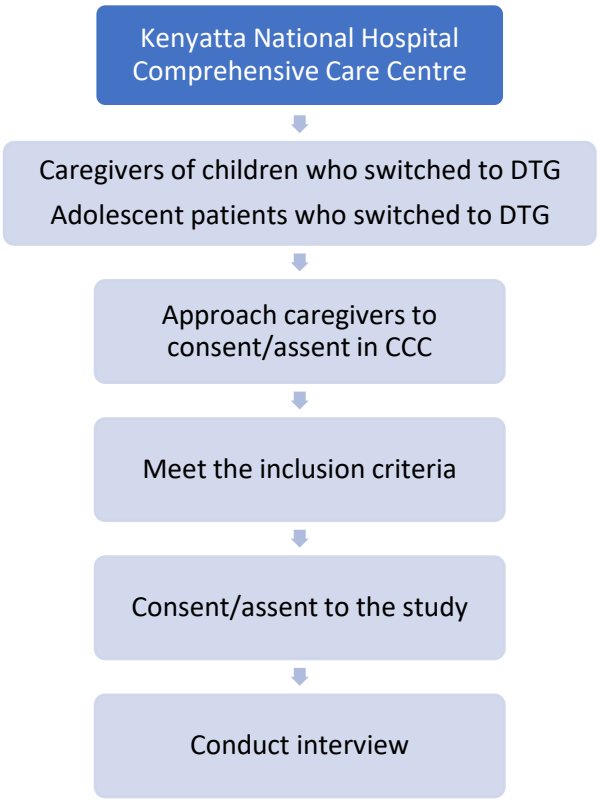

Figure 3: Study flow chart

3.12 Variables in the study

The child characteristics investigated in this case include gender, age, presence of underlying condition and weight. HIV-specific factors that were investigated include viral load, WHO classification, change of ART regimen history, high viral load, advanced disease (viral neurotoxicity/inflammation), long duration of illness (chronic inflammation) and adverse effects of ARVs. The dependent variable will include switching to DTG based ART regimen and change in viral load after initiation of DTG-based ART.

3.13 Data management

Data entry and cleaning

Responses obtained from the questionnaires were coded and entered into excel using excel forms. The data was then imported into R version 4.1.2 where recoding was done. The data was then cleaned and the responses from the open-ended questions were parsed and converted into themes and subthemes, and presented with the exact quotations from the

patients and caregivers. The secondary data was obtained in soft copy form in an excel sheet. It was then imported into R version 4.1.2 for cleaning. Variables that were not directly linked to this study were removed. columns were removed.

Data storage

The completed questionnaires have been kept in a locked cabinet that only the principal investigator can access. Soft copy data backup has been stored in a password-protected flash disk. The data will be kept for five years, after which time the hardcopy papers will be shredded and the soft copy data will be maintained in the repository.

Data analysis

Data analysis was done using R version 4.1.2. Categorical variables e.g., gender and adverse effects were analysed using frequencies and proportions and presented in graphs and charts. Continuous data e.g., age was analysed using Median and Interquartile ranges (IQR) and presented using density plots. The inferential analysis utilized McNemar's test for correlated categorical data to compare differences in viral load before and after initiation of DTG. Tests were interpreted at 5% significance level and p-values less than 0.05 were considered significant.

Qualitative data was analysed by first creating themes from the interview responses through thematic analysis. A set of subthemes were then generated under each theme. The themes were presented together with the subthemes under them. Direct responses from the respondents were included under the subthemes using quotation marks.

3.14 Ethical consideration

Before data collection, approval from the KNH-UoN Ethics Committee was sought. Permission to conduct the study will also be sought from KNH. Participants were asked to participate voluntarily, and consent was sought from all respondents before participation. Assent to participate was sought from the adolescent children.

At all times, confidentiality was maintained. Each study participant was allocated a unique study number as the only identifier. The participants had the option to leave the study at any time.

All completed questionnaires were kept in a secure environment at all times. Following the completion of the study, these records will be stored for the required amount of time before being destroyed.

Dissemination of study findings

After the completion of this study, the findings will be presented to a panel of lecturers at the University of Nairobi, Department of Paediatric and Child Health. A soft copy of the report will also be published in the University of Nairobi Repository. Other copies of the report will be presented to the Kenyatta National Hospital; CCC, Research and programs Department and KNH-UoN ethics review committee.

Limitations of the study

The study is being conducted in one healthcare institution and information therefore cannot be generalized to other institutions. The CD4 count were not available before and after initiation. The secondary data was acquired from the CCC register. It was therefore difficult to verify the truthfulness of the data as we had no control over its collection.

4.0 CHAPTER FOUR: RESULTS

PHASE A: RETROSPECTIVE MEDICAL RECORDS ABSTRACTION ARM OF THE STUDY

Data was collected over the period from January 2018 to December 2022. There were 562 children and adolescents in active care at KNH CCC potentially eligible children and adolescents living with HIV. After screening of these 562, 67 were not eligible for the following reasons: Sixty-one children and adolescents had been started on DTG-based ART in their initial regimen and six were above 18 years.

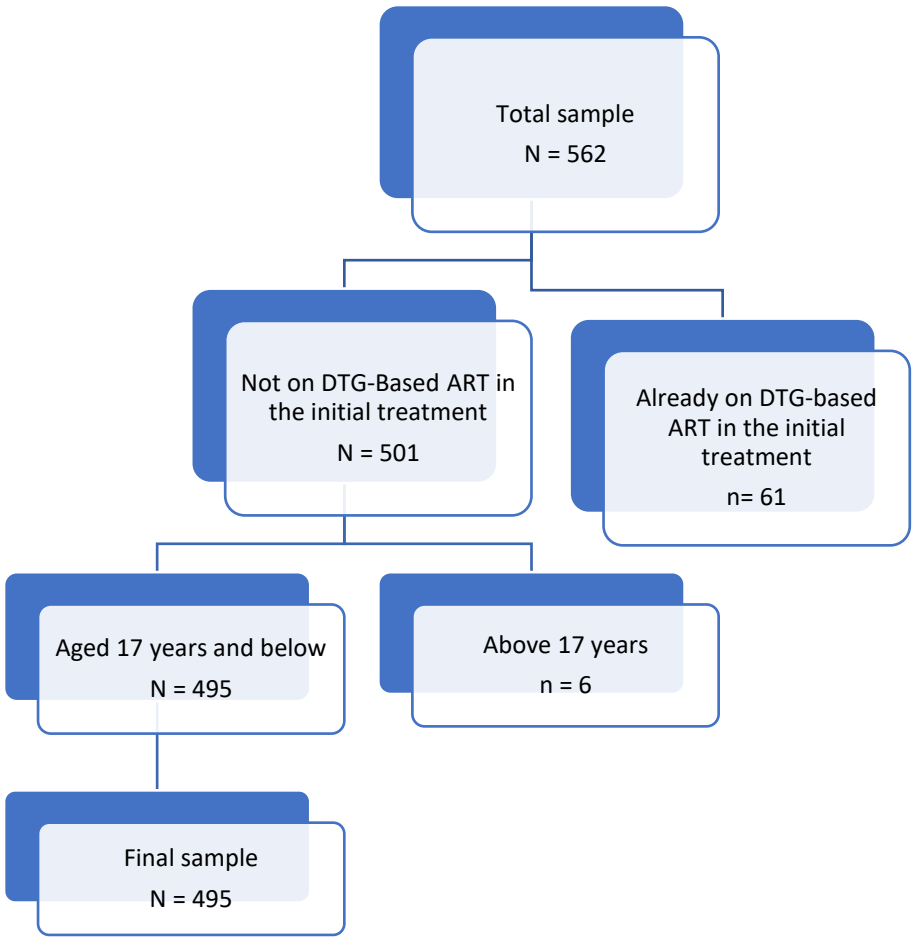

Figure 4: Study flow – screening and eligibility

4.1 Characteristics of study participants

Of the 495 children from the CCC records, 52.8% (258 out of 495) were males and age ranged from 6 months to 17.9 years. The median age was 14.3 years with an interquartile range of 10.1 to 16.3 years.

The schooling status for the majority 77.6% (384 out of 495) of the respondents was not documented. Of the children who were schooling, most of them are in primary school, 17.8% (88 out of 495) and the remaining in secondary school. The least recorded weight was 4.0 kilograms while the highest weight was 168.5 kilograms. The median weight was 43.2 kilograms (interquartile range of 29.8 to 55.0 kilograms), the median height was 145.2 centimetres (interquartile range of 133.8 cm to 162.0 cm).

Table 1: Demographic characteristics of study participants

Variable	**Description**	**Frequency or Median. N = 495**	**Percent or IQR**
Gender	Female	237	47.8
	Male	258	52.2
Age	Age in years	14.3	(10.1, 16.3)
Education level	Primary	88	17.8
	Secondary	23	4.6
	*Not documented	384	77.6
Nutritional status based on height for age z-scores (HAZ)	Normal (-1 <HAZ <0)	290	59
	Mild stunting (-2 <HAZ <-1)	104	21
	Moderate stunting (-3 < HAZ < -2)	45	9
	Severe stunting (HAZ < -3)	56	11
On TB treatment	Yes	4	0.8
	No	491	99.2
Chronic illnesses	Asthma	3	0.6
	Epilepsy	4	0.8
	Hypertension	1	0.2
	None	487	98.4

***Not documented – information not provided**

Nutritional status was computed using height for age z scores (HAZ). Of the total study participants, 59% (290 out of 495) were well nourished, 21% (104 out of 495) had mild

stunting and 11% (56 out of 495) had severe stunting. The educational status for the majority 77.2% (382 out of 495) of the children was not documented, 17.6% (87 out of 495) were in primary school, 4.2% (21 out of 495) were in secondary school and the rest were in tertiary institutions (table 1).

4.2 Clinical information

Baseline and after switch to dolutegravir ART treatment

Before switch to DTG-based ART, the majority of the children i.e., 98% (485 out of 495) were on child first line ART which consisted of multiple regimens and the rest were on child second line. The majority 92.8% (459 out of 495) of the children were on child first-line treatment after switch to DTG, 6.9% (34 out of 495) were on child second line and the rest were on child third line (Figure 5).

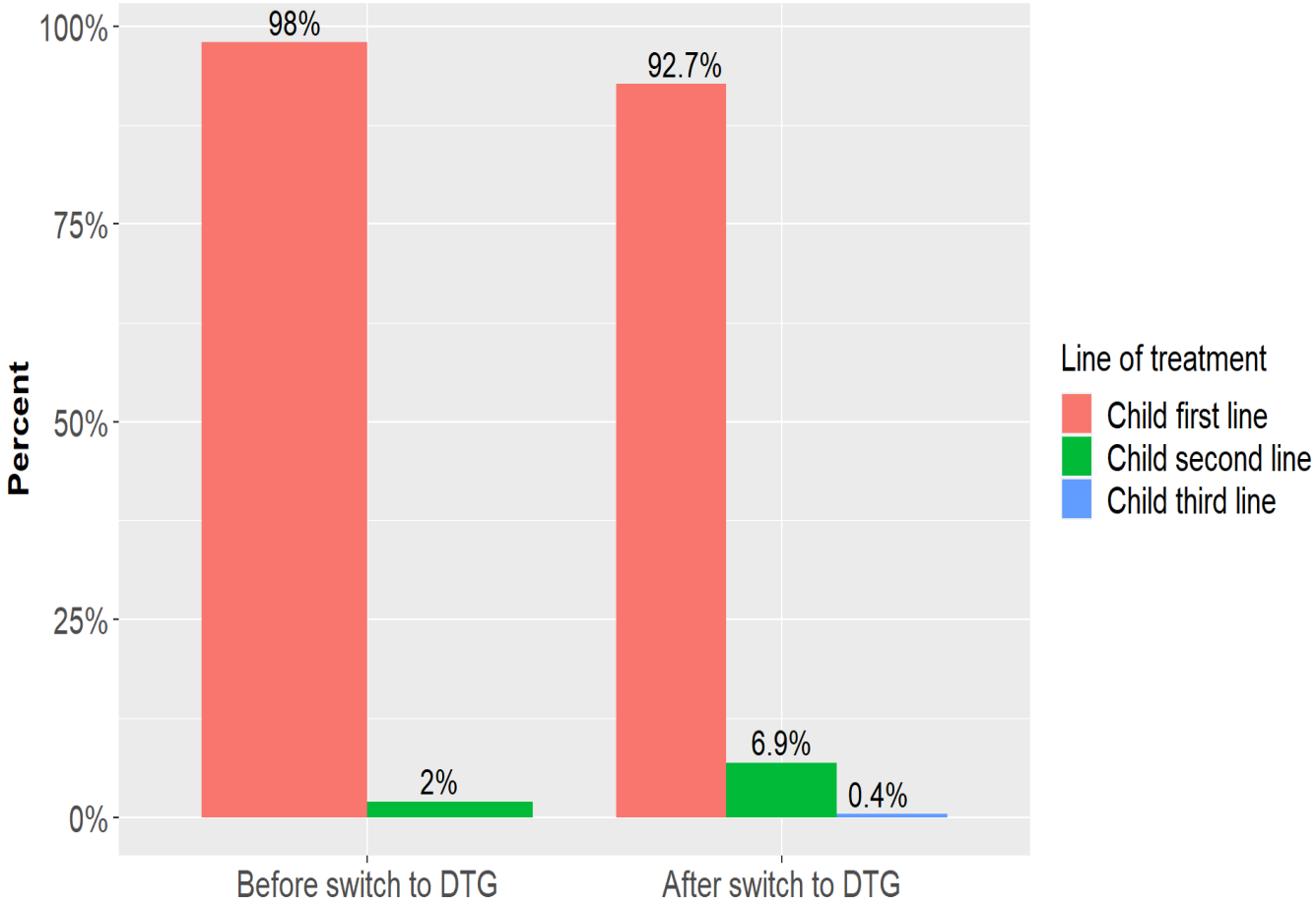

Figure 5: Line of antiretroviral therapy treatment

Antiretroviral therapy regimens before the switch to dolutegravir

Before being switched to dolutegravir-based ART regimens, the children were on either child first line or second line ART. All the regimen before switch were fixed dose combinations with NRTIs backbone as presented in table 2 below. The majority of the children were of child first line therapy of which 307 (62%) were on ABC-based fixed drug combination, 135 (27.3%) were on AZT-based fixed drug combinations, 43 (8.7%) were on TDF-based fixed drug combination and two on D4T-based FDC. Of those on child second line therapy, seven were on ABC-based fixed drug combination, two were on AZT-based fixed drug combinations and one was on D4T-based FDC.

Table 2: ART regimens before switch to dolutegravir (N = 495)

Line of treatment	**NRTI-based drug combinations**	**Freq**	**Percent**
Child first line	ABC-based FDC	307	62
	AZT-based FDC	135	27.3
	TDF-based FDC	43	8.7
Child second line	ABC-based FDC	7	1.4
	AZT-based FDC	2	0.4
	TDF-based FDC	1	0.2

FDC-Fixed drug combination

Actual regimen before and after switch to dolutegravir-based ART regimen

Before the switch to the current regimen, 153/175 (32.2%) were on lopinavir/r-based ART regimen, 132 (27.8%) were on nevirapine-based ART regimen and 190 (40%) were on efavirenz-based Art regimen.

After the switch to DTG-based regimen, among those who were on lopinavir/r-based ART regimen, 106 (69.3%) were switched to TDF/3TC/DTG, 42 (27.5%) were switched to ABC/3TC/DTG-based ART and 5 (3.3%) were switched to AZT/3TC/DTG-based ART.

Among the children who were on nevirapine-based ART regimen, 122 (92.4%) were switched to TDF/3TC/DTG, 9 (6.8%) were switched to ABC/3TC/DTG and 1 (0.8%) to AZT/3TC/DTG. Those on efavirenz-based ART regimen were switched to: TDF/3TC/DTG 123 (64.7%), ABC/3TC/DTG 64 (33.7%) and AZT/3TC/DTG 3 (1.6%) Table 3.

Table 3: The regimens before and after switch to the current regimen N = 475

Initial Regimen	Switch regimen	Freq	Percent
Lopinavir-ritonavir based (N=153)	TDF/3TC/DTG	106	69.3
	ABC/3TC/DTG	42	27.5
	ABC/3TC/DTG	5	3.3
Nevirapine (N=132)	TDF/3TC/DTG	122	92.4
	ABC/3TC/DTG	9	6.8
	ABC/3TC/DTG	1	0.8
Efavirenz based (N=190)	TDF/3TC/DTG	123	64.7
	ABC/3TC/DTG	64	33.7
	ABC/3TC/DTG	3	1.6

World Health Organization staging

Before the switch to DTG-based ART, 41% (203 out of 495), 19% (94 out 495), 33% (161 out of 495) and 7% (37 out of 495) of the children were in WHO stage 1,2,3 and 4 respectively. After the switch to DTG-based ART, there was a shift to WHO stage 1 where we have 98.7% (489 out of 495) of the children, stage 2 had 0.2% (1 out of 495), stage 3 0.9% (4 out of 495) and stage 4 0.2% (1 out of 495) (Table 4 & Figure 6).

Table 4: WHO HIV Clinical staging of the patients before and after dolutegravir optimisation (N = 475)

	Before DTG optimisation		**After DTG optimisation**	
WHO HIV clinical staging	**Freq**	**%**	**Freq**	**%**
Stage 1	195	41	469	98.7
Stage 2	90	19	1	0.2
Stage 3	157	33	4	0.9
Stage 4	33	7	1	0.2

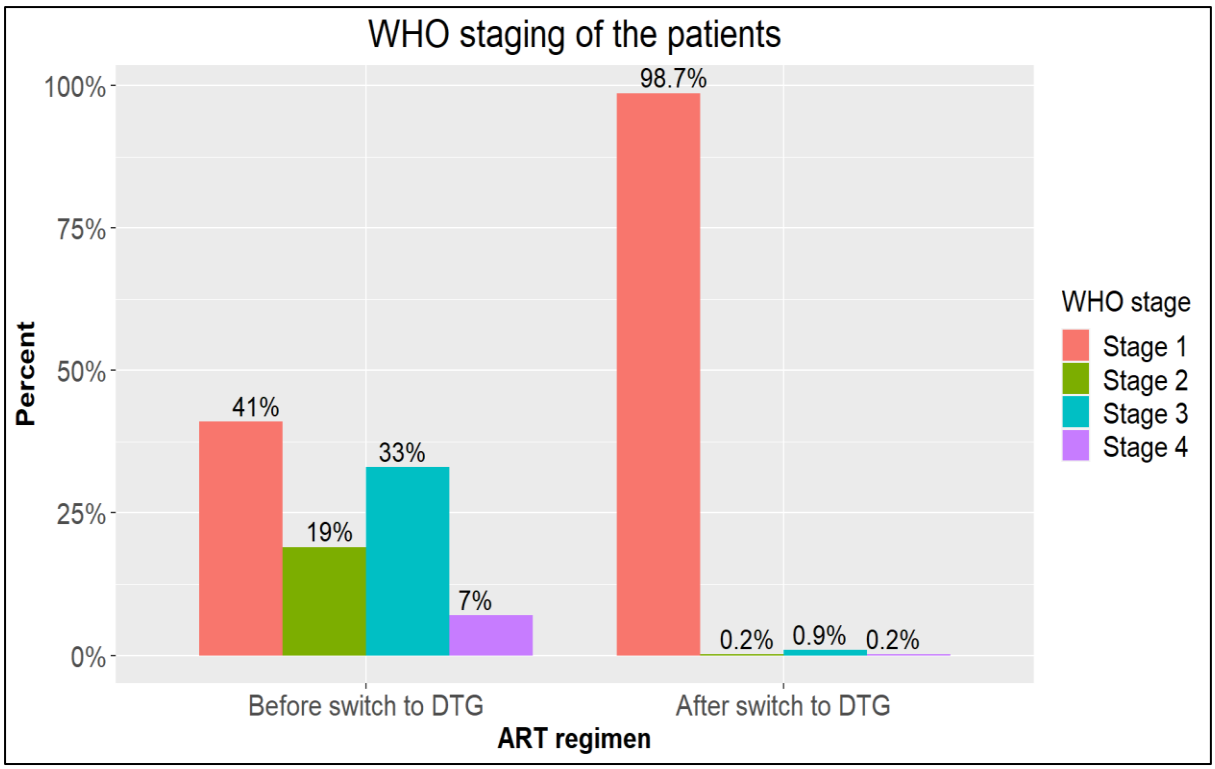

Figure 6: WHO HIV Clinical staging of the patients before and after dolutegravir optimisation

Other clinical information

Table 5 below presents other clinical characteristics of the children who participated in this study. This is general information and is not specific to either before switch or after switch to DTG-based ART Regimen.

Adherence to ARVs was assessed using **Mmas 4 score**: 0 = Good, 1-2 = Inadequate, 3-4 = Poor

On adherence to antiretroviral drugs, 78.5% (389 out of 495) of the participants were ranked good adherence. Those with inadequate adherence were 1.3% (6 out of 495) and 0.2% (1 out of 495) had poor adherence. Children without information on adherence were 20% (99 out of 495). The children were also on prophylaxis against opportunistic infections. The majority 68.1% (337 out of 495) of them were on cotrimoxazole and isoniazid followed by 20.2% (100 out of 495) who were on cotrimoxazole alone.

Reasons for switch to dolutegravir-based ART regimen

Among the children whose initial regimen did not contain DTG-based ART and were switched to DTG-based ART, the reasons given for switching were: Regimen optimization 42.6% (211 out of 495), treatment optimization 26.3% (130 out of 495), Nevirapine phase out 17.7% (87 out of 495) and 2% (10 out of 495) were due to virological failure. Age transition and drug toxicity accounted for 0.4% (2 out of 495). The remaining 11.1% (55 out of 495) had DTG as part of their initial regimen. The majority 446 (90.1%) of the children had signs of TB, 46 (9.3%) did not have TB and 3 (0.6%) were presumed to have TB. Only 4 (0.9%) of the children were on treatment for TB (table 5).

Table 5: Clinical information of the children

Variable	Description	Frequency N = 495	Percent (%)
Adherence to antiretroviral drugs (both before and after switch to DTG)	Good	389	78.5
	Inadequate	6	1.3
	Poor	1	0.2
	Not indicated	99	20
Prophylaxis	Cotrimoxazole and Isoniazid	337	68.1
	Cotrimoxazole	100	20.2
	Cotrimoxazole, rifampicin, isoniazid	13	2.6
	Isoniazid	20	4
	Rifapentine and isoniazid	1	0.2
	None	24	4.8
Reasons for regimen switch to DTG-based regimen	Age transition and drug toxicity	2	0.4
	Nevirapine phase out	87	17.6
	Regimen optimization	211	42.6
	Treatment optimization	130	26.3
	Virological failure	10	2
	Not switched (already on DTG)	55	11.1
TB screening results	No TB	46	9.3
	Signs of TB present	446	90.1
	Presumed TB	3	0.6
On anti-TB drugs	Yes	4	0.9
	No	491	99.1

****Treatment optimization***: to enhance the long-term efficacy, tolerability, convenience, safety and affordability of ART combination.

Regimen optimization: maintain viral suppression without jeopardizing future treatment options

The proportion of children that was switched to dolutegravir-based regimen

The proportion of children who were switched to a DTG-based regimen was 96% (475 out of 495). The 95% confidence interval was 93.7%, 97.4% (figure 7).

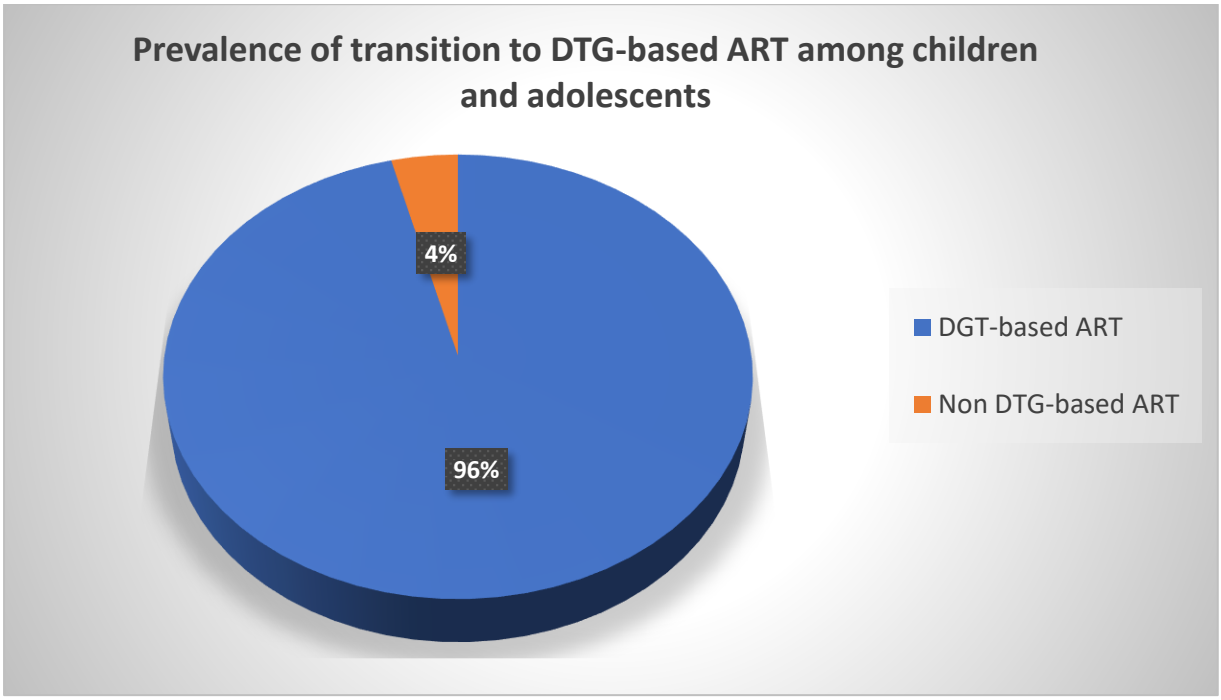

Figure 7: Proportion of children switched to dolutegravir-based regimen

Table 7 below highlights the proportion of children switched to DTG-based ART based on age. The highest percentage of children who were switched from the initial regimen to DTG-based regimen were aged below 10 years 116/119 (97.5%) followed by those aged above 14 to 17 years 250/261 (95.8%) Table 6

Table 6: Proportion that switched to dolutegravir-based ART based on age

Age in years	**Before switch N = 495**	**After switch N = 475**	**Percent**
Less than 10 years	119	116	97.5
10 to 14 years	115	109	94.8
Above 14 to 17 years	261	250	95.8

Time taken to switch to dolutegravir-based ART regimen

The minimum time taken to switch to DTG-based ART regimen was 7 months and maximum was 12 years. The median time to switch was 6.4 years with an interquartile range of 2.6 to 7.4 years (table 8).

Table 7: Time of switch to dolutegravir-based ART

Summary	Time
Minimum	7 months
Maximum	12 years
Median	6.4 years
Interquartile range	2.6, 7.4 years

4.3 Comparison of viral load before and after the introduction of dolutegravir-based ART

Before initiation of dolutegravir-based ART, 54% (257 out of 475) of the children had a viral suppression of below 500 copies per ml. Twelve months after the initiation of dolutegravir, viral suppression increased from 54% to 85% (404 out of 475) figure 8.

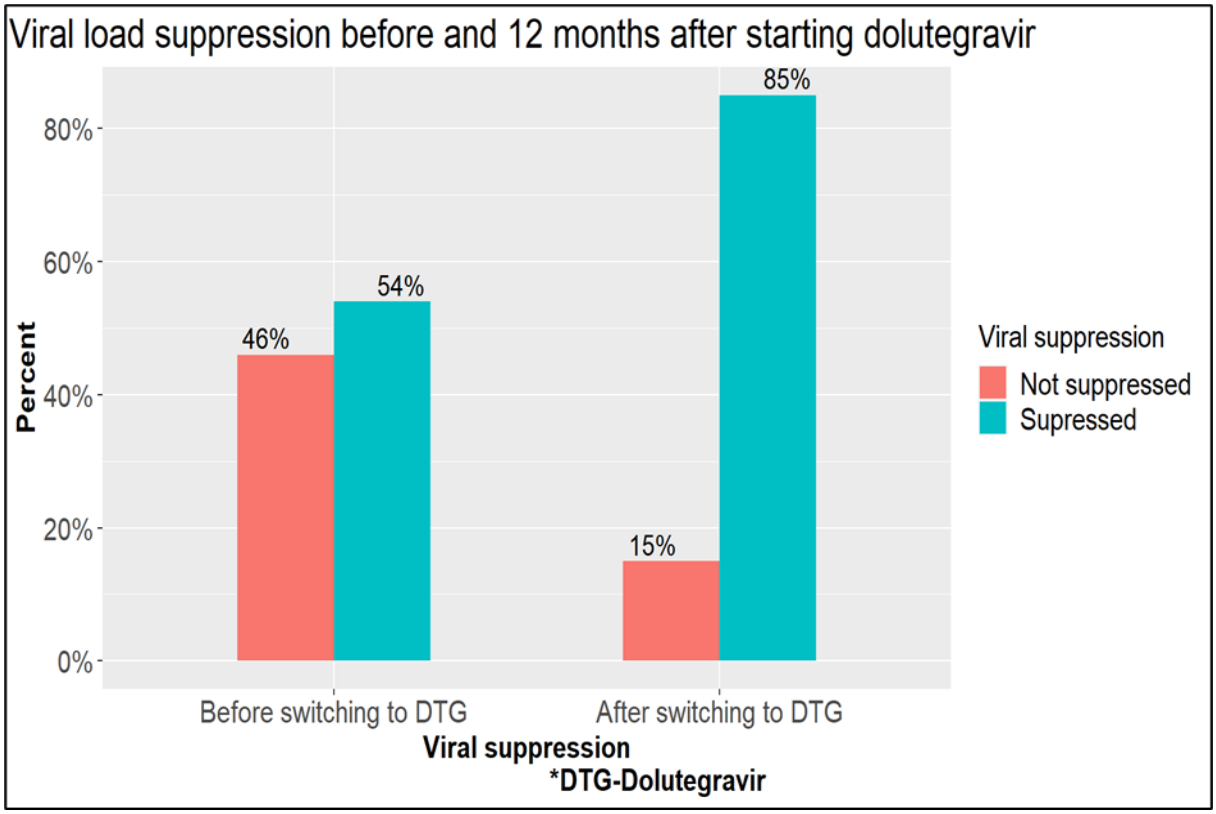

Figure 8: Viral load before and after starting dolutegravir-based ART

Difference in change in viral load after introduction of dolutegravir

To assess the changes in viral load after starting the DTG-based regimen, we took the viral load results that were generated before starting the DTG-based ART regimen and after.

Before the initiation of DTG, 254 (53.5%) of the children and adolescents were virally suppressed and 221 (46.5%) were not virally suppressed. Of the 254 children and adolescents who were virally suppressed before initiation of DTG, 248 (97.6%) remained virally suppressed while 6 (2.4%) had their viral load increase above suppression levels. Of the 221 children and adolescents who were not virally suppressed before initiation of DTG, 158 (71.5%) became virally suppressed while the rest remained the same (Table 8).

Table 8: Change in viral load after initiation of DTG-based ART regimen (N = 475)

Viral load suppression	**Before switch to DTG**	**After switch to DTG**
Virally Suppressed	254 (53.5%)	Virally suppressed = 248 (97.6%) Not virally suppressed = 6 (2.4%)
Not virally suppressed	221 (46.5%)	Virally suppressed = 158 (71.5%) Not virally suppressed = 63 (28.5%)

We ran a McNemar's test of association to determine whether there was a significant change in the proportion of children with viral suppression after introduction of dolutegravir based ART. The test result (p value < 0.001 at 5% significance level) indicates a significant increase in viral suppression after introduction of DTG-based ART ((Table 9).

Table 9: Difference in the number of children who were virally suppressed before and after initiation of dolutegravir

	After switch to DTG		Total	OR (95% CI)	P value *(paired test-McNemar)*
Before switch to DTG	Not virally suppressed Freq (%)	Virally Suppressed Freq (%)			
Not virally suppressed	63 (28.5%)	158 (71.5%)	221 (46.5%)	16.48 (6.97, 38.98)	<0.001
Virally suppressed	6 (2.4%)	248 (97.6%)	254 (53.5%)		
Total	69 (14.5%)	406 (85.5%)	475 (100%)		

Body mass index before and after switch to dolutegravir-based regimen

We evaluated change in body mass index as a known adverse effect of DTG. Table 10 below presents the comparison of body mass index before and after switch to DTG-based ART regimen.

Table 10: Difference in body mass index before and after switch to dolutegravir-based regimen

	Status after switch to DTG				
Status before switch to DTG	**BMI 25+**	**BMI <25**	**Total**	**Odds Ratio (95% CI)**	**P value *(paired test-McNemar)***
	Freq (%)	Freq (%)			
BMI 25+	235 (99.1%)	2 (0.1%)	237 (48.6%)	282.38 (68.05,1171.70)	<0.001
BMI <25	62 (29.4%)	149 (70.6%)	211 (51.4%)	***Reference***	
Total	297 (66.3%)	151 (33.7%)	**448**		

To determine whether there was a significant difference in body mass index categories before and after switch to DTG-based ART, we ran a McNemar's test for correlated samples. The test p value was <0.001 at 5% significance level hence we conclude that there was a significant change in BMI categories before and after switch to DTG-based ART. The odds of having a BMI of 25 and above before switch were 282.38 times the odds of having a BMI of 25 and above after switch, OR 282.38 (95% CI 68.05, 1171.70)

PHASE B: QUALITATIVE ARM OF THE STUDY – IN DEPTH INTERVIEWS OF SUBSET OF STUDY PARTICIPANTS

Data on patients' experiences with DTG-based regimens was collected from children aged 15 years and above, and parents of children aged less than 15 years through in-depth interviews. The respondents were selected as described in the sampling procedure. A total of 20 respondents took part in the in-depth interviews.

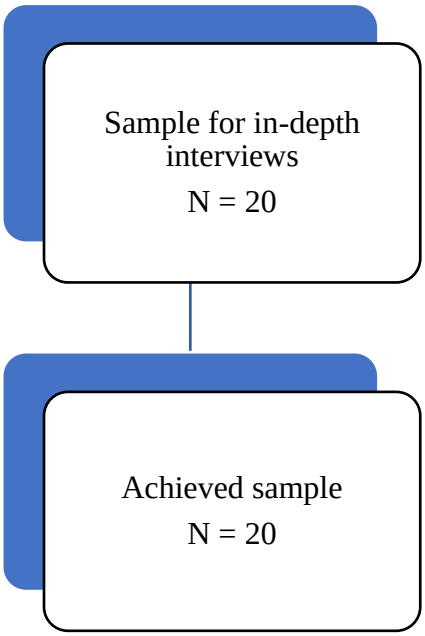

Figure 9: Study flow chart for in-depth interviews

4.4 Patients' experience with dolutegravir-based regimen

Descriptive characteristics of participants who participated in in-depth interviews

The majority, 65% (13 out of 20) of the children were male and the rest were females. Children aged 15 years and above, 30% (6 out of 20) responded to the interviews and those aged less than 15 years had parents respond on their behalf. The median age of the children was 14.0 years with an interquartile range of 9.0 to 15.0 years. The majority, 55% (11 out of 20) of the children were in primary school and the rest were in secondary school (table 11).

Table 11: Descriptive characteristics of the IDI participants

Characteristic	Detail	Frequency N = 20	Percent (%)
Gender	Male	13	65
	Female	7	35
Age	<15 years	14	70
	≥15 years	6	30
Education level	Primary	11	55
	Secondary	9	45

Reported experience with dolutegravir-based ART regimen

The themes generated for the parents and children experiences with DTG-based regimen are shown in table 12 below. The most prominent theme that came out was nutrition. Other themes that were reported by both parents and children were on drug administration, adverse effects and sickness.

Table 12: Parents and children experiences with dolutegravir-based regimen

Themes	**Subthemes**
Nutrition	• Improved appetite • Improved weight
Drug administration	• Timing of administration • Difficulty in swallowing the pill
Adverse effects	• Reduced adverse effects • No adverse effects
Sickness	• Reduced episodes of sickness • Improved health

Nutrition

The parents and the children reported that there was improvement in the nutritional status after being switched to DTG-based regimen. The subthemes that came out under nutrition were; improvement in appetite and weight.

Improved appetite

Some parents reported that since the switch to DTG-based regimen, their children's appetite had improved than before the switch. They said that before switching, children did not eat well due to nausea and other abdominal issues.

"*Since my child got switched to DTG-based ART, my child's appetite has improved and is eating well unlike before*." [Pint1]

"I have noticed improved feeding since my child was switched to the new drug" [Pint2]

A child who responded to the interview reported that unlike before starting the new drug when she never felt like eating, now she was eating well and that her health had even improved.

"*Before starting to use the new drug, my eating was bad. I never felt like eating most of the time but now I can eat well*" [Cint1]

Improved weight

Some of the parents and children reported that there was weight improvement after being switched to the new drug. A parent said that the child had a problem with poor weight gain for some years but after being put on the new drug, the weight had improved and the child looked healthy.

"*My child has had a problem with weight gain for years. Now I have noticed change since she was started on the new drug. She now looks healthy*" [Pint3]

One of the children who reported that her appetite had improved also reported that she had gained weight.

"*This new drug helped me gain weight. I think after I started eating well my weight is also increasing*" [Cint1]

Drug administration

Drug administration also came up as a theme. This was reported by both parents and children. The DTG-based regimen comes in tablet form and maybe difficult for small children to swallow. Another challenge is scheduling the time for taking the medicine. The drug is taken at the same time and may be difficult for children to take it on time without parents being close. The subthemes that came up under this theme were; timing of taking the drug and difficulty swallowing the pill.

The timing of taking the pill

Some secondary school students reported that taking the drug during weekdays had no problem. The problem arose during weekends. Since students don't wake up for preps during weekends, taking the drug on time becomes a problem.

"*Unlike during weekdays when I wake up early for preps and in the process take my medicine, I get a challenge scheduling the drug during weekend*." [Cint2]

A parent reported that the child was a student and waking up to take the pill on weekends was a challenge.

"*He is a student and waking up to take the pill on weekends is a challenge*" [Pint5]

Another reported that his main challenge was scheduling to take the drug every day at 5.30 am.

"*I have a challenge scheduling the drug every day at 5.30 am*" [Cint3]

Another 15-year-old girl reported that she had a problem taking the drug same time every day.

"*Managing time to take the drug every time same day*" [Cint4]

Difficulty swallowing pill

Some parents of small children reported the challenge of swallowing the whole pill for the children. According to them, the pill was too big and could not be swallowed whole.

"*The pill can't be taken in full since my son is only 9 years old*" [Pint4]

Another parent reported that there was a challenge with the size of the tablet. The child was 12 years old and the parent had a challenge administering the pill whole.

"*Because of the size of the pill, my child is unable to take it in full*" [Pint 6]

Adverse effects

Prior to taking DTG-based regimen, parents and children reported that the former regimen had more adverse effects which are not seen under the current regimen. The main subthemes that came up under this theme were; reduced adverse effects and no adverse effects.

Reduced adverse effects

A 15-year-old-child reported she experienced nausea and vomiting initially. The vomiting was reported to have stopped and even nausea came once in a while.

"*Vomiting has improved and now I get nausea once in a while*" [Cint4]

One caregiver reported that the only side effect they were experiencing was a history of weakness.

"The only side effect is a history of weakness". [Pint5]

A patient reported that she was getting left-sided abdominal pain.

"I get abdominal pain often, left side". [Cint4]

No adverse effects

A parent reported that the child had no adverse effects since starting the new regimen. This the parent said could not be compared to the previous regimen.

"*With the other drug my child complained of adverse effects. But now there is no side effect to complain of*." [Pint3]

"*No complain of adverse effects*" [Pint1]

Sickness

The parents and children reported that episodes of sickness had reduced since the start of the new regimen. This was reported as a reduction in admissions, improvement of health and decrease in the frequent illnesses experienced before. The main subthemes identified under this theme were; reduced episodes of sickness and improved health.

Reduced episodes of sickness

Some of the parents who responded to the interview questions reported that the rates of infections had reduced. They reported that their children were not sickly anymore.

"*Since my child was put on the new drug, the rates of illness have decreased*" [Pint7]

"*My child is currently experiencing a decrease in sickness unlike before and is even more active*" [Pint2]

"*My child used to be sickly and has now improved*" [Pint1]

"*My child used to vomit and has now reduced*" [Pint3]

Improved health

One child reported that her health had improved and that there were no more admissions in hospital. She said that prior to starting the new drug, she used to get admitted in hospital several times which had reduced to zero.

"*Nowadays there are no admissions since my health has really improved*" [Cint1]

A parent reported that the health of her child had despite having a mental illness. There was even a report of improvement in milestones.

"*My child's health has improved since the beginning of this drug. There is improvement in walking as well*" [Pint4]

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATION

An estimated 37.7 million people were living with HIV in 2020. Dolutegravir is recommended for first-line and second-line treatment of HIV in combination with other drugs. (18) Dolutegravir is preferred to other drugs in its class due to a shorter half-life, once-daily dosing frequency and higher barrier to resistance or superior virological suppression. (18)(19) Studies have that DTG-based ART is highly effective compared to other treatments in children and adolescents. In addition, the same studies have shown that dolutegravir does not have more adverse effects than other ART drugs. (20)

The median age of the participants in this study was 14.3 years (IQR 10.1 to 16.3 years). The median age of the children in Bruzzese et al.'s study that was conducted in a referral hospital in Nepal was 17 years; the age range was 12 to 18 years. A multi-site study by Bacha et al had participants with a median age of 14.1 years (IQR 11.3 to 16.78 years). (21)

Our study revealed a drop in the WHO stages 3 and 4. There were no similar studies in literature to compare with this finding. The median time to switch to DTG-based ART was 6.4 years. With an interquartile range of 2.6 to 7.4 years. A study on experiences of dolutegravir conducted in Uganda found that it took 5.6 years (IQR 4.3 to 10.4 years) for children to be switched to DTG-based ART. Our findings are similar to the one in this study. (17)

Uptake of dolutegravir-based antiretroviral therapy

The prevalence of uptake of DTG-based ART in our study was 96% (95% CI 93.7%, 97.4%). The World Health Organization (WHO) recommended DTG-based ART treatment for infants and children since the year 2018. (26) In most settings and based on the recommendations of the World Health Organization, ART therapies are usually optimized to DTG-based ART other factors notwithstanding. Due to this reason, it was difficult to find similar studies on the proportions of DTG uptake to compare with our study.

Comparison of viral load before and after the transition to dolutegravir-based ART

There was a significant change in viral load after 1 year of transition to DTG-based ART in terms of proportion of children achieving viral suppression (Mc'Nemar's test). This shows that dolutegravir has more efficacy compared to previous regimens. Studies have shown significant viral suppression after 12 months of the introduction of DTG-based ART. (22)

These findings are similar to the current study where there was a significant change in viral load between 1-year pre-DTG and 12 months post-DTG initiation.

A study by Bruzzese et al. found that after being on non-DTG-based ART and developing multiple drug resistance due to non-adherence and developing ART-related adverse effects, 6 children ranging between 12 and 18 years were switched to a DTG-based regimen. After only four to eight weeks of being on DTG, a complete viral suppression was observed. (1)

Our study also shows that there was an increase in viral load suppression 12 months after the initiation of dolutegravir from 54% to 85%. In agreement with our study is the control of hypertension in pregnancy trial that reported suppression rates of 84% 6 months after initiation of dolutegravir. (23) Other studies in children and adolescents have found suppression levels of 70.2% e.g., in a study conducted in Tanzania (24). The difference between our study and the Tanzanian study may have resulted from differences in viral load levels before initiation of DTG.

The importance of maximal viral suppression includes

Viral load suppression improves the health of people living with HIV, reduces the chances transmission of the virus to others during sexual intercourse and syringe sharing. In addition, it also reduces the chances mother to child transmission during pregnancy, birth and breastfeeding. (25)

Experiences with dolutegravir-based ART

Four themes came out of the in-depth interviews on patient and caregiver experiences with the DTG-based ART regimen; Nutrition, Drug administration, adverse effects and sickness. Under these themes, two subthemes were identified in each case.

In terms of nutrition, patients and caregivers reported improved appetite and weight. A parent reported that since her child was switched to DTG-based ART regimen, the child had developed a good appetite and was eating well.
In support of the findings from our study, an observational study conducted in Nigeria among patients who were put on DTG-based ART regimen reported that increase in appetite was reported more than other adverse effects among the patients. In the Nigerian study; twenty percent of the patients reported improved appetite at two months, nineteen percent at six months and fifteen percent at 12 months. (27)

It was also reported that weight had improved among study participants. From the parent who reported weight gain in her child, the weight gain came out as a positive effect attributed to DTG-based ART.

Contrary to the finding of weight as a positive effect of DTG-based ART, studies have reported weight gain as a side effect of dolutegravir. In one particular study, excessive weight gain associated with dolutegravir had been seen in a 10-year old female patient with acquired HIV. (28)

Drug administration

Dolutegravir comes in tablet form and was reported to be difficult to swallow among small children. A parent reported that it was difficult to take the pill whole by her 9-month-old son.

Literature shows that there are dispersible tablets for small children on DTG-based ART. (29) This formulation may not be available in the setting where this study was conducted and therefore the size of the pill may have come out as a negative effect of dolutegravir. A search of the literature did not yield studies where small children have been observed having difficulties with swallowing DTG-based ART pills.

Adverse effects

One of the adverse effects that we identified from the quantitative analysis was an increase in the patients with obesity from 144 (30.3%) to 231 (48.6%). Though this was not reported in the in-depth interviews, studies have shown an increase in weight among the patients on dolutegravir-based ART therapy compared to those on efavirenz. (30)(31) In the in-depth interviews, patients reported improved weight which did not come out as a side effect.

This study did not show that adverse effects had increased after the initiation of DTG-based ART regimen. Most of patients and caregivers who participated in the in-depth interviews either reported a reduction in adverse effects or no adverse effects at all. One patient reported they had developed a history of weakness after the initiation of DTG-based ART.

A 15-year-old-child reported she experienced nausea and vomiting initially. The vomiting was reported to have stopped and even nausea came once in a while.
A parent reported that the child had no adverse effects since starting the new regimen. This the
parent said could not be compared to the previous regimen.

An observational study done in Uganda among patients who had been switched to DTG-based regimen found that some patients had stopped having the adverse effects they used to have before the switch. (17)

"**Hmmm, there are many changes, Musawo [doctor]; like I no longer feel the dizziness and hallucinations I used to... I have no concern at all because even now, I can swallow it in the morning, and I reach 12 noon or 1pm working, without having eaten anything. But before, I could not do it; I had to eat food before I swallow the drug. If I do not eat, I cannot even see where I am going**". [IDI Male patient general clinic_SOD_10]

Body weakness has been reported among patients on DTG-based regimen. (17) The study cited here found body weakness in eight percent of the patients.

Another patient reported that she was getting left-sided abdominal pain.

Mayo clinic reports upper right abdominal pain as one of the adverse effects of dolutegravir unlike the left sided abdominal pain reported in this study. (32)

Sickness

Patients and caregivers reported a reduction in episodes of illness and improvement in the health of the patients. It was reported that after the initiation DTG-based ART, the episodes of illnesses had reduced and admissions had become fewer to none.

On reduced adverse effects, a caregiver reported that since her child was switched to DTG-based ART, the rates of infections had decreased. A study on efficacy of dolutegravir found that the drug was effective in viral load suppression and that could be the cause of reduction in the rates of infections. (33)

A parent reported that the health of her child had despite having a mental illness. There was even a report of improvement in milestones. Dolutegravir has been reported to reduce treatment failure in children living with HIV/AIDs and this can be attributed to improvement in health seen in the findings of this study. (34)

5.2 Strengths and limitations

Strengths

The use of secondary data made this study cost-effective as it did not include data collection on a large sample. It also saved time.

This study had a high internal validity since it was possible to pick all the study variables from the secondary data.

The high sample size also increased the power of finding a true difference in the study.

This study is representative of the study population as all the children who met the inclusion criteria were sampled.

Limitations

This was a single-centre study and hence cannot be generalized to populations outside the catchment areas.

5.3 Conclusions

1. Uptake of DTG optimisation/based ART was high with 96% of participants switching to DTG during the five-year period.
2. Viral suppression improved from 54% to 85% due to switch to DTG in the five-year period under study.
3. Dolutegravir-based ART regimen was associated with fewer adverse effects, there was improvement in appetite and, a reduction in episodes of sickness and admissions.

5.3 Recommendations

From the findings of this study, we recommend that;

1. DTG-based ART to be started as first-line treatment as per the WHO recommendations as it is superior in viral load suppression compared to other ART regimens.
2. Larger quantitative studies be conducted to determine the frequencies of adverse effects experienced by children receiving DTG-based ART treatment at Kenyatta National Hospital
3. We also recommend that the data capture in the comprehensive care centre at Kenyatta National Hospital includes adverse effects experienced by children on DTG-based ART regimen.

GANNT CHART

Activity	**Dec. 2021 to April 2022**	**May-OCT 2022**	**Nov 2022**	**Dec/2022 Jan/2023**	**Feb 2022**	**March 2022**
Proposal Development						
Ethical review						
Data acquisition						
Data analysis						
Final write-up of results						
Presentation of results						

STUDY BUDGET

Item Description	Unit Cost (Kshs.)	Quantity	Total (Kshs.)
Proposal and questionnaire development			
Files	500.00	2	1000.00
Pens	200.00	6	1200.00
Flash Disk	2000.00	3	6,000.00
Internet	5,000	3	15,000.00
Printing	10.00	50	500.00
Photocopying	5.00	50*5	1,250.00
Binding	250.00	5	1,250.00
Sub-total			26,200
Data Collection and Analysis			
Research assistant	30,000.00	2	60,000.00
Data entry and cleaning	15,000.00	1	15,000.00
Statistician	60,000.00	1	60,000.00
Sub-total			165,000
Dissertation Development			
Printing	10.00	100	1,000.00
Binding	500.00	5	2,500.00
Photocopying	5.00	100	2,500.00
Sub-total			6,000
Grand Total			**156,530**

REFERENCES

1. Bruzzese E, Lo Vecchio A, Smarrazzo A, Tambaro O, Palmiero G, Bonadies G, et al. Dolutegravir-based anti-retroviral therapy is effective and safe in HIV-infected paediatric patients. Ital J Pediatr [Internet]. 2018 Mar 20 [cited 2023 Jan 30];44(1):1–5. Available from: https://ijponline.biomedcentral.com/articles/10.1186/s13052-018-0469-x

2. World Health Organisation (WHO). Progress report on HIV, viral hepatitis and sexually transmitted infections 2019: Accountability for the global health sector strategies, 2016–2021. Who. 2019;

3. NASCOP. An operational manual for the delivery of HIV Self-Testing services in Kenya. Who. 2019;

4. Jamieson D, Kellerman SE. The 90 90 90 strategy to end the HIV pandemic by 2030: Can the supply chain handle it? Journal of the International AIDS Society. 2016.

5. Golin R, Samuel JM, Phelps BR, Persaud U, Malati CY, Siberry GK. The promise of paediatric dolutegravir. Journal of the International AIDS Society. 2021.

6. AVERT. HIV and AIDS in Kenya | AVERT. Hiv and Aids in Kenya. 2019.

7. Kenya MoH. Framework for the Implementation of Pre-Exposure Prophylaxis of HIV In Kenya. Kenya Minist Heal. 2017;

8. Kuznik A, Iliyasu G, Habib AG, Musa BM, Kambugu A, Lamorde M. Initiation of antiretroviral therapy based on the 2015 WHO guidelines. AIDS. 2016;

9. World Health Organisation (WHO). Policy Brief: Update of Recommendations on First-and Second-Line Antiretroviral Regimens. WHO Libr Cat Data. 2019;

10. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: Week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr. 2015;

11. Mendoza I, Lázaro A, Torralba M. Effectiveness, Durability, and Safety of Dolutegravir and Lamivudine Versus Dolutegravir, Lamivudine, and Abacavir in a Real-Life Cohort of HIV-Infected Adults. Ann Pharmacother. 2021;

12. P.L. M. Dolutegravir: A review of its use in the management of HIV-1 infection in

adolescents and adults. Drugs. 2014.

13. Viani RM, Ruel T, Alvero C, Fenton T, Acosta EP, Hazra R, et al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: Results of the impaact p1093 study. J Pediatric Infect Dis Soc. 2020;

14. Thivalapill N, Simelane T, Mthethwa N, Dlamini S, Lukhele B, Okello V, et al. Transition to Dolutegravir Is Associated With an Increase in the Rate of Body Mass Index Change in a Cohort of Virally Suppressed Adolescents. Clin Infect Dis. 2021;

15. Wiznia A, Alvero C, Fenton T, George K, Townley E, Hazra R, et al. IMPAACT 1093: dolutegravir in 6-to 12-year-old HIV-infected children: 48-week results. Top Antivir Med Conf 23rd Conf retroviruses opportunistic Infect CROI 2016 United states Conf start 20160222 Conf end 20160225. 2016;

16. Ward D, Ramgopal M, Riedel DJ, Garris C, Dhir S, Waller J, et al. Real-World Experience with Dolutegravir-Based Two-Drug Regimens. AIDS Res Treat. 2020;

17. Twimukye A, Laker M, Odongpiny EAL, Ajok F, Onen H, Kalule I, et al. Patient experiences of switching from Efavirenz- to Dolutegravir-based antiretroviral therapy: a qualitative study in Uganda. BMC Infect Dis. 2021;

18. Sarode IM, Jindal AB. Current status of dolutegravir delivery systems for the treatment of HIV-1 infection. J Drug Deliv Sci Technol. 2022 Oct 1;76:103802.

19. Kandel CE, Walmsley SL. Dolutegravir – a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther [Internet]. 2015 Jul 7 [cited 2023 Feb 2];9:3547. Available from: /pmc/articles/PMC4500604/

20. Carlos del Rio M. Preeminence of Dolutegravir-Based Antiretroviral Therapy in Children and Adolescents. NEJM J Watch [Internet]. 2022 Jan 10 [cited 2023 Feb 2];2022. Available from: https://www.jwatch.org/NA54457/2022/01/10/preeminence-dolutegravir-based-antiretroviral-therapy

21. Bacha JM, Dlamini S, Anabwani F, Gwimile J, Kanywa JB, Farirai J, et al. Realizing the Promise of Dolutegravir in Effectively Treating Children and Adolescents Living With HIV in Real-world Settings in 6 Countries in Eastern and Southern Africa. Pediatr Infect Dis J [Internet]. 2023 Jul 14 [cited 2023 Jun 22];42(7):576. Available

from: /pmc/articles/PMC10259212/

22. Paul NI, Ugwu RO. Dolutegravir (DTG) Based Fixed Dose Combination (FDC) of Tenofovir/Lamivudine/Dolutegravir (TLD) and Viral Load Suppression in Children in Port Harcourt, Nigeria. J Sci Res Reports. 2020;26(2):52–9.

23. Magee LA, Von Dadelszen P, Singer J, Lee T, Rey E, Ross S, et al. The CHIPS randomized controlled trial (control of hypertension in pregnancy study). Hypertension [Internet]. 2016 Nov 1 [cited 2023 Feb 3];68(5):1153–9. Available from: /pmc/articles/PMC5058640/

24. Mutagonda RF, Mlyuka HJ, Maganda BA, Kamuhabwa AAR. Adherence, Effectiveness and Safety of Dolutegravir Based Antiretroviral Regimens among HIV Infected Children and Adolescents in Tanzania. [cited 2023 Feb 3]; Available from: https://us.sagepub.com/en-us/nam/open-access-at-sage

25. HIV Treatment as Prevention | HIV Risk and Prevention | HIV/AIDS | CDC [Internet]. [cited 2023 May 5]. Available from: https://www.cdc.gov/hiv/risk/art/index.html

26. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV [Internet]. [cited 2023 Feb 3]. Available from: https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51

27. Weight gain with dolutegravir-based ART in Nigerian cohort | HTB | HIV i-Base [Internet]. [cited 2023 Apr 15]. Available from: https://i-base.info/htb/39183

28. Li J, Yusuf EH, Agwu AL. Excessive Weight Gain Associated With Dolutegravir Initiation in a 10-Year-Old Female With Perinatally Acquired Human Immunodeficiency Virus: A Case Report and Review of the Literature. J Pediatric Infect Dis Soc [Internet]. 2021 Mar 1 [cited 2023 Apr 15];10(3):373–5. Available from: https://pubmed.ncbi.nlm.nih.gov/32448908/

29. Waalewijn H, Chan MK, Bollen PDJ, Mujuru HA, Makumbi S, Kekitiinwa AR, et al. Dolutegravir dosing for children with HIV weighing less than 20 kg: pharmacokinetic and safety substudies nested in the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. Lancet HIV [Internet]. 2022 May 1 [cited 2023 Apr 15];9(5):e341. Available from: /pmc/articles/PMC9046096/

30. Griesel R, Kawuma AN, Wasmann R, Sokhela S, Akpomiemie G, Venter WDF, et al. Concentration-Response Relationships of Dolutegravir and Efavirenz with Weight Change After Starting Antiretroviral Therapy. Br J Clin Pharmacol [Internet]. 2022 Mar 3 [cited 2023 Apr 15];88(3):883. Available from: /pmc/articles/PMC7612404/

31. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad. 2019 Jan 1;5(1):41–3.

32. Dolutegravir (Oral Route) Adverse effects - Mayo Clinic [Internet]. [cited 2023 Feb 2]. Available from: https://www.mayoclinic.org/drugs-supplements/dolutegravir-oral-route/side-effects/drg-20061287

33. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV [Internet]. 2022 Jun 1 [cited 2023 Apr 15];9(6):e381–93. Available from: http://www.thelancet.com/article/S2352301822000923/fulltext

34. Turkova A, White E, Mujuru HA, Kekitiinwa AR, Kityo CM, Violari A, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. N Engl J Med. 2021 Dec 30;385(27):2531–43.

APPENDICES

Appendix I: Consent Form

Introduction

Greetings, I am, Dr Fahmo M. Yusuf a resident doctor carrying out a study on **UPTAKE OF DTG BASED ART IN CHILDREN AND ADOLESCENTS LIVING WITH HIV AT KENYATTA NATIONAL HOSPITAL**

Purpose

This study aimed to determine the proportion of CLHIV who switched to DTG- containing ART regimens over the past 12 months at Kenyatta National Hospital.

Procedure

Participants who meet inclusion criteria shall sign consent forms in the presence of chief investigator/ research assistants. This will be followed by filling research questionnaire with open and closed questions. No interference or influencing shall be done during filling of questionnaires. This may take up to half an hour of your time. Questions shall be cross checked for completion and entry into the data base done. All information obtained shall be treated with highest level of confidentiality.

Risks

The study is safe and you will not be exposed to any harm or physical injury. Some questions asked may be sensitive and touching on private matters however this is not meant to embarrass you. You are therefore kindly requested that you answer all questions including the most uncomfortable. You are free to ask for clarification of questions.

Benefits

Participating in this study shall not have any direct benefits however information obtained shall be used to better understand the level of utilization of instructional materials in learning and possible approaches to improve the current situation. No monetary rewards or token shall be advanced to you as a result of participation.

Voluntary Participation/ Withdrawals

Your participation is voluntary. If you decide not to continue along the way you are at will to stop at any point.

Confidentiality

High degree of confidentiality shall be observed. Your name or address shall not be recorded in the interview form. Your responses shall be combined with others and no person will be

able to identify them. The forms shall be placed in safe custody and all recorded information obtained shall only be used for study.

Contact Person

The contact information of chief investigator shall be availed to you. If you have any other area of concern such as your rights as a participant, how the study is being conducted or something that was not clearly explained to you, you are at liberty to contact me or the secretary – UON/KNH Ethics/Research Review Committee

CONTACTS- Fahmo M. Yusuf

CONFIRMATION OF CONSENT

Participants Statement

All the above information concerning my participation in this study has been read and understood I am authorized to ask any question before giving my consent and during filling of the questionnaire. I understand that the information I will give is entirely for study purpose. This information shall be treated with highest level of confidentiality and kept in safe custody. I fully understand that I may choose not to go ahead with the interview at any point without any dire consequences whatsoever. I therefore voluntarily choose to give my informed consent to participate in this study.

SIGNATURE OF PARTICIPANT…….

DATE……

Kiambatisho I: Fomu ya Idhini Utangulizi

Salamu, mimi ni Dkt Fahmo M. Yusuf daktari mkazi akifanya utafiti kuhusu UPTAKE OF DTG BASED ART IN CHILDREN AND ADOLESCENTSCENTS WANAOISHI NA VVU KATIKA HOSPITALI YA TAIFA YA KENYATTA

Lengo Utafiti huu unalenga kuzuia idadi ya CLHIV ambao walibadilisha hadi DTG- iliyo na tawala za ART katika kipindi cha miezi 12 iliyopita katika Hospitali ya Kitaifa ya Kenyatta.

Utaratibu

Washiriki ambao wanakidhi vigezo vya ujumuishaji watasaini fomu za idhini mbele ya mchunguzi mkuu / wasaidizi wa utafiti. Hii itafuatiwa na kujaza dodoso la utafiti na maswali ya wazi na yaliyofungwa. Hakuna uingiliaji au ushawishi utakaofanyika wakati wa kujaza dodoso. Hii inaweza kuchukua hadi nusu saa ya muda wako. Maswali yatakuwa msalaba kukaguliwa kwa kukamilika na kuingia katika msingi wa data uliofanywa. Taarifa zote zitakazopatikana zitashughulikiwa kwa kiwango cha juu cha usiri.

Hatari

Utafiti ni salama na hautapata madhara yoyote au jeraha la kimwili. Baadhi ya maswali yanayoulizwa yanaweza kuwa nyeti na kugusa masuala binafsi hata hivyo hii haimaanishi kukuaibisha. Kwa hiyo unaombwa kwa huruma kwamba ujibu maswali yote ikiwa ni pamoja na wasiwasi zaidi. Uko huru kuuliza ufafanuzi wa maswali.

Faida katika utafiti huu

Faida Kushiriki katika utafiti huu hakutakuwa na faida yoyote ya moja kwa moja hata hivyo habari zilizopatikana zitatumika kuelewa vizuri kiwango cha matumizi ya vifaa vya kufundishia katika kujifunza na njia zinazowezekana za kuboresha hali ya sasa. Hakuna zawadi ya fedha au ishara itakayoendelezwa kwako kama matokeo ya ushiriki.

Ushiriki wa Hiari/ Uondoaji

Ushiriki wenu ni wa hiari. Ukiamua kutoendelea njiani uko tayari kusimama wakati wowote. Usiri Kiwango cha juu cha usiri kitazingatiwa. Jina au anwani yako haitarekodiwa katika fomu ya mahojiano. Majibu yako yataunganishwa na wengine na hakuna mtu atakayeweza kuyatambua. Fomu hizo zitawekwa mahabusu salama na taarifa zote zilizorekodiwa zitakazopatikana zitatumika kwa ajili ya utafiti tu.

Usiri

Kiwango cha juu cha usiri kitazingatiwa. Jina au anwani yako haitarekodiwa katika fomu ya mahojiano. Majibu yako yataunganishwa na wengine na hakuna mtu atakayeweza kuyatambua. Fomu hizo zitawekwa mahabusu salama na taarifa zote zilizorekodiwa zitakazopatikana zitatumika kwa ajili ya utafiti tu.

Mtu wa mawasiliano

Maelezo ya mawasiliano ya mpelelezi mkuu yatapatikana kwako. Ikiwa una eneo lingine lolote la wasiwasi kama vile haki zako kama mshiriki, jinsi utafiti unavyofanywa au kitu ambacho hakikuelezewa wazi, uko huru kuwasiliana nami au katibu - UON / KNH Kamati ya Mapitio ya Maadili / Utafiti

MAWASILIANO- Fahmo M. Yusuf UTHIBITISHO WA IDHINI

Kauli ya Washiriki Maelezo yote hapo juu kuhusu ushiriki wangu katika utafiti huu yamesomwa na kueleweka nimepewa mamlaka ya kuuliza swali lolote kabla ya kutoa ridhaa yangu na wakati wa kujaza dodoso. Ninaelewa kuwa habari nitakayotoa ni kwa madhumuni ya kujifunza kabisa. Taarifa hizi zitachukuliwa kwa kiwango cha juu cha usiri na kuwekwa chini ya ulinzi salama. Ninaelewa kabisa kwamba ninaweza kuchagua kutoendelea na mahojiano wakati wowote bila matokeo yoyote mabaya. Kwa hivyo ninachagua kwa hiari kutoa idhini yangu ya habari kushiriki katika utafiti huu. SAINI YA MSHIRIKI..... TAREHE.....

Appendix II: Assent Form

Project Title: **UPTAKE OF DTG BASED ART IN CHILDREN AND ADOLESCENTS LIVING WITH HIV AT KENYATTA NATIONAL HOSPITAL**

Investigator(s): Dr. Fahmo Mohammed

We are investigating uptake of DTG based ART regimen in children and adolescents living with HIV at Kenyatta National Hospital. the proportion of all children and adolescent living with HIV, and experiences of patients/caregivers who switched to DTG- containing ART regimens over a 12-month period at Kenyatta National Hospital.

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. ____)

This research study is a way to learn more about people. A total of 500 children and adolescents will be participating in this research study with you.

If you decide to be part of this study, you will be asked some simple questions about yourself and your condition... Questions shall be cross checked for completion and entry into the data base done. All information obtained shall be treated with highest level of confidentiality.

There are some things about this study you should know. The procedure conducted in the study is non-invasive hence it will not have any negative or harmful influence on the study participants. Most of the information will be obtained from the patient file hence the patient and their guardians will not be at any risk. The time taken will be 30 minutes.

However, participating in this study is extremely beneficial to your health as you continue treatment. In cases where you are found to be having side affects you will be referred to appropriate healthcare provider for immediate further management.

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 III: Questionnaire

Section A: Parent/Caregiver demographic characteristics

1. Gender
2. Date of birth
3. Marital status
4. Religion
5. Education
6. Monthly income
7. Residence

Section B: Demographic characteristics of the child

8. Gender
9. Age
10. Religion
11. Height
12. Weight (all columns)
13. Schooling/grade (latest if available)
14. Comorbidities

Section C: HIV Specific characteristics

15. Date of HIV diagnosis
16. Time of first ART initiation
17. HIV stages (columns)

Medications

18. Current antiretroviral therapy regimen (all columns): First line ☐ Second line ☐ Third line ☐ -with respective dates when started
19. Antiretroviral therapy regimens-specific drugs (All columns with respective dates when initiated)
20. Patient put on DTG-based regimen

Yes () No ()

21. Date when DTG was initiated (column)
22. Reasons for change of regimen (columns)
23. Other medicines other than ARVs (columns)

Adverse events

24. All columns with adverse events and respective columns with dates when the adverse effects were recorded

Lab works

25. All columns with viral load and respective columns with dates when they were done
26. All columns with Hb levels with respective columns with dates when they were done
27. All columns with ALT levels with respective columns with dates when they were done
28. All columns with urinalysis results with respective columns with dates when they were done
29. All columns with fasting blood sugar with respective columns with dates when they were done
30. All columns with lipids with respective columns with dates when they were done

Other diseases recorded

31. Comorbidities (columns)

Admissions

32. Hospitalizations/admissions (columns)

Appendix IV: Interview guide Questions

1. Is there any improvement since your child was put on DTG? Yes () No ()
2. Are there any adverse effects that you can associate with the switch to DTG? Yes () No ()
3. Are the adverse effects worsening? Yes () No ()
4. Do you prefer that your child remain on DTG? Yes () No ()
5. Are there any challenges that you are facing with DTG? Yes () No ()
6. If yes in question 5 above, please indicate the challenges……
   ……
   …….
7. What do you like about the new medication (DTG)?
   a. Convenient when administering
   b. Fewer adverse effects
   c. Easily available in CCC
8. Would you like to add anything about DTG?.....
   ……
   ……..

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Ref: KNH-ERC/A/371

26th September, 2022

Dr. Fahmo M. Yusuf
Reg. No. H58/38655/2020
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

26 SEP 2022

Dear Dr. Yusuf,

RESEARCH PROPOSAL: UPTAKE OF DTG BASED ART IN CHILDREN AND ADOLESCENT LIVING WITH HIV AT KENYATTA NATIONAL HOSPITAL (P286/03/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P286/03/2022.** The approval period is 26th September 2022 – 25th September 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

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