EVALUATION OF TREATMENT OUTCOMES IN PATIENTS RECEIVING DOLUTEGRAVIR- CONTAINING FIRST -LINE ANTI-RETROVIRAL THERAPY AT THE KATUTURA INTERMEDIATE HOSPITAL IN NAMIBIA

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ABSTRACT

There is currently insufficient information regarding the safety and effectiveness of Dolutegravir (DTG)-based ART regimen in Namibia. This study was conducted to evaluate the treatment outcomes of dolutegravir containing first line antiretroviral therapy (ART).

Methods: This was a retrospective quantitative study that included ART-naïve adults who initiated dolutegravir containing first-line ART from January 2020 to March 2021 at the Intermediate Hospital Katutura (IHK) in Namibia.

Results: 120 patients were included in the study. Most (n=89, 74%) experienced weight gain, and 15 experienced treatment failure. At the end of 18 months, 75% of the cohort remained virally suppressed. The prevalence of treatment failure was found to be 12.5% with the prevalence rate of treatment failure of 8.3 cases per 100 patient years. But considering the switching as confirmation of virological failure, the prevalence rate was 2.2 cases per 100 patient years. Active tuberculosis (TB) was found to be statistically associated with treatment failure with a P value < 0.001. PLWH co-infected with TB on TLD were 18 times more likely to have treatment failure (OR=18.1,95% CI: 4.65,70.45). Only 3.3% (n = 4) had their DTG-based ART regimen changed or switched due to treatment failure. The only reported adverse effect observed in the study was weight gain. The proportion of patients who experienced clinically significant weight gain (defined as weight gain > 3kg) after 18 months of ART initiated was 20.2%. The prevalence rate for clinically significant weight gain was 13.5 cases per 100 patient years. The mean weight gain was found to be 4 kg (SD 59.45 ± 16.89). There was statistical significance between weight gain and gender with a p-value =0.026 with females being four times more likely to have gained weight (OR=3.9,95% CI: 1.3,12.4).

Conclusion: DTG-containing regimens effectively achieved viral suppression among treatment-naive HIV patients, with weight gain reported as the only adverse effect. More research with a larger patient sample across multiple centres is needed to explore the long-term treatment outcomes of DTG.

Keywords: Dolutegravir, Tenofovir/Lamivudine/Dolutegravir, TB, antiretroviral therapy, adverse drug effect, Treatment failure.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ACRONYMS AND ABBREVIATIONS

ADR	Adverse drug reaction
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
cART	Combination antiretroviral therapy
CAPRISA	Centre for AIDs Programme of Research in South Africa
DTG	Dolutegravir
EDT	Electronic Dispensing Tool
EFV	Efavirenz
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
INRAMS	Integrase resistance associated mutations
INSTI	Integrase strand transfer inhibitor
IRIS	Immune reconstitution inflammatory syndrome
IHK	Intermediate Hospital Katutura
MOHSS	Ministry of Health and Social Services
NAMPHIA	Namibia Population-Based HIV Impact Assessment
NMRC	Namibia medicine regulatory council
NTD	Neural tube defects
PLWH	People Living with HIV
PMTCT	Prevention of mother-to-child transmission
RIF	Rifampicin
TB	Tuberculosis
TLD	Tenofovir/Lamivudine/Dolutegravir
TND	Target not detected
WHO	World Health Organisation

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DEDICATIONS

I would like to dedicate this thesis to my beloved parents, who have been my source of encouragement and support in my education.

To my loving partner for your love and support,

To my so beloved son Diamante Marco Antonius who was born on the 26th of October 2023, the day after my final thesis submission. May this be a testament to you that with God anything is possible.

And lasty, I would like to dedicate this study to the Lord Almighty for his everlasting love and Grace.

DECLARATIONS

I, **Naambo Taimi Amakutuwa**, hereby declare that this study is a true reflection of my own research and that this work has not been submitted for a degree at any other educational institution.

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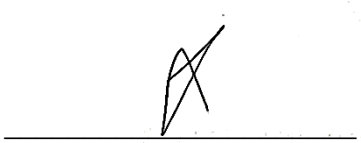

Naambo Taimi Amakutuwa Date: OCTOBER 2024

1 INTRODUCTION

1.1 Background

Clinical data from The Namibia Population-Based Human Immunodeficiency Virus (HIV) Impact Assessment (NAMPHIA) report of 2017 reported that the outcome of HIV interventions in Namibia have been very good (1). The report further states that Women in Namibia have achieved the UNAIDS 90-90-90 goal (1). Although initiating people living with HIV (PLWH) on antiretroviral therapy (ART) can lead to great achievements, loss to follow-up and poor adherence can result in drug resistance, and death may ensue (2,3).

It is estimated that over 200,000 Namibians are living with HIV (4,5). In 2003, The Ministry of Health and Social Services (MOHSS) introduced free ART to the public (4) In September 2018 the ART guidelines recommended a transition from a 600mg-containing Efavirenz (EFV) ART regimen to a low dose EFV 400mg-containing ART (4) . In 2016, Botswana was the first African country to recommend use of DTG-containing ART as a first-line treatment In 2019, dolutegravir (DTG) was introduced as a first-line ART regimen by the World Health Organization (WHO) because of its good safety profile and effectiveness compared to other alternatives (2,6). In 2016, Botswana became the inaugural African country to endorse the utilization of DTG-comprised antiretroviral therapy (ART) as a primary treatment option. In 2019, the World Health Organization (WHO) adopted dolutegravir (DTG) as a first-line ART regimen due to its favourable safety profile and superior efficacy when contrasted against alternative choices (2,6). In January 2019, Namibia implemented DTG as part of its first-line ART regimen (4).

In May 2018, a study in Botswana found cases of neural tube defects in foetuses of women who became pregnant while receiving DTG-containing ART (7) .This raised concerns regarding DTG's safety. However, new data from the TSEPAMO study in Botswana showed a reduction in prevalence of neural tube defects (8). In July 2021, supporting information regarding the safety data of DTG was published by the WHO, and it was the preferred option in first- and second line ART for all patients, including women and adolescent girls (9). As of mid-2022, Dolutegravir had been incorporated into the preferred initial ART regimen in approximately 108 countries (10)

The Namibia ART guidelines recommend DTG-containing ART as the preferred first-line regimen. Furthermore, the guidelines recommend the replacement of EFV with DTG in patients receiving EFV-containing ART who are virally suppressed (4). Furthermore, DTG forms part of the second-line regimen prescribed following treatment failure of the EFV-containing first-line regimen (4). Interestingly, an international study found that DTG sustained viral suppression over 96 weeks in 66% and 84% of patients who had and those who did not have resistance mutations to EFV, respectively (11). Another important issue concerning DTG is that it has been associated with weight gain (12).

While ART has considerably increased the survival of individuals with the HIV, its safety and effectiveness must be continually investigated and ensured, especially with the expanding arsenal of antiretroviral drugs (13).

1.2 Statement of the problem

There is limited information on the real-world safety and effectiveness of the DTG-containing first-line regimen (Tenofovir/ Lamivudine/ Dolutegravir – TLD) among ART naïve and ART-experienced people living in Namibia. A comprehensive evaluation of dolutegravir's treatment outcomes is crucial for individuals living with HIV, healthcare providers, and the broader healthcare system. Without such an assessment, suboptimal patient care, compromised treatment effectiveness, and broader challenges in managing HIV may arise, leading to potential negative consequences.

The Namibian ART guidelines introduced a more effective anti-retroviral therapy (ART), dolutegravir. Dolutegravir has been documented for its favourable efficacy, tolerability and safety(4). A systematic analysis of virologic suppression, immunologic response, treatment adherence, safety profile, resistance development, and the influence on patients' quality of life is lacking.

Dolutegravir was first introduced in other SADC countries such as Botswana and South Africa. Various factors may account for potential discrepancies in treatment outcomes between Namibia and other SADC countries. These factors MAY include differences in healthcare infrastructure, access to medications, patient demographics, cultural factors, and the prevalence of comorbidities such as TB and other infections (13). Additionally, variations in healthcare policies, guidelines, and implementation strategies across countries may impact treatment outcomes (13). Socioeconomic factors, such as poverty and education levels, could also influence treatment adherence and effectiveness. Furthermore, geographic and environmental factors, including climate and geography, may affect disease epidemiology and treatment response. Consequently, while there may be commonalities in treatment outcomes across SADC

nations, unique contextual factors specific to Namibia may impact the effectiveness and safety of DTG-containing regimens.

Not much is known about the use of Dolutegravir as a first line ART in the management of HIV in Namibia. There was a need for further research to understand the interconnections between these factors and how they impact the overall success of dolutegravir in HIV therapy. In this research, the effectiveness of DTG was assessed using multiple parameters, including virologic suppression, immunologic response, treatment adherence, safety and tolerability, resistance monitoring, long-term impact on quality of life, pharmacokinetics, drug interactions and patient-reported outcomes. This study has been designed to investigate and fill the information gap regarding the safety and effectiveness of Dolutegravir.

1.3 Objectives

1.3.1 Main Aim

The main aim was to evaluate the treatment outcomes of dolutegravir- containing first-line regimen in Namibia for a period of 18 months from January 2020 to March 2021. The specific objectives of this study were as follows:

1.3.2 Specific Objectives

1. To determine the prevalence adverse reactions associated with DTG, in patients receiving DTG-containing first line ART.
2. To identify the potential predictors of adverse effects associated with DTG-containing first line regimen.

3. To determine the prevalence of treatment failure in patients receiving DTG-containing first line ART (viral load >1000 copies per/ml).
4. To identify predicators of treatment failure in patients receiving DTG-containing first line ART.

1.4 Significance

The insights from this study addressed knowledge gaps and offered valuable information across various sectors in healthcare. Crucial to this study was understanding whether its findings on the safety and effectiveness of dolutegravir (DTG)-containing regimens were comparable to existing studies. The primary goal of this research was to add to the current knowledge base of DTG, ultimately resulting in a comprehensive understanding of its efficacy. Namibia has one of the highest HIV prevalence rates in sub-Saharan Africa, making it an essential region for introducing a potent and well-tolerated drug like DTG, which may lead to improved life expectancy and quality of life for people living with HIV (PLWH). This study aimed to provide essential information that can help healthcare professionals feel more confident in using dolutegravir, potentially reducing HIV transmissions by improving viral suppression. The study was designed to boost the confidence of healthcare workers in using DTG and to support its role in reducing HIV transmissions through viral suppression. The objective of this research was to provide a solid foundation for further studies. Additionally, the study is exploratory, paving the way for larger, multi-centre research to confirm or challenge the findings, including the prevalence of adverse drug reactions. This research may offer valuable insights into the practical use of DTG-containing ART, which can deepen current theories on HIV treatment and enrich academic discussions on antiretroviral therapy, especially in regions with high HIV

rates like Namibia. The study's findings have the potential to impact public health policies and practices and contribute to the broader understanding of HIV management in Namibia's context.

2 LITERATURE REVIEW

In this chapter, relevant literature and theoretical framework of this study are presented, which include:

2.1 Search strategy

The search strategy was applied using Online Databases such as Google Scholar, clinicalinfo.hiv.gov and PubMed; only full text articles and literature with a 10year publication limit were used. The following keywords were used with no date limit; Dolutegravir, effectiveness, treatment outcomes, adverse drug reactions and prevalence. In addition, the reference lists of systematic reviews or meta-analysis as well as eligible trials or ancillary publications were reviewed in order to identify studies in grey literature.

2.2 Conceptual Framework

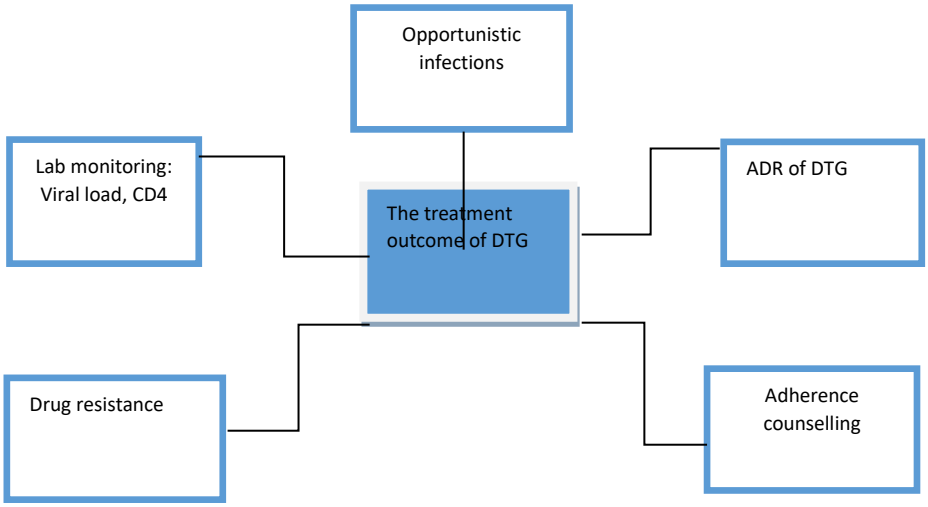

Figure 1: Conceptual framework on the treatment outcomes of dolutegravir containing first line ART.

A conceptual framework was developed to illustrate the link among all components or factors that contribute to the treatment outcomes of dolutegravir based ART (figure1).

The evaluation of treatment outcomes is organized around essential areas in the conceptual framework above. Virologic suppression is a key factor in assessing dolutegravir's effectiveness; it measures the medication's ability to maintain low levels of HIV in the body over time. This is complemented by monitoring the CD4 cell count, which provides valuable information on dolutegravir's effectiveness in restoring the immune system. Assessing patient adherence to DTG and monitoring adverse effects are crucial for ensuring patient safety and gaining insight into the drug's influence on overall health. Additionally, tracking drug resistance mutations is crucial for ensuring dolutegravir's long-term effectiveness. All these factors have a long-term impact on quality of life, encompassing mental health and social well-being, providing a comprehensive understanding of the broader implications of the disease or treatment on overall well-being.

Understanding these factors can improve treatment efficacy and minimize potential side effects or drug interactions. It is essential to carefully monitor patients on dolutegravir therapy and adjust the treatment regimen as needed to achieve the best possible outcomes. By gathering patient-reported outcomes, incorporating patient perspectives becomes possible, resulting in a more comprehensive evaluation process that considers their subjective experiences and preferences. The impact of the healthcare system can be assessed by examining its cost-effectiveness, resource utilization, and sustainability, offering valuable insights into the wider societal consequences. The effectiveness of dolutegravir in preventing the transmission of HIV from mother to child during pregnancy is being assessed in various scenarios.

These interconnected components form a comprehensive framework that allows for a holistic evaluation of dolutegravir's treatment outcomes and supports evidence-based decisions in clinical practice. The regular monitoring of adverse drug reactions (ADRs) and viral load is important to ensuring treatment success. Effective ART has led to prolonged healthy lives of people living with HIV. However, poor adherence to ART can lead to worsening treatment outcomes, such as switching to a different line, treatment failure, increased hospitalizations, and death.

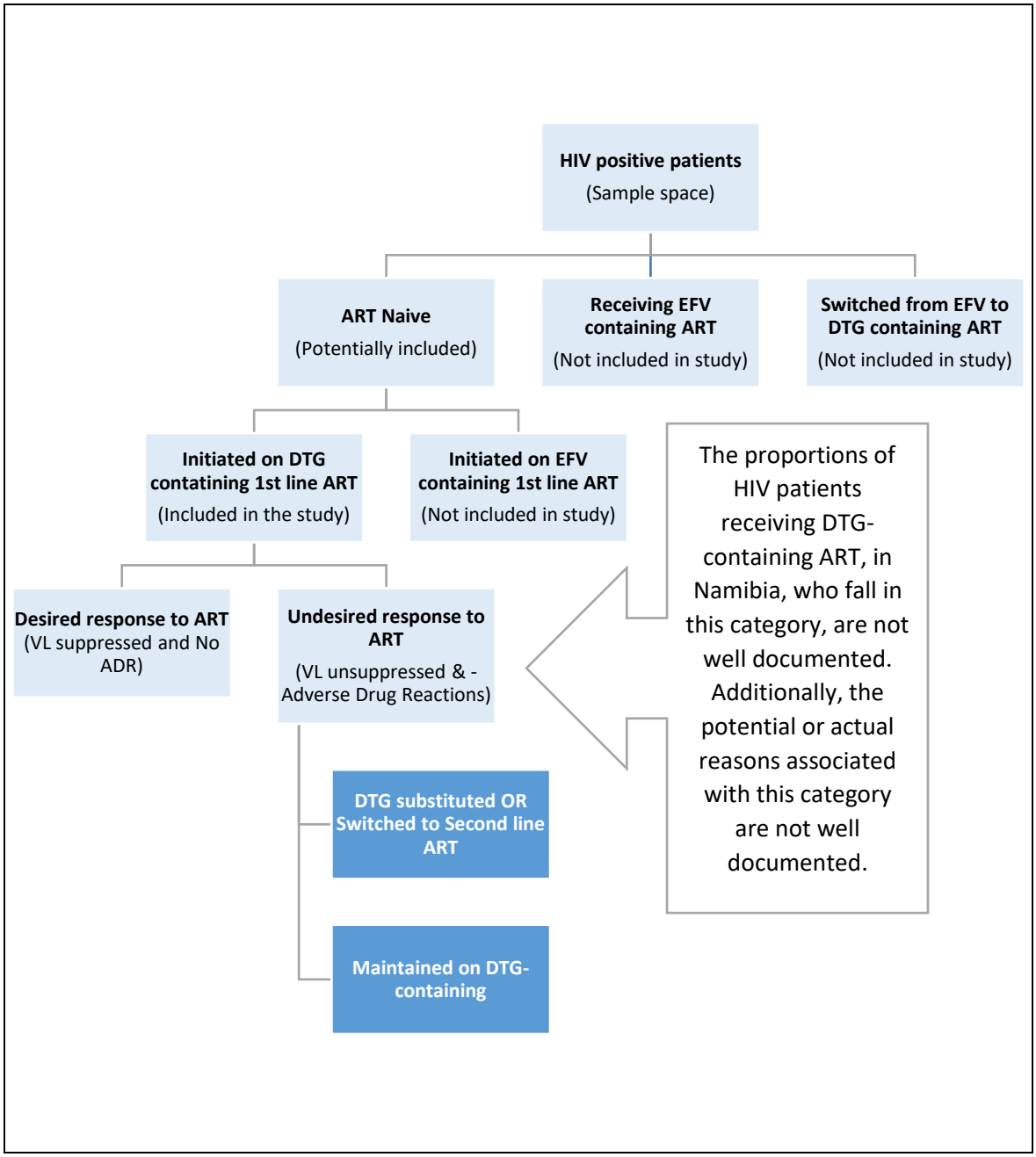

Figure2: Flow chart of the outcomes of HIV-Naive patients taking DTG

The treatment outcomes of DTG containing ART depend on the desired response to ART **(**VL suppressed and no ADR) versus an undesired response to ART (VL unsuppressed and/or adverse drug reactions). For undesired responses we determined if DTG was switched or if patients are maintained on DTG.

The regular monitoring of ADRs and viral load of a patient is important to ensuring treatment success (14). Effective ART has led to prolonged healthy lives of PLWH.

2.3 The use of Dolutegravir containing first line regimens

The Global HIV & AIDS statistics 2022 fact sheet states that in 2022 there were 39 million PLWH and 29.8 million people were accessing antiretroviral therapy in 2022 (15). Combination antiretroviral therapy (cART) can control, but not cure, HIV infection. ART may include dolutegravir (DTG) which is known to be highly effective (16).

Dolutegravir is an integrase strand transfer inhibitor (INSTI) registered under the Namibia Medicines Regulatory Council (NMRC) since 2019 with the indication to treating HIV in combination with other agents. DTG was originally approved by the US FDA in2013 for the management of treatment-naïve and treatment-experienced HIV-infected patients (17). Roll-out of DTG as part of a first line ART regimen occurred in January 2019 in line with WHO recommendations (ref). Currently, dolutegravir is included among the preferred first line anti-retroviral regimens to be combined with an NRTI backbone of one of the following: abacavir and lamivudine or TDF/TAF-emtricitabine (18). Dolutegravir has been documented to have good virological suppression, good tolerability, a high threshold for resistance, and few drug–drug interactions (17).

To maximize adherence for treatment naïve patients, dolutegravir should be co-administered with Tenofovir/Emtricitabine(4). DTG demonstrates increased potency when administered twice daily, including individuals with INSTI resistance and those who are treatment experienced (18). Dolutegravir is known to have a high resistance barrier, which may result in the reduced transmission of resistance mutations (17,19).

The scope of this review will include studies that will identify the safety and effectiveness of dolutegravir.

2.4 The Safety of Dolutegravir as an antiretroviral therapy

There is a lack of sufficient documentation on the adverse effects and predictors of adverse effects associated with DTG among the Namibian population**.** In low-income countries such as Namibia where dolutegravir-based ART has recently been introduced there is need for active monitoring for potentially new and emerging adverse drug reactions.

Concerning the safety of DTG the following studies were reported from limited resource settings. A retrospective study carried out at Amhara comprehensive specialized hospitals in Ethiopia determined that the prevalence of adverse events linked to dolutegravir was 37.6%. The ADRs documented were 60.7% with mild neuropsychiatric symptoms, 23.6% with gastrointestinal symptoms, and 7.14% with hepatic problems, none of which were life-threatening (20). Similar results were observed in central Uganda where they assessed the acceptability and viral suppression of DTG-based first-line ART. This study reported that 33.1% patients had experienced ADRs (21). In these studies, neuropsychiatric ADRs were mostly reported as an adverse event. Similarly, the Zambian Medical Journal found that 30% of patients who received DTG-based treatment experienced neurological and neuropsychiatric side effects (14).

Data from the 2018 TSEPAMO study group led to a signal of potential discovery of the risk of neural tube defects (NTDs) among women with peri-conception exposure to DTG (7). The TSEPAMO study in Botswana showed that the prevalence of neural tube defects among females taking DTG has appeared to have stabilized to two per

1000 births(7,22). Updated Tsepamo study results published in March 2022 showed that a difference in prevalence between DTG and all other exposures at conception is no longer statistically different and has reduced to 0.11% (8).

In Eswatini a study concluded that people taking DTG have a higher risk of becoming obese and overweight(23). Clinically significant weight gain occurs when BMI increases from overweight (25-29.9kg/m^2 to obesity (>30kgm^2)(24). This was also supported by the results obtained by the ADVANCE clinical trial conducted in Africa and 12 PEPFAR-supported treatment sites in Kenya Nigeria, Tanzania, Uganda (25). Weight gain may place PLWH at higher risk of cardiovascular disease, diabetes and high blood pressure. In Namibia, a multi-centre study that occurred across four major state hospitals has investigated the weight gained after transition from EFV containing regimens to DTG containing regimens. This study included predominately Black Namibians of which two thirds were black women who gained significantly more weight compared to men (26). The national ART guidelines in Namibia have listed the following adverse effects of DTG(4)

Table 1: Adverse drug Reactions of Dolutegravir

Adverse drug reaction OF DTG	
Skin	Skin rashes
hypersensitivity reactions	pyrexia, rash, malaise, nausea, headache, myalgia, arthralgia, diarrhoea, shortness of breath, systematic anaphylaxis
Neuropsychiatric changes	abnormal changes, depression, suicidal ideation, mental confusion, insomnia especially in woman over the age of 60
Fat distribution	Lipoatrophy and lipodystrophy: Significant loss of subcutaneous fat and abnormal fat distribution a
Dyslipidemia	

Skin rash, allergic reactions, liver problems and drug interactions have been noted to be very serious life-threatening side effects. DTG may cause people with pre-existing liver infections such as hepatitis B virus infection (HBV) or hepatitis C virus infection (HCV), or elevated liver function tests to develop severe liver problems(27). Any sign of a skin rash needs immediate action. Other severe adverse effects of DTG include immune reconstitution inflammatory syndrome or (IRIS). IRIS occurs after treatment with an HIV medicine and the CD4 count has recovered. A weaker immune system may result in a greater response to a hidden infection(27). These symptoms may include fever, night sweats, swollen glands, cold sores, cough, wheezing, diarrhoea, weight loss, difficulty speaking or swallowing, problems with balance or eye

movement, weakness, or a prickly feeling, and enlarged thyroid and menstrual changes (28).

The prevalence and nature of adverse events related to dolutegravir in Namibia are like those reported in other African countries, including Ethiopia, Uganda, Zambia, South Africa, and Eswatini. However, the demographic composition of the Namibian population studied, which includes predominantly Black Namibians and two-thirds Black females, may have an impact on the observed prevalence and severity of adverse events as well as treatment response to DTG-containing regimens. The specific healthcare infrastructure, adherence support programs, and implementation of national ART guidelines in Namibia may also play a role in variations in treatment outcomes compared to other countries. Further research and comparative analysis are needed to determine the unique factors influencing DTG-related adverse events and treatment outcomes in Namibia.

2.5 The efficacy of Dolutegravir as an antiretroviral therapy

The updated national ART guidelines recommend a transition from an efavirenz containing first line ART regimen to a dolutegravir containing first line ART regimen(29). Namibia has one of the highest prevalence rates for HIV in sub-Saharan Africa. Dolutegravir could be a potentially effective antiretroviral therapy in sub-Saharan Africa because of its high potency and barrier to resistance, good tolerability, and low cost, but there is uncertainty over the effectiveness and potential for drug resistance in African countries like Namibia. Based on efficacy of DTG, several studies have been reported in other settings. In India, a study demonstrated an 18-month viral suppression rate that was enhanced, especially in individuals who started ART treatment with dolutegravir. (30). Whereas, in Cameroon the NAMSAL study compared the non-inferior efficacy of the DTG-regimen and non-emergence of DTG

resistance at 96 weeks. This study supports its use as a first line ART as the viral load suppression was reached more quickly(31)

In a phase 2b, multicentre, SPRING-2 study, treatment-experienced adults were randomly assigned to receive 10 mg, 25 mg, or 50 mg dolutegravir or 600 mg efavirenz. The findings reported from the SPRING-2 noted that there were no integrase inhibitor mutations observed or any serious adverse events were related to dolutegravir(32). These findings support the assessment of a once daily 50 mg dolutegravir for the treatment of HIV amongst the Namibian population as a first line ART. Furthermore, a multicentre FLAMINGO study, patients with a viral load of 1000 copies/mL or more and no resistance at screening were randomly assigned to receive either dolutegravir 50 mg once daily or darunavir 800 mg plus ritonavir 100 mg once daily. During the study there was no record of resistance observed in either group. The following observation was noted from FLAMINGO: Termination due to an adverse reaction was more common in patients taking darunavir plus ritonavir (27). The findings had revealed that dolutegravir better performance characteristics compared to darunavir plus ritonavir. While there may be commonalities in treatment outcomes across SADC nations, unique contextual factors specific to Namibia may impact the effectiveness and safety of DTG-containing regimens There are no studies which documented the efficacy of DTG among Namibian population, hence the importance of this study.

2.6 Treatment Failure of Dolutegravir-Containing Antiretroviral Therapy

Treatment failure and development of drug resistance mutations can still occur, particularly in settings with suboptimal adherence, limited HIV care expertise, and lack of robust drug resistance monitoring systems (33). When used as part of first-line

antiretroviral therapy (ART), DTG is the only HIV drug that has not selected for resistance mutations in the clinic. This is believed to be due to the long binding time of DTG to the integrase enzyme and the greatly diminished replication capacity of viruses that might become resistant to DTG (34). This is believed to be due to the long binding time of DTG to the integrase enzyme and the greatly diminished replication capacity of viruses that might become resistant to DTG (34). However, treatment failure and development of drug resistance mutations can still occur, particularly in settings with suboptimal adherence, limited HIV care expertise, and lack of robust drug resistance monitoring systems (33). Non-adherence is likely the most common reason for treatment failure with DTG-containing regimen (34). Factors contributing to non-adherence include psychosocial issues, lack of support, substance abuse, and adverse effects. In cases of treatment failure, empirical treatment changes based on a comprehensive drug history, followed by good adherence, can lead to good treatment outcomes (35). However, limitations such as self-reported adherence and variability in laboratory testing may impact the assessment of treatment outcomes (35)

Resistance to DTG is possible, but rare, and may be more likely in treatment-experienced patients with previous exposure to other integrase inhibitors (33). The development of multidrug resistance, including resistance to DTG, highlights the need for continued monitoring of viral load, robust drug resistance surveillance systems, and access to specialized HIV care, particularly in resource-limited settings (33).

Cellular factors, such as defective intracellular metabolism of antiretrovirals and the overexpression of multidrug transporters, may also contribute to treatment failure and drug resistance (36). Pharmaceutical care and patient education play a crucial role in promoting adherence, addressing barriers to treatment, and ultimately improving treatment outcomes (36).

2.7 Gaps in literature

It is crucial to explore the underlying causes of treatment failure and mortality in Namibia, including potential factors, such as drug resistance, adherence issues, and other healthcare system-related factors. DTG has become one of the most frequently prescribed antiretroviral therapies (ART) in Namibia, as recommended by the Namibian ART guidelines, and has demonstrated high effectiveness and a low potential for resistance based on substantial evidence (4). Additional studies are necessary to evaluate the safety and efficacy of DTG in Namibia as there is currently a lack of understanding in this area. The favorable outcomes of DTG in other African nations may not be duplicated in Namibia. Therefore, it is crucial to examine the contributing elements to any potential disparity, considering the healthcare infrastructure, access to healthcare, and socioeconomic factors in Namibia. DTG was recently introduced in Namibia. Conducting comparative studies is crucial to comprehend DTG's performance in Namibia when compared with other African countries after considering geographical disparities. There is little information concerning the safety and effectiveness of this drug among the Namibian population. This investigation was conducted to acquire information about the safety and efficacy of dolutegravir (DTG) as part of a first-line regimen in Namibia. Although exploratory studies are valuable, there is a need for broader and prolonged research to offer a more comprehensive understanding of the long-term safety and efficacy of DTG in Namibia.

Enhancing the understanding of the safety and efficacy of DTG in Namibia is crucial, and this can be achieved by addressing the existing gaps in knowledge, which can offer invaluable insights for healthcare professionals and decision makers in the region.

3 RESEARCH METHODS

3.1 Research Design

A retrospective quantitative study was conducted which consisted of adults newly initiated on dolutegravir containing first-line Anti-retroviral therapy (ART). The study included ART-naive patients, who were initiated on DTG-containing ART and started treatment from January 2020 to March 2021. The data was retrospectively observed for 18 months after initiation of therapy.

3.3 Study Setting

Records of patients who received therapy at the outpatient ART department in Intermediate Hospital Katutura (IHK) were collected and reviewed. The hospital is a public health facility, located in the central Namibia in the Khomas region and serves a catchment population of around 106 017 people. It is one of two State Hospitals in the Windhoek area, and Namibia's only general referral hospital. At KIH the outpatient ART department provides patients with: HIV testing services, Prevention of mother-to-child (PMTCT) services, ART (including, but not limited to, multi-month prescriptions, and the treatment of opportunistic infections). The clinic provides pre-exposure prophylaxis for pregnant and breast-feeding women, as well.

3.4 Study population

The study population was comprised of HIV-infected formerly ART-naive patients who received Dolutegravir containing first-line ART. ART naïve is defined as having no prior history of any antiretroviral agent exposure.

3.4.1 Inclusion criteria

This study included records of HIV-infected treatment naïve patients, 18 years or older who were initiated on DTG-containing first-line ART and had ART-related data for at least 18 months. Based on the above, the following exclusion criteria was applied.

3.4.2 Exclusion criteria

Women who were pregnant at the time of ART initiation or became pregnant at any time during the study period were excluded. Patients were excluded from the study if they stopped or switched their initial ART regimen within the first 6 months of starting therapy. The study also excluded patients with missing or had incomplete data.

3.4.3 Sample Size

The population was utilized to calculate the number of patients required to determine a clinically significant treatment effect (37). The Pharmaceutical Dashboard is a Web based information tool for aggregating patient and inventory management report for decision making at multiple levels of the health care system in Namibia. The dashboard was used to estimate the sample size. The appropriate sample size was calculated as shown below:

Over a six-month period, 146 patients were initiated on first-line ART containing DTG at IHK, as indicated by the pharmaceutical dashboard data**.** Therefore, on average 25 ART naïve patients were initiated on DTG-containing first line ART per month. This study looked at outcomes in patients who had initiated on antiretroviral therapy from January 2020 to March 2021 (these patients were followed for 18 months, using August 2022 as the end of the follow-up period). The population was estimated to be 375 (25 patients multiplied by 15 months). A sample of 191 patients (patient files, to be specific) was calculated using the OpenEpi® calculator, based on the following parameters:

a. Population = 375
b. The hypothesized % frequency of outcome factor in the population (p): 50%
c. Confidence level = 95% and confidence limit = 5%
d. The design effect = 1.

3.4.4 Sampling

The list of patients who received the DTG-containing first line ART in the specified period was generated from the electronic dispensing tool (EDT) in Excel format and was numbered sequentially from the first to the last patient. A list of random numbers (n=230) was generated in Excel (Appendix 2) using the "RandBetween" function, with the minimum = 0, and maximum = 376. This list was used to select the files for inclusion in the study. The table was followed sequentially from top to bottom starting with the column on the far left, until 191 files were selected. When the file was selected, it was reviewed for critical data before abstraction but excluded if critical data were missing.

3.5 Data collection Tool

A data collection tool was designed (appendix 4) to collect data for the requisite variables to achieve the study objectives. The tool was divided into FIVE sections. The sections were divided into as follows:

Part A: Socio-demographic information of the patient which included the sex, age, ethnicity, date when ART was initiated, residence, employment status, marital status, date when ART was initiated, smoking and alcohol use.

Part B: Adverse drug reaction was defined by the national ART guidelines as skin rash with or without hypersensitivity reactions, Neuropsychiatric changes: abnormal changes, depression, suicidal ideation, mental confusion, insomnia especially in

woman over the age of 60. Lipoatrophy and lipodystrophy: Significant loss of subcutaneous fat abnormal fat distribution. Dyslipidaemia (asymptomatic), Hepatotoxicity (29). Weight gain was defined as: all patients in the cohort who have gained weight over 3kg do not have any opportunistic infections.

Part C: Opportunistic infections as defined by the ART guidelines which include pneumocystis pneumonia, toxoplasma encephalitis, malaria episodes, bacterial pneumonia, Cryptococcal Meningitis and Kaposi Sarcoma.

Part D: Baseline Laboratory tests included CD4 count, level of adherence, viral load, creatinine clearance, liver function test, renal function test, creatinine clearance and haemoglobin. VL monitoring was used to detect treatment failure at a VL > 1000 copies per ml. Viral suppression was referred to as the viral load below the detection threshold using viral assays VL < 40 or Target Not detected (TND) (29). Low level viremia was defined VL between 40-1000 copies/ml (29)

Part E: Treatment outcomes included treatment success, treatment failure and switch to second line ART. Treatment failure was determined clinically by the participants history, physical examination, by clinical development of opportunistic infections, immunologically by CD4 counts and virologically by VL>1000 copies/ml after 6 months of starting ART or after a period or viral rebound to VL> 1000 copies/ml on 2 consecutive measurements after a period of viral suppression(29). Treatment success was said to occur when the viral load remained supressed and when there was an increase in CD4 count. Also, patients who persistently have had a VL < 40 copies per ml are said to be experiencing treatment success(4)

3.5.1 Study Variables

Independent variables:

These were the independent variables, their levels presented in parenthesis: Sex (male and female); Body Mass Index (BMI); Age (years, continuous data); Viral load categories (VL1 and VL2)(date); Adverse drug effects (date); Co-morbidities and co-medications (date); Height; Level of adherence; Clinical history; Renal function; Employment status; Opportunistic infection; Education status; CD4 count (date;); body weight (date).

Dependent (outcome) variables

Two dependent variables were investigated dichotomously: Drug safety and effectiveness of therapy. Drug safety was judged as adverse drug events present or not; and effectiveness was judged as treatment failure and treatment success. For Drug safety participants with no opportunistic infections (TB) had gained weight over 3kg at the end of 18 months. TB can cause significant weight loss and muscle wasting, which can negatively impact treatment outcomes (38). To determine the number of patients that had gained weight we removed all patients who had TB. To identify individuals who may have gained weight due to DTG-based ART, we measured the average weight gain observed in the NAMSAL (5kg) and AFRICOS (1.3kg) studies, which resulted in a total average weight gain of 3kg (31) (39). The two studies reflected the sociodemographic characteristics of the study population and setting. Analysis was conducted on all patients in the cohort without TB who had gained weight by more than 3kg. For those whose viral loads were conducted in accordance with the guidelines, compliance of the guidelines was observed by healthcare workers, and we

continued to follow the guidelines in determining treatment failure. The remaining group whose viral loads were not conducted in accordance with the guidelines we determined if we could measure treatment failure.

3.6 Piloting of data collection tool

Piloting took place at the Katutura Intermediate Hospital (KIH). The study tool was piloted before the study period to serve as validation procedure. Ten patient files were randomly selected and used to extract data. A mini analysis was done after which the tool was modified. The following parts were added to the data collection tool to improve the data abstraction process. Certain socio-demographic characteristics such as alcohol use (yes/no) and smoking (yes/no) were added to the tool. In addition, information regarding BMI, weight gain, and visit weights recorded at 0,6,12 and 18 months were added to the tool. For the laboratory findings dates were added to determine when the clinical monitors were taken.

3.7 Data collection procedure

After obtaining approval from the University of Namibia Research and Ethics Committee and the Ministry of Health and Social Services Ethics review board and with the permission of the medical superintendent, HIV clinic manager, and the chief pharmacist at the IHK, the data collection process commenced as follows.

A list of patients who initiated DTG in the study period was generated from EDT. For inclusion in the study, patients were randomly selected using a table of random numbers. The identifiers (unique ART numbers) that linked the patient to the files were used to access files in the physical data base but were not included in the collected

data. Lastly, the data was collected and data from the files was transcribed into the excel data abstraction tool.

3.8 Validity and Reliability of the study

The weights were taken using calibrated weighing machine. Reliability of the results was maintained by extensive training was administered to the data abstractors on the study protocol, data abstraction techniques, and criteria for identifying relevant information. Additionally, continuous support and feedback was encouraged to aid in maintaining uniformity among the reviewers.

3.9 Data Analysis

The mean, median, and range for continuous variables, and proportions for categorical variables, were calculated for descriptive purposes. For analysis, chi-square and Fisher's exact tests were used for categorical variables to assess the relationship between variables and treatment outcomes (safety and effectiveness) (40). Drug safety was measured by identifying any adverse effects (weight gain) of DTG, and effectiveness was determined by measuring a viral load of less than 40 copies/mL. To identify potential predictors of adverse drug reactions and treatment failure, logistic regression analyses were used (40).

Simple logistic regression was conducted for the following comparisons: TB status by treatment failure, TB status by viral load <1000 copies/mL, TB status by detectable viral load, and gender by weight gain. A 95% confidence interval was used, with a significance level set at a p-value less than 0.05. Bivariate analysis was conducted using chi-square and Fisher’s exact tests on a cohort of 89 patients who had gained weight.

A small sample size was used with logistic regression. This decision is supported by existing research that highlights the feasibility and validity of such an approach under certain conditions. Notably, Chow and Rodgers (2005) in their study "Another Look at Resampling: Replenishing Small Samples with Virtual Data through S-SMART," demonstrate methods to enhance the robustness of small sample studies. They argue that small sample sizes can still yield meaningful and reliable results, especially when complemented with resampling techniques and robust statistical methods [64]. This aligns with the approach taken, where steps have been taken to ensure data quality and appropriate techniques have been implemented to mitigate the limitations typically associated with small samples. IBM SPSS

Statistics Version 27.0.1 (IBM Corporation, Armonk, NY, USA) was used for data analysis.

3.10 Research Ethics

3.10.1 Informed Consent

An Ethical clearance certificate was issued by the Decentralized Ethics Committee from the University of Namibia as seen in annexure 1 (Ethical Clearance Reference Number: SOP0002) in accordance with the University of Namibia Ethics Policy Guidelines. Permission to conduct the study was issued by Ministry of Health and Social Services (MOHSS) as seen as in annexure 2. Permission was granted conduct research at the Intermediate Hospital Katutura to access patient records as seen in annexure 3.

3.10.2 Beneficence: No direct benefits were received by the patients or health care professionals at the facility.

3.10.3 Non-maleficence: This study used secondary data and thus there were minimal risks involved in this study.

3.10.4 Respect for anonymity and confidentiality: Patient identity was kept anonymous and personal information regarding patient outcomes was kept confidential. The obtained data were kept under lock and key, and password protected on the computer.

4 RESULTS

Introduction

Chapter 3 focussed on describing the research methodology that was used to meet the objectives of this study. Chapter 4 will consequently present the study findings.

4.1 Socio demographic characteristics

A sample size of 191 was calculated. However, out of 180 patient charts available only 120 were included in the analysis (figure 2). All patients were Namibian and of Black race. Sixty patients were excluded due to pregnancy or missing data e.g. viral load, CD4 T cell count, sociodemographic information, patients who did not have enough follow-up data or defaulted appointments (figure 3).

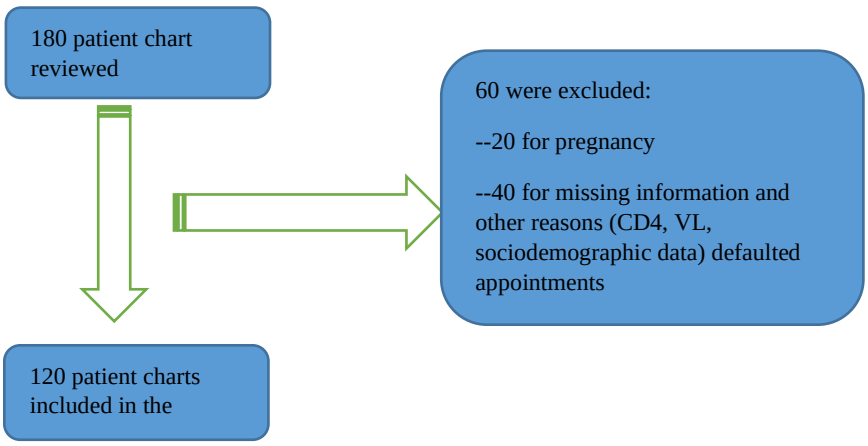

Figure3: Summary of study sample

Table 1 describes socio-demographic and clinical data. There were slightly more males (55%)), n=66) males in the cohort. The median age was found to be 36.5 (18-66) for the entire cohort. Most had no comorbidities; 7% (n=8) had hypertension, 1 had cholesterol and 1 had diabetes. Additional demographic characteristics are provided in table 1.

Table 2: Socio-Demographic characteristics of patients at baseline

Variables	n (%)
Residence Outside of Windhoek	3(2.5)
Windhoek	117 (97.5)
Gender Male	66 (55.0)
Female	54 (45.0)
Age Less 20	3 (2.5)
20 – 29	31(25.8)
30 – 39*	40(33.3
40 – 49	29(24.2)
Equal/greater 50	17(14.2)
Marital status Married	9(7.5)
Single	111(92.5)
Employment status Formal	31(25.8)
Informal	24 (20)
Self	5 (4.2)
Unemployed	60 (50)
Alcohol Yes	18 (15)
No	102 (85)
HBSAg Positive Non-reactive	104 (87)
Reactive	16(13)
Smoking Yes	14 (11.7)
No	106 (88.3)

*33% from the age group between (30-39) initiated on DTG containing ART

4.2 Clinical Data: Baseline and after ART initiation

The baseline CD4 + T-cell count at the time of ART initiation showed a median of 144.5 (range 2-1276), with 58% of patients having a CD4 + T-cell count less than 200. Additionally, data revealed that 95% of patients maintained a good level of adherence throughout the study period. Seventy-four percent of the cohort received their second

viral load (VL2) at the recommended 12-month interval, with 75% remaining virally suppressed at the end of 18 months. However, 15 patients exhibited VL2 >1000 copies/ml, with the highest recorded viral load reaching 72,592 copies/ml. Furthermore, the analysis found that 35% of patients with TB had a CD4 <200 at baseline, decreasing to 23% by the end of the study, with a viral load >1000. Table 3 illustrates the mean weight changes over the study period, indicating an average increase of 4kg for both males and females from baseline to 18 months. Finally, 31% of the patients were overweight by the end of the 18-month period, whereas 18% experienced a weight gain of over 10%. Additional clinical information can be found below in Table 2.

Table 3: Clinical Data of patients taking DTG containing ART

Variables	n (%)
Baseline CD4 T-cell count, cells/µL	
<200	70 (58)
>200	50 (42)
Viral Load (VL1) (copies/mL)	
<40 (undetectable)	91 (76)
40-1000	23 (19)
>1000	6 (5)
Viral Load (VL2) (copies/mL)	
<40 (Undetectable)	90 (75)
40-1000	15 (12.5)
.>1000	15 (12.5)
Treatment Failure	
Yes	15 (12.5)
No	115 (87.5)
Opportunistic infections	
TB*	31 (25.8)
No opportunistic infections	69 (74.2)
Level of Adherence	
Good	115 (95.8)
Fair	2 9 (1.7)
Poor	3 (2.5)

*Only TB was recorded as an opportunistic infection from the patient files

Table 4: The changes in weight up to 18 months

	Male (mean weight in kg)	Female (mean weight in kg)
Weight (kg)		
Weight at baseline	63	64
Weight at 6 months	65	66
Weight at 12 months	66	67
Weight at 18 months	67	68
Weight changes at 18 months	4	4
BMI (kg/m^2)		
Baseline BMI	22	22
BMI at 6 months	23	23
BMI at 12 months	23	24
BMI at 18 months	24	24
BMI changes at 18 months	1	1

4.3 The Prevalence and Predictors of Adverse Effects for DTG containing ART

The only reported adverse effect observed in the study was weight gain, with 20.2% of patients experiencing clinically significant weight gain, corresponding to a prevalence rate of 13.5 cases per 100 patient years. Notably, these patients gained weight over 3kg. A statistically significant association between weight gain and gender was found (p-value = 0.026), as detailed in Table 6. Additionally, the sex of the patient showed a statistically significant association with adverse drug reactions (ADRs), while other socio-demographic and clinical variables did not exhibit statistical significance, as shown in Tables 6 and 7, respectively. Table 6 further reveals that 72.2% of females without TB experienced weight gain compared to 27.8% of males. Moreover, females without TB living with HIV on TLD were four times more likely to have gained weight, with a 95% confidence interval of 1.3 to 12.4, as demonstrated in Table 8.

Table 5: Participants that have experienced Weight Gain without TB

	Weight Gain		
Variables	**Yes n%**	**No n(%)**	**P-value**
Gender			
Male	5 (27,8)	43 (60.6)	
Female	13 (72,2)	28 (39.4)	0.026*
Age			
Less 20	1 (5.6)	1 (1.4)	
20 – 29	7 (38.9)	16 (22.5)	
30 – 39	5 (27.8)	25 (35.2)	
40 – 49	3 (16.7)	18 (25.4)	
≥50	2 (11.1)	11 (15.5)	0.473
Marital status			
Married	1 (5.6)	7 (9.9)	
Single	17 (94.4)	64 (90.9)	0.913
Employment status			
Formal	6 (33.3)	18 (25.4)	
Informal	2 (11.1)	15 (21.1)	
Self	0	3 (4.2)	
Unemployed	10 (55.6)	35 (49.3)	0.572
Alcohol use			
Yes	3 (16.7)	15 (21.1)	
No	15 (83.3)	56 (78.9)	0.926
Smoking			
Yes	2 (11.1)	10 (14.1)	
No	16 (88.9)	61 (85.9)	1

*Chi Square significant at a P value < 0.050

Table 6: The Association between Clinical characteristics by Weight Gain

Variables	Weight Gain Yes n%	No n(%)	P-value
Comorbidities			
Yes	2 (11.1)	10 (14.1)	
No	16 (88.9)	61 (85.9)	1
Level of adherence			
Good	16 (88.9)	69 (97.2)	
Fair	1 (5.6)	0	
Poor	1 (5.6)	2 (2.8)	0.181
Viral load 1			
<1000	17 (94.4)	67 (94.4)	
≥1000	1 (5.6)	4	1
Viral load 2			
<1000	18 (100)	68 (95.8)	
≥1000	0	3 (4.2)	0.876
Viral load 1			
Non Detectable	16 (88.9)	51 (71.8)	
Detectable (≥40)	2 (11.1)	20 (28.2)	0.233
Viral load 2			
Non Detectable	15 (83.3)	59 (83.1)	
Detectable (≥40)	3 (16.7)	12 (16.9)	1

Chi- Square Significant at a P value < 0.050

Table 7: Bivariate logistic regression models of factors associated with Gender by Weight gain.

Gender	OR 95%CI	P
Female	3.993 (1.282-12.434	0.017*
Male	1.000	-

*Bivariate logistic regression significant at a P value < 0.050

4.3 The Prevalence and Predictors of Treatment failure for DTG containing ART

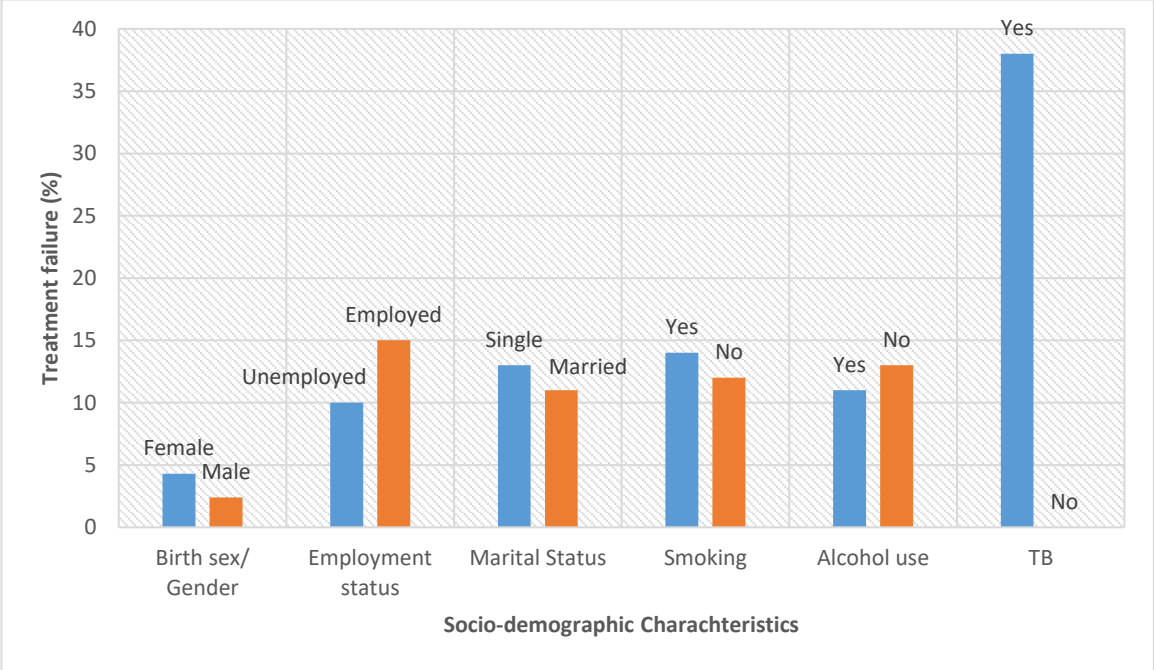

Figure 4: Shows Socio-economic factors and clinical data and their influence on Treatment failure.

Fifteen (n=15) patients taking DTG containing ART experienced treatment failure. Based on the documented evidence of treatment failure, the prevalence was 12.5% (n=15). The Treatment failure was higher in the prevalence rate of treatment failure was 8.3 cases per 100 patient years. But considering the switching as confirmation of treatment failure, the prevalence rate was 2.2 cases per 100 patient years. Females taking DTG-containing ART (13%) than males (53.3%) p= 1. Most of these patients who had experienced treatment failure were employed (15%) and single (13%). Only six of these patients who had opportunistic infections like tuberculosis were having pre-existing co-morbidities. It was found that all of the patients who experienced treatment failure had TB (figure 3). Although 15 patients taking DTG containing ART appeared to have treatment failure, no other socio demographic characteristics appeared to be statistically significant. There was a strong significance between TB and treatment failure with a P value < 0.001. Analysis showed that PLWH on TLD co-

infected with TB were 18 times more likely to have treatment failure (95% CI: 4.65,70.45) as seen in Table 5. Due to treatment failure experienced, only 4 patients (3.3%) had their DTG-based antiretroviral regimen changed or switched. There were several but weak statistical significance determined by Pearson chi-square test. These included results between various variables such as sociodemographic and clinical characteristic by treatment failure respectively (Table 4).

Table 8: The association between variables by Treatment Failure

Treatment Failure			
Variables	**Yes n%**	**No n(%)**	**P-value**
Gender			
Male	8 (53.3)	58 (55.2)	1
Female	7 (46.7)	47 (44.8)	
Age			
Less 20	0	3 (2.9)	
20 – 29	4 (26.7)	27 (25.7)	0.641
30 – 39*	4 (26.7)	36 (34.3)	
40 – 49	6 (40.0)	23 (21.9)	
≥50	1 (6.7)	16 (15.2)	
Marital status			
Married	1 (6.7)	8 (7.6)	1
Single	14 (93.3)	97 (92.4)	
Employment status			
Formal	4 (26.7)	27 (25.7)	
Informal	4 (26.7)	20 (19.0)	0.614
Self	1 (6.7)	4 (3.8)	
Unemployed	6 (40.0)	54 (51.4)	
Alcohol use			
Yes	2 (13.3)	16 (15.2)	1
No	13 (86.7)	89 (84.8)	
Comorbidities (non-TB)			
Yes	3 (20)	16 (15.2)	0.925
No	12 (80)	89 (84.8)	
Smoking			
Yes	2 (13.3)	12 (11.4)	1
No	13 (86.7)	93 (88.6)	
TB Status			
Yes	12 (80)	19 (18.1)	<0.001*
No	3 (20)	86 (81.9)	
Level of adherence			
Good	14 (93.3)	101 (96.2)	0.268
Fair	1 (6.7)	1 (1.0)	
Poor	0	3 (2.9)	

*Chi Square Significant at P value < 0.050

Table 9: Bivariate logistic regression analysis model of TB by treatment failure

TB Status	OR 95%CI	P-value
Yes	18.105 (4.651-70.486)	<0.001*
No	-	-

*Bivariate logistic regression analysis significant at a P value <0.050

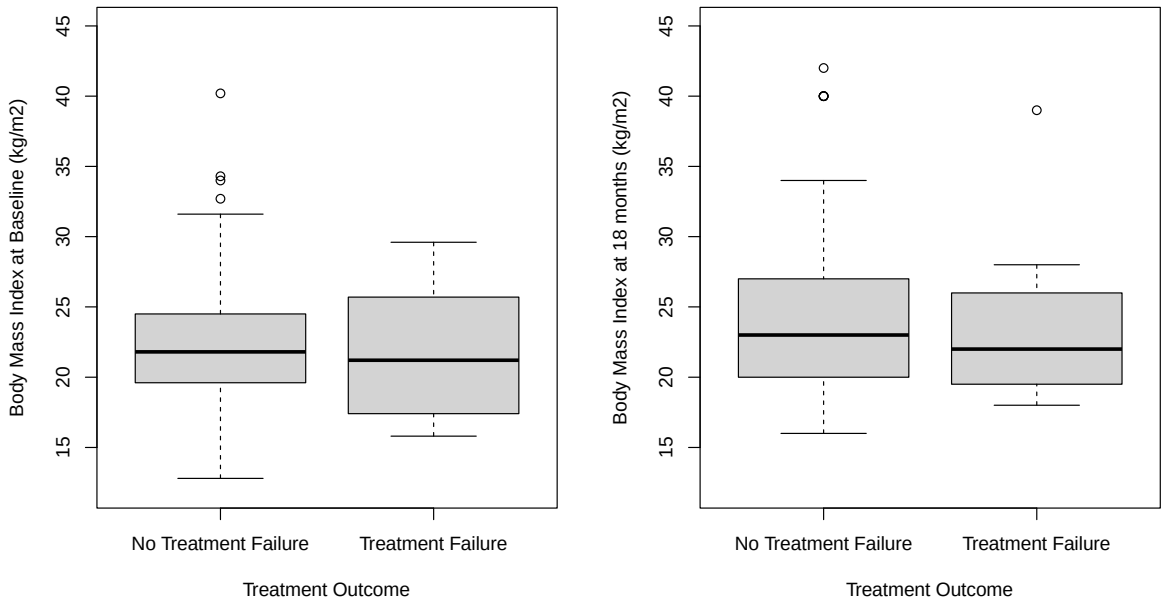

Figure 5. Comparison of median BMI values at baseline vs at 18 months for patients on dolutegravir showed no statistically significant difference (p-value = 0.10). Comparison of BMI values for patients with no treatment failure at baseline vs at 18 months also shows no statistical difference (p-value = 0.117).

In figure 4 the changes of BMI at baseline vs 18 months for patients on dolutegravir for those with treatment failure and those without. The results showed that the true location shift was not equal to zero (P = 0.10). There was no statistical significance found between the BMI at baseline and the BMI at 18months. Although there was an increase observed in BMI in patients with no treatment failure. The patients with no treatment failure at baseline and at 18 months were compared statistically. The results showed that a true location shift was not equal to zero with a P value = 0.17, the null hypothes.is indicated a true location shift equal to zero. Accepting the null hypothesis meant that there was no significance or shift. The P value was only accepted if it was

less than 0.05, the P value = 0.17 hence we failed to accept the null hypothesis and accepted the alternative. If the alternative hypothesis was true, this meant that there was a difference in BMI at baseline and at18 months in patients with no treatment failure. Hence it can be said that although there was a difference in association, it was not statistically significant.

5 DISCUSSIONS ON STUDY RESULTS

5.1 Introduction

This chapter will focus on discussing the results as well as comparing findings with reports in other studies of a similar nature.

5.2 Discussion

5.2.1 The Prevalence of adverse drug events

Despite its size, this single-facility exploratory study utilized real-world data captured electronically, which is available for research purposes, among others, representing a positive aspect of the study. Secondly, this is amongst the novice studies on DTG's safety and effectiveness in Namibia. Regarding the findings, being female was identified as a risk factor for clinically significant weight gain associated with DTG. Secondly, the manifestation of TB was found to be a potential predictor of treatment failure. Although this study provides shorter-term data compared to a larger, multicentre study in South Africa, our findings may still provide some guidance for clinicians on the importance of monitoring the adverse effects of dolutegravir (42).

The proportion of patients who experienced clinically significant weight gain was 20.2 % with the prevalence rate for weight gain being 13.5 cases per 100 patient years. Weight gain for PLWH on certain antiretroviral therapy medications may signify a return to health, but rapid or excessive weight gain may potentially lead to obesity(43). ART initiation in treatment naïve HIV patients is frequently associated with a short period of weight gain, which has conventionally been documented as a return to health (21,44). The mechanisms by which some ART agents contribute to weight gain are not well understood (45) . The prevalence of other adverse events associated with DTG

have been reported in other settings. For instance, in Uganda the prevalence of allergies and other adverse events associated with DTG was documented at 33.1% (20); and in Ethiopia, it was documented at 37.6%, with neuropsychiatric symptoms and gastrointestinal symptoms being the most reported, followed by hepatic and renal events (34). All reported adverse events were mild, and none were severe or life-threatening**.**

The only ADR documented was weight gain, a familiar finding amongst treatment naïve PLWH (27). In this study population a mean weight gain of 4 kg was observed. The following results were observed in other settings like our study population. For instance, the NAMSAL (NCT02777229) study documented a median weight gain of up to 5 kg and 3 kg in the DTG and EFV groups, respectively (31). Similar findings were reported in the SCOLTA project (45), which also found that ART-naive individuals who took DTG combinations of TDF/FTC and TAF/FTC were more likely to gain weight. In Namibia, a study conducted across the country at four of the largest state hospital facilities investigated weight gain among patients who switched from an EFV-containing regimen to a DTG-containing regimen. This study reported no major changes for males but reported major changes for females at 12 months (+1.58kg) and 18 months (+1.49kg) respectively(26). The AFRICOS study is an observational study that was held in Nigeria, Kenya, Uganda, and Tanzania, showed an average weight gain 1.3kg at 12 months (46). In another study, it was documented that patients gained an average of 2.9 kg at 18 months when switched to an INSTI-containing regimen (47). In the UK a retrospective analysis was conducted on HIV suppressed patients to assess the effects on weight after transitioning to a DTG-containing or Raltegravir (RAL)-containing regimen. There was no evidence of an overall increase in the rate of weight gain in individuals who were virologically suppressed after switching to INSTI

(48). This could partly be due to patient characteristics in a high-income population. The association between weight gain and INSTI regimens in treatment naive PLWH may be due to higher rates of viral suppression compared to older regimens (45).

5.2.2 The Predictors of adverse effects

Regarding risk factors, the sex of the patient was found to be statistically significantly associated with ADR, with the females experiencing higher risk of pathologic weight gain. Similar results were observed in a study conducted in Namibia which investigated the changes in weight gain when switching from efavirenz-to dolutegravir-containing regimen. This study observed that Black females gained significantly greater amount of weight than males (26). Additional testing options are available for assessing the potential implications of weight gain. These include thyroid function tests, cortisol level evaluations, measurements of insulin or glucose levels, liver function tests, and lipid profile assessments. These diagnostic examinations provide valuable insights into various physiological aspects that may contribute to weight gain, enabling a more comprehensive understanding of an individual's health status and guiding appropriate interventions, if necessary. In the AFRICOS study, women were found to have had a greater weight gain one year post TLD switch, but this difference was not significant after the first year (46). More studies have demonstrated a significance between increases in BMI and females. For newer ART regimens like DTG, weight gain was greater in female sex and Black race(49). The gender difference may be explained by leptin, a hormone produced by the adipose tissue and regulates fat metabolism and energy utilization. Woman have shown to exhibit leptin resistance making it harder to breakdown fat in the body which could be a possible reason why woman have been more likely to gain weight compared to men (50). Nonetheless, a systematic review was conducted to determine whether fat loss or

gain was more common in HIV-infected patients on ART than in uninfected controls. This review concluded that there were no differences in weight gain between patients on ART and those who were not infected with HIV (51). A study based in Namibia indicated that obesity of a women is associated with age, highest level of education, economic status, contraceptive use, smoking habits, and age of female at first birth (52), however, these findings were not replicable in our study. Further, it was not possible to conclude that the weight gain observed was solely associated with DTG-based ART regimen. Some patients gained a high magnitude of weight leading to obesity, which may increase the risk of cardiovascular disease, diabetes, chronic kidney disease, non-alcoholic steatohepatitis, and cancer (53). More research is necessary to explore these findings and to examine the mechanisms connecting antiretroviral drugs and weight gain in the Namibian population through larger,

5.2.3 The prevalence of treatment failure

Based on the documented evidence of treatment failure, the prevalence was 12.5% (n=15). The prevalence rate of treatment failure was 8.3 cases per 100 patient years. But considering the switching as confirmation of treatment failure, the prevalence rate was 2.2 cases per 100 patient years. Four (3%) patients discontinued TLD and were switched to a second line ART which is consistent with data obtained from a cohort study in Sub-Saharan Africa of 4.1% (54). The remaining patients who were not switched and were suspected of treatment failure or had poor adherence. We do not know if they were eventually switched. This calls for follow-up and further research in this area. The patients who were not switched to second line ART were reported as having good adherence and remained virally suppressed at 18 months. It is possible that a poor prognosis in these patients was not noticed, or they got better as time went by, meaning that they could have had poor adherence prior to the notification of

'treatment failure'. It is recommended to wait 1 year to switch from DTG to a second ART.

The four patients who were switched to second line ART had record of virological failure. Of these, two had a poor adherence record. Patients who are not adhering well to ART are susceptible to virological failure and the development of drug resistance(4). Adherence and drug resistance have an impact on the virological outcomes on DTG containing ART. For instance, a systematic review concluded that the odds of having virological failure were 6 times more likely amongst patients with poor adherence compared to those who had good adherence(55). In resource limited settings such as Namibia there is no genotype resistance testing which could provide laboratory evidence of the cause of treatment failure. Nonetheless, virological failure identified by HIV-RNA testing provides sufficient evidence for clinical decision making (56). Two clinical trials named ADVANCE and NAMSAL were conducted exclusively in sub-Saharan Africa, which studied the effectiveness of DTG-based first-line regimens for individuals who were ART-naïve. In the ADVANCE trial, 14% of participants were found to have mutations that confer resistance to NNRTIs (non-nucleoside reverse transcriptase inhibitors), while 2% had mutations that confer resistance to NRTIs (nucleoside reverse transcriptase inhibitors) (54,57). Similarly, in the NAMSAL trial, 6% of participants had NNRTI mutations, while 1% had NRTI mutations(54). Both clinical trials indicated a lack of DTG resistance in patients who were ART-naïve. Eight cohorts from Canada, South Africa, Europe contributed data on genotypic resistance testing on DTG based ART. In our setting, patients that have failed the first line regimen and have been switched to a second line ART are not eligible for HIV resistance testing (4). Hence, it may not be possible to conclude that the DTG-based ART regimen may have been failing due to resistance based on

insufficient information on drug resistance. Nonetheless, DTG-related mutations have been observed elsewhere. In Brazil a relatively high frequency of Integrase Resistance Associated Mutations (INRAMS) was discovered among patients failing on DTG associated regimen due to possible delays in requesting genotype testing and monotherapy with DTG(58). INSTI naïve patients have a very low risk of developing drug resistance in case of virologic failure. This could possibly be an indication that the DTG regimen had failed due to poor adherence, although we cannot prove this as we do not have a lot of information after 18 months of DTG based ART. After 18 months it is not known whether, they continued taking DTG based ART regimen and improvement was recorded or if there were records of switching to a more effective treatment. A follow up study would be good to tease out this evidence.

It is worth-the-while to note how VL tests were conducted and to discuss the required response in such instances. What needs to be done when a high VL is observed with DTG if VLs are not being monitored in accordance with the guidelines? In most resource-limited countries like Namibia and South Africa, timely repeat testing is not performed as recommended, which would be crucial for guiding clinical care (23,59). This can have negative consequences such as serious morbidity, onward transmission, moreover of resistant strains. A research project in South Africa investigating delays in transitioning HIV patients to second-line antiretroviral treatment at a public hospital in eThekwini, KwaZulu-Natal, found that patient delays and systemic factors were the root causes of delays in monitoring viral load (23). Delays in the clinical decision making could offer negative effects to the treatment outcomes during patient care. They concluded that switching should be done at VL> 1000 copies/ml regardless of timing. A similar conclusion was made by Kalemeera et al (2022) in Namibia (59). In our study adherence counselling was always conducted in timely manner after viral

load tests as required by the ART guidelines. Further research needs to be done in similar settings as Namibia and South Africa, to find out if patients receiving DTG-containing ART with detectable viral loads should be switched to second line therapy, immediately.

5.2.4 The predictors of treatment failure

Regarding predictors of treatment failure, TB was identified. It is well documented that the risk of TB is associated with high viral loads > 1000 copies/ml (60). A retrospective cohort study was conducted in Botswana for patients with HIV who were co-infected with TB. This study investigated the treatment outcomes of patients taking DTG-based regimens and Rifampicin (RIF). The results from the Botswana study indicated that co-administration of DTG with RIF based TB regimens was associated with viral suppression and successful TB outcomes (61). Also, this study found that a single daily dose of 50mg dolutegravir produced slightly superior outcomes than a double daily dose of 50mg dolutegravir (62). This is important because the current National ART guidelines recommend a twice daily dose of 50mg DTG based ART(29). In our study it is not known if the patients in the cohort were being treated for TB with RIF during the time of the study. Hence, we cannot conclude that the rates of treatment failure in this cohort could be due to patients not receiving a second daily dose of RIF. More research may need to be done in Namibia regarding twice daily dosing of RIF in patients co-infected HIV and TB to determine if patients will have better treatment outcomes.

A systematic review and meta-analysis reported on the impact of tuberculosis on virologically unsuppressed PLWH in Ethiopia. The results indicated a higher prevalence for those with HIV-TB coinfection and were virally unsuppressed compared to those who were HIV positive and virally unsuppressed (63). In addition, the chances of virological failure among those with HIV-TB co-infection were significantly higher than among those with HIV only (58). Hence, it is important to strengthen TB prevention strategies, by early identification and management of new cases. It is also critical to ensure that VL monitoring, and adherence support are conducted in accordance with the guidelines (58).

Integrating TB and HIV services is crucial to address the challenges of dual infections effectively. Developing strong TB prevention strategies, such as early detection and effective management of new TB cases among PLWH, is essential for healthcare providers. By prioritizing targeted screening, prompt diagnosis, and timely initiation of TB treatment in HIV-positive individuals, the impact of the coinfection can be mitigated. Adhering to guidelines that recommend regular viral load monitoring for individuals with HIV-TB coinfection is also crucial for healthcare facilities. Following monitoring protocols allows for timely adjustments to treatment plans and minimizes the risk of virological failure. The study findings emphasize the need for closer integration between TB and HIV programs, particularly in areas with increased prevalence of viral load not suppressed and higher chances of virological failure among individuals with concurrent HIV-TB coinfection. Improved collaboration between health systems is necessary for better management of HIV-TB coinfection. The study's findings could significantly impact HIV-TB coinfection management guidelines. By focusing on early detection, integrated care, and adherence support, health education and training programs for healthcare providers can improve their

ability to address the unique needs of individuals with dual infections. Public health campaigns can also use these findings to raise awareness about the risks and management strategies associated with HIV-TB coinfection. Advocacy efforts can leverage the study's results to influence policy decisions, directing resources towards comprehensive support and integrated care models for individuals facing both HIV and TB. Future research should focus on improved TB screening, targeted interventions, and long-term outcomes for individuals with HIV-TB coinfection.

The results of this exploratory study on Dolutegravir (DTG) in Namibia have significant implications for clinical practice and public health strategies. The discovery that being female is a noteworthy risk factor for excessive weight gain with DTG underscores the need for gender-specific monitoring and interventions. This information will enable healthcare providers to develop patient management strategies that mitigate the risk of weight gain among females receiving DTG-based antiretroviral therapy (ART). Although weight gain is generally associated with improved health, it is crucial to closely monitor patients to prevent potential complications, such as obesity. The challenges in resistance testing, especially in resource-limited settings, highlight the need for alternative strategies to accurately assess the causes of treatment failure. Health systems must prioritize timely viral load monitoring, as indicated by the suboptimal rate observed in the study, to enable prompt clinical decision-making and reduce the risk of developing resistance. Furthermore, the study findings show that tuberculosis is a predictor of treatment failure, emphasizing the interconnectedness of HIV and TB management and the importance of comprehensive care and timely initiation of antiretroviral therapy for co-infected individuals. The results of this study can be used to inform the development or revision of clinical guidelines, patient counselling and education, public health interventions,

research prioritization, and policy development, ultimately optimizing patient outcomes and the effectiveness of DTG-based ART in Namibia.

6 CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS OF THE STUDY

6.1 Conclusions from the study

The aim of the study was to examine the outcomes of dolutegravir-based first-line treatments at Katutura Intermediate Hospital in Namibia.

6.2.1 Objective 1: To estimate the prevalence adverse effects associated with DTG, in patients receiving DTG containing first line ART.

The only reported adverse drug reaction was weight gain. Our analysis revealed that the mean weight gain was 4 kg after 18 months of ART use, with a prevalence of 20.2%. Weight gain in HIV patients taking DTG-based ART may be a return to good health, but excessive increases in weight gain can lead to obesity and associated medical complications. The mechanisms by which certain ART agents contribute to weight gain are unknown. Some patients had profoundly high increases in weight and there is need to look out for these observations to devise strategies to prevent obesity related illnesses.

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6.2.2 Objective 2: To identify the potential predictors of adverse effects associated with DTG containing first line regimen.

Being female was found to be statistically significant with weight gain. We could not conclude that the weight gain observed was due to DTG based ART regimen or not. There may be confounding factors which could have contributed to weight gain. Weight gain may increase the risk of obesity related diseases such as cardiovascular disease, diabetes, chronic kidney disease, non-alcoholic steatohepatitis, and cancer. It may be important to implement lifestyle changes such as changes in diet and nutrition

or exercise for weight management. Therefore, future studies are needed for appropriate strategies to be devised.

6.2.3 Objective 3: To estimate the prevalence of treatment failure in patients receiving DTG containing first line ART (viral load >1000 copies per/ml)

Being female was found to be statistically significant with weight gain. We could not conclude that the weight gain observed was due to DTG based ART regimen or not. There may be confounding factors which could have contributed to weight gain. Weight gain may increase the risk of obesity related diseases such as cardiovascular disease, diabetes, chronic kidney disease, non-alcoholic steatohepatitis, and cancer. It may be important to implement lifestyle changes such as changes in diet and nutrition or exercise for weight management. Therefore, future studies are needed for appropriate strategies to be devised.

6.2.4 Objective 4: To identify predicators of treatment failure in patients receiving DTG containing first line ART.

Based on our findings TB was associated with treatment failure. The presence of TB may be an indication of treatment failure, suggesting that the DTG regimen may have failed due to poor adherence, drug resistance or drug interactions with rifampicin. However, we cannot confirm this as we have limited information on the patients' treatment history beyond 18 months. It is unclear whether they continued the DTG-based ART regimen and experienced improvement, or if they switched to a more effective treatment. A follow-up study would be beneficial to further investigate this potential evidence.

6.3 STUDY LIMITATIONS

The following passages provide an overview of the obstacles discovered within the healthcare system that impact data completeness and medication safety monitoring. The researchers found a significant issue with missing data in patient clinical records, which led to the exclusion of 60 individuals from the study due to insufficient clinical information. Additionally, a significant disparity in the timing of viral load tests was observed, which deviated from the guidelines outlined in the Namibian ART guidelines and hindered accurate monitoring of the virologic response to ART treatment. Furthermore, a lack of adverse drug reaction (ADR) recordings by nurses at Katutura Intermediate Hospital, despite the availability of ADR reporting forms, was observed. The under-reporting of ADRs, with weight gain being the only documented adverse event, emphasizes the need for improved pharmacovigilance efforts and ADE reporting practices. In 2019, the Therapeutic Information and Pharmacovigilance Centre (TIPC) affiliated with the Namibia Medicines Regulatory Council (NMRC) joined forces with the Directorate of Special Programs (DSP) to establish a National Technical Working Group (TWG). The creation of the TWG was prompted by various factors, including the introduction of innovative anti-TB medications and pioneering treatment plans for managing multi-drug resistant TB (MDR/XDR TB), as well as new HIV medications in Namibia, where the safety profile is not yet well-defined. However, the limitations of the study's scope, which was conducted solely at one facility, restrict the generalizability of the results to other health care facilities in Namibia. Moreover, the discrepancy between the calculated sample size and number of files accessed during the study period raises concerns about

the study's internal and external validity, highlighting the importance of adequately sized samples to ensure robust research outcomes. Addressing these challenges is essential for enhancing data quality, medication safety, and overall effectiveness of healthcare delivery in Namibia.

6.4 DELIMITATION OF THE STUDY

Only participants with complete patient records for the previous eighteen months were included in the study.

6.5 RECOMMENDATIONS

6.5.1 Introduction

There are several recommendations arising from this study. These recommendations are for the Ministry of Health and Social Services to improve on ADE reporting among healthcare providers and to conduct Viral load tests at the times recommended by the Namibian ART guidelines.

6.5.2 Ministry of Health and Social Services to improve on ADE reporting among healthcare care providers.

At the Katutura Intermediate Hospital healthcare workers do not report ADR although there is an ADR form included in the patient files to record these events. Some improvements in reporting can be made by:

Training healthcare workers on pharmacovigilance has been shown to enhance adverse drug reaction (ADR) reporting, as evidenced by research indicating that health professionals who have undergone such training are more inclined to report ADRs (64) To further bolster ADR reporting, it is imperative to prioritize ADR awareness and education among healthcare workers involved in reporting. By providing comprehensive training and education on ADR identification, documentation, and reporting protocols, healthcare professionals can be better

equipped to recognize and report adverse reactions effectively. This cohesive approach ensures that healthcare workers are not only aware of the importance of ADR reporting but also possess the necessary knowledge and skills to contribute effectively to pharmacovigilance efforts.

6.5.3 Viral load tests should be conducted at the times recommended by the Namibian ART guidelines.

Diagnosis and viral load monitoring is key to early and accurate disease detection ensuring efficiency.

Enhancing laboratory testing and training for healthcare workers and laboratory personnel necessitates increased budget allocation for these purposes. The additional funding enables the allocation of necessary resources toward expanding laboratory infrastructure, acquiring equipment and supplies, and establishing comprehensive training programs. Furthermore, the Ministry of Health and Social Services (MOHSS) must ensure the continuation of these efforts by consistently training healthcare workers and laboratory personnel in the delivery of new tests and task shifting. Providing ongoing training and support enables healthcare professionals to stay current with advancements in testing methodologies and effectively adapt to evolving healthcare needs. In situations where it may not be practical to fully introduce routine viral load (VL) testing immediately, a phased implementation approach can be adopted as a practical strategy. This approach allows for the gradual establishment of logistical and technical laboratory capacity, ensuring that the necessary infrastructure and expertise are in place before widespread scale-up. By initiating phased implementation, healthcare systems can effectively manage resources, address operational challenges, and pave the way for successful and sustainable expansion of VL testing services.

6.5.3 Recommendations for Future Research

The following are recommendations for future research:

It is essential to conduct additional research into the relationship between antiretroviral agents and weight gain in Namibia's healthcare landscape, as this could advance research in the field. By building upon existing studies, delving into the intricate interactions between antiretroviral therapies and weight fluctuations could yield valuable insights into optimizing treatment regimens and mitigating associated health risks. Furthermore, more research is needed on adverse drug reactions (ADRs) specifically related to dolutegravir (DTG)-containing antiretroviral therapy (ART). Examining the ADR profiles associated with DTG could assist healthcare providers in better understanding and managing treatment-related complications, thereby enhancing patient safety and treatment efficacy. Additionally, it is important to conduct robust studies with larger sample sizes across multiple centres to investigate the treatment outcomes associated with DTG. Such efforts could yield comprehensive data on treatment efficacy, tolerability, and long-term outcomes, informing evidence-based clinical practice guidelines. Lastly, further research is needed on the feasibility and efficacy of twice-daily dosing of rifampicin (RIF) in patients co-infected with HIV and tuberculosis (TB). By investigating the potential impact of dosing frequency on treatment outcomes, healthcare providers can tailor therapeutic approaches to optimize patient care and achieve favourable treatment outcomes in this vulnerable population. Through concerted research efforts, Namibia's healthcare system can enhance its capacity for evidence-based decision-making and improve patient outcomes across various therapeutic domains.

6.6 SUMMARY

Chapter 6 presented the conclusions of this study, limitations and described the recommendations for MOHSS. All the objectives of this study were met.

6.7 CONCLUSION OF THE STUDY

DTG-containing regimens effectively achieved viral suppression among treatment-naive HIV patients, with weight gain reported as the only adverse effect. The National Technical Working Group (TWG) was established to monitor anti-TB and ARV medications, yet healthcare workers still underreport adverse drug reactions. More research with a larger patient sample across multiple centres is needed to explore the long-term treatment outcomes of DTG.

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APPENDICES

ANNEX 1: Ethical Clearance Reference Number: SOP0002

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOP0002 Date: 24 October 2022

This Ethical Clearance Certificate is issued by the University of Namibia Ethics Committee (REC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the ethics committee.

Title of Project: **Evaluating the treatment outcomes in patients receiving dolutegravir containing first line anti-retroviral therapy in Namibia**

Principal researchers: **Naambo Taimi Amakatuwa**

Student number: **200631861**

Remarks: **The research meets requirement for Ethical Clearance**

Centre for Research Services

Take note of the following:

1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the ethics committee. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the ethics committee

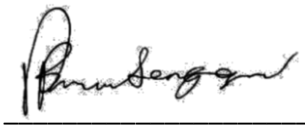
3. The Principal Researcher must report issues of ethical compliance to the ethics committee (through the Chairperson) at the end of the Project or as may be requested by the ethics committee
4. The ethics committee retains the right to:

i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected, ii) Request for an ethical compliance report at any point during the course of the research.

The ethics committee wishes you the best in your research.

_____

(Chairperson Decentralized Ethics Committee)



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Prof. Davis Mumbengegwi (Head, Multidisciplinary Research)

ANNEX 2: Letter of Approval from Ministry of Health and Social Services (MOHSS)

REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

Ministerial Building
Harvey Street
Private Bag 13198, Windhoek

OFFICE OF THE EXECUTIVE DIRECTOR

Tel: No: 061 -203 2507
Fax No: 061-222 558
Andreas.Shipanga@mhss.gov.na

Ref: 22/4/2/3
Enquiries: Ms. C. Narib

Date: 24 November 2022

Ms. Naambo T. Amakutuwa
PO Box 2863
Windhoek
Namibia

Dear Ms. Amakutuwa

Re: ***Evaluating the treatment outcomes in patients receiving dolutegravir containing first line anti-retro viral therapy in Namibia.***

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
   - 3.1 The data to be collected must only be used for academic purpose;
   - 3.2 No other data should be collected other than the data stated in the proposal;
   - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
   - 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
   - 3.5 Preliminary findings to be submitted upon completion of the study;
   - 3.6 Final report to be submitted upon completion of the study;
   - 3.7 Separate permission should be sought from the Ministry for the publication of the findings.
4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

All official correspondence must be addressed to the Executive Director.

My NAMIBIA

ANNEX 3: Permission to conduct research at the Intermediate Hospital Katutura

Republic of Namibia

Ministry of Health and Social Services

Private Bag 13215
WINDHOEK
Namibia

Intermediate Hospital Katutura
Independence Avenue
WINDHOEK

Telephone (061) 203 4004/5
Telefax (061) 222706

Enquiries: Sr. I. Thele

Date 30 November 2022

OFFICE OF THE MEDICAL SUPERINTENDENT

MS. NAAMBO TAIMI AMAKUTUWA
UNIVERSITY OF NAMIBIA (UNAM)

Ms. Amakutuwa

RE: **EVALUATING THE TREATMENT OUTCOMES IN PATIENTS RECEIVING DOLUTEGRAVIR CONTAINING FIRST LINE ANTI-RETRO VIRAL THERAPY IN NAMIBIA**

The above mentioned subject refers:

This office hereby grants you permission to do a research on the treatment outcomes in patients receiving dolutegravir containing first line anti-retro viral therapy at Intermediate Hospital Katutura, Windhoek, Khomas Region, Namibia.

Please provide this office with a copy of your findings.

Thank you

Yours in Health,

30/11/2022

DR. F.M. SHIWEDA
CHIEF MEDICAL OFFICER

MINISTRY OF HEALTH AND SOCIAL SERVICES
P/Bag 13215, Windhoek Namibia
2022 -11- 30
INTERMEDIATE HOSPITAL KATUTURA

ANNEX 4: Data Abstraction Tool

TITLE: Evaluating the treatment outcomes in Dolutegravir containing first line anti-retroviral therapy (ART) in Namibia

Part A: Socio-demographic information of the patient		
101) patient no:	Initials of data collector: _____ Date: _____	
102) Sex of the patient 1. □ Male 2. □ Female	103) Age (years): _____ 104) ethnicity	105)date when treatment was initiated:
106) Residence 1. □ Windhoek 2. □ Windhoek suburbs 3. □ Other regions_____	107) Employment status 1. □ Formal employment 2. □ Informal employment 3. □ Not employed	108) Marital status 1. □ Married 2. □ Not married 3. □ Divorced/widowed
109) Smokes 1. □ Yes 2. □ No	110) Alcohol use 1. □ Yes 2. □ No	
Part B: adverse drug reactions		
112) weight gain 1. □ Yes 2. □ No	113) Neuropsychiatric changes 1. □ Yes 2. □ No	116) Lipoatrophy and lipodystrophy
114) Skin rash with or without hypersensitivity reaction 1. □ Yes □ No	115) Hepatotoxicity; Hepatitis 1. □ Yes 2. □ No	117) Dyslipidemia
118**) Co-morbidities:** 1. □ hepatitis B virus 2. □ Hypertension	2. □ Diabetes Mellitus 3. □ Cancer	4. □ COPD 5. □ Obesity 6. deperession 7. □ Other:_____
Part C: opportunistic Infections		
119) 1. □ pneumocystis pneumonia 2. □ toxoplasmic encephalitis	3. □ malaria episodes 4. □ bacterial pneumonia 5.□ Cryptococcal Meningitis 6.□ karposi Sarcoma	
Part D: Baseline Laboratory tests		
123) CD4 count	124 level of adherence □ good □ fair □ Poor ≥ 95% □ Yes □ No	125) VL (copies/ml) **6 months** □ Yes □ No <40 □ 40-999 □ >1000 □ **12months** □ Yes □ No <40 □ 40-999 □ >1000 □ **18months** □ Yes □ No <40 □ 40-999 □ >1000 □
127) Creatinine Clearance □ months 6 □ month 12 □ month 18 □ month 24		128) haemoglobin _____
129) Liver function test □ Yes □ No	130) Renal function test □ Yes □ No	
Part E: Treatment outcomes		
Treatment successful 1. □ Yes 2. □ No	Treatment failure 1. □ Ye 2. □ No	Switch to second line 1. □ Ye 2. □ No

ANNEX 5: List of Random Numbers

195	51	120	125	352
300	176	2	245	204
49	24	340	123	126
212	101	171	114	324
341	306	235	25	200
213	210	340	168	307
360	175	351	296	
77	254	9	222	
126	45	106	280	
162	18	202	134	
186	107	224	240	
12	335	29	287	
71	89	127	262	
233	239	117	111	
260	110	34	64	
279	109	140	341	
242	347	34	73	
34	44	340	143	
254	229	205	213	
292	304	255	20	
303	240	159	99	
113	233	139	251	
360	39	45	161	
48	66	150	299	
97	299	82	30	
266	145	188	64	
210	235	78	249	
296	43	6	202	
11	28	370	283	
246	360	237	303	
286	271	237	18	
376	31	222	25	
174	255	72	195	
323	101	8	47	
371	178	70	101	
275	99	198	30	
376	91	323	69	
133	3	251	175	
363	220	333	355	
209	26	248	26	
336	276	181	293	
273	331	239	187	
0	85	49	275	
354	325	74	107	
187	291	281	194	
144	135	328	297	
164	106	11	365	
75	58	58	43	
202	201	22	153	
338	117	241	280	
129	193	195	365	
10	247	50	120	
129	110	83	361	
322	208	181	190	
327	263	282	211	
92	322	33	54	