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DOLUTEGRAVIR REPORTED ADVERSE DRUG REACTIONS: A SYSTEMATIC REVIEW

Lesley Wadesango

A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Pharmacy"

Johannesburg,

23 June 2022

Supervisors: Neelaveni Padayachee, Ebenezer Wiafe, Kofi Boamah Mensah, Varsha Bangalee

DECLARATION

I declare that the thesis, *Dolutegravir Reported Adverse Drug Reactions: A Systematic Review* is my work, and has not been submitted for any degree or examination in any other university, and that all the sources used or quoted have been indicated and acknowledged by complete references.

Lesley Wadesango

Signature 

ABSTRACT

The first-line regimen for the management of Human Immunodeficiency Virus (HIV) has evolved over the years and until recently was Tenofovir (TDF)-Emtricitabine (FTC) and Efavirenz (EFV). However, the use of EFV has now been limited due to adverse neurosensory effects and a low genetic barrier to resistance. This EFV-based regimen has been replaced with a Dolutegravir (DTG)-based regimen due to its high genetic barrier to resistance. Studies have reported a higher risk of Immune Reconstitution Inflammatory Syndrome (IRIS), weight gain, insomnia, and neural tube defects amongst people who received DTG. This review aimed to assess the adverse drug reaction (ADR) profile of Dolutegravir by identifying and classifying Dolutegravir-associated adverse drug reactions.

A search of the published literature for studies reporting ADRs to DTG was conducted using specified terms: ‘‘Dolutegravir’’, ‘‘Antiretroviral’’, “Highly active antiretroviral”, ‘‘combination’’, ‘‘regimen’’, ‘‘Human Immunodeficiency Virus’’, ‘‘Adverse effects’’, ‘‘Acquired Immunodeficiency Syndrome’’, ‘‘Adverse drug reactions’’, “pharmacovigilance” and ‘‘Adolescent’’. A review of all titles and abstracts to determine eligibility based on set criteria was conducted. An evaluation of the full texts of the articles was done and studies were assessed for their final eligibility for data extraction. After the selection of the final study sample, a data extraction form was used to extract data. Data was classified, categorized and summarized into tables. A narrative synthesis was done to describe and discuss the outcomes.

Nausea and diarrhea were the most reported gastrointestinal (GI) ADRs. Headache, dizziness and fatigue were reported in most studies reporting on central nervous system ADRs. Insomnia was the most commonly reported neuropsychiatric ADR while rash featured highest amongst the dermatological ADRs. Of all the other ADRs recorded of particular interest is weight gain, high Alanine Transaminase (ALT) and Immune Reconstitution Inflammatory Syndrome (IRIS). The ADRs reported are similar to the reactions described in most of the package inserts.

This study has demonstrated that the prevalence of ADRs can affect treatment continuity and thus cause treatment resistance. These findings can be employed by physicians to identify ADRs as early as possible to target and support earlier interventions for patients to be able to continue their treatment even after experiencing ADRs.

DEDICATION

I dedicate this work to God Almighty who has made it possible for me to complete this research.

ACKNOWLEDGEMENTS

I would like to thank My God and Father for being with me every step of the way. I would also like to thank my supervisor Dr Neelaveni Padayachee for her support, advise, patience, encouragement and commitment. I would also like to thank Dr Ebenezer Wiafe for the excellent suggestions, valuable contributions and brilliant discussions during the research and writing process. I would like to thank Dr Kofi Mensah for his contributions during the research.

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TABLE OF CONTENTS

DECLARATION ii
ABSTRACT iii
DEDICATION iv
ACKNOWLEDGEMENTS v
LIST OF TABLES ix
LIST OF FIGURES x
LIST OF APPENDIXES xi
ABBREVIATIONS xii
CHAPTER 1 1
INTRODUCTION 1
1.1 Background information 1
1.2 Justification of the study 3
1.3 Aim of the study 3
1.4 Objectives 3
1.5 Research Question 3
1.6 Thesis overview 4
CHAPTER 2 5
LITERATURE REVIEW 5
2.1.1 Introduction 5
2.1.2 Pharmacovigilance 5
2.2.1 HIV and Epidemiology 7
2.2.2 Pathophysiology and Pathogenesis of HIV and AIDS 8
2.2.3 Signs, Symptoms of HIV 10
2.2.4 Transmission and Risk factors for HIV 11
2.2.5 Diagnosis of HIV 12
2.3 Management of HIV 16
2.3.1 Treatment of HIV 16
2.3.1.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitor drug class. 18
2.3.1.2 Integrase Strand Transfer Inhibitor drug class of antiretroviral drugs 19
2.3.1.3 Non-Nucleoside Reverse Transcriptase Inhibitor drug Class of antiretroviral drugs 20
2.3.1.4 Protease Inhibitor drug Class Of antiretroviral drugs 20

2.3.2 Regimens in South Africa 21
2.3.2.1 Management of patients being initiated on first-line therapy (ART naïve patients) 21
2.3.2.2 Management of patients currently receiving first-line therapy 22
2.3.2.3 Management of patients starting or currently receiving second-line therapy 22
2.3.3 Opportunistic Infections treatment/Prophylaxis 22
2.4 Vaccination Efforts and New variant 22
2.5 Chapter summary 23
Dolutegravir Reported Adverse Drug Reactions: A Systematic Review Protocol 24
CHAPTER 3 38
METHODOLOGY 38
3.1 Introduction 38
3.2 Study Design 38
3.3 Search Strategy for Identification of Studies 38
3.3.1 Data sources 38
3.3.2 Electronic searches 38
3.3.3 Inclusion criteria 39
3.3.4 Exclusion criteria 39
3.4 Risk of Bias 40
3.5 Data Extraction and Management 43
3.6 Data Synthesis and Analysis 43
3.7 Ethics 43
3.8 Chapter Summary 44
CHAPTER 4 45
RESULTS 45
4.1 Introduction 45
4.2 Description of the literature search 45
4.3 Characteristics of included studies 47
4.4 Risk of bias and quality assessment 56
4.5 Adverse Drug Reactions Reported 61
4.5.1 Gastrointestinal ADRs 61
4.5.2 Central Nervous System ADRs 61
4.5.3 Neuropsychiatric ADRs 62

4.5.4 Dermatological ADRs 63
4.5.5 Other 64
4.5.6 Adverse Drug Reactions causing discontinuation 64
4.5.7 Adverse Drug Reactions in Pregnancy 64
4.6 Chapter Summary 65
CHAPTER 5 66
DISCUSSION 66
5.1 Introduction 66
5.2 Adverse Drug Reactions Reported 66
5.3 Implication for clinical practice 67
5.4 Implication for public health practice 68
5.5 Implication for research 68
5.6 Limitations 68
5.7 Conclusion 68
References 70
Appendix 1 82
Draft Search Strategy using PubMed/Medline 82
Appendix 2 83
Data extraction form 83
APPENDIX 3 85
Excluded Full Text articles with reasons for exclusion 85
Appendix 4 – Acceptance letter 86

LIST OF TABLES

2.1 Medical Reasons to Defer ART

2.2 The nucleoside/nucleotide reverse transcriptase Inhibitor drugs available in South Africa

2.3 The Integrase Strand Transfer Inhibitors available in South Africa

2.4 The Non-nucleoside Reverse Transcriptase Inhibitors available in South Africa

2.5 The Protease Inhibitors available in South Africa

3.1 Risk of bias assessment tool

4.1 Study Characteristics

4.2 Risk of bias assessment of included studies using the Holy 2012 tool

4.3 Studies reporting on Gastrointestinal ADRs

4.4 Studies reporting on Central Nervous System ADRs

4.5 Studies reporting on neuropsychiatric ADRs

4.6 Studies reporting on Dermatological ADRs

LIST OF FIGURES

1.1 Illustration of the layout of the dissertation

2.1 HIV life cycle

2.2 HIV cascade

2.3 HIV testing algorithm

4.1 PRISMA flow diagram of selection of publications

LIST OF APPENDIXES

Appendix 1 Search Strategy

Appendix 2 Data extraction form

Appendix 3 Excluded articles with reasons

Appendix 4 Acceptance letter

ABBREVIATIONS

HIV	Human Immunodeficiency Virus
TDF	Tenofovir
EFV	Efavirenz
DTG	Dolutegravir
FTC	Emtricitabine
IRIS	Immune Reconstitution Inflammatory Syndrome
ADR	Adverse Drug Reaction
GI	Gastrointestinal
ALT	Alanine Transaminase
WHO	World Health Organization
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AIDS	Acquired Immunodeficiency Syndrome
NTDS	Neural Tube Defects
HAART	Highly Active Antiretroviral Therapy
PV	Pharmacovigilance
SAHPRA	South African Health Products Regulatory Authority
NADEMC	National Adverse Drug Event Monitoring Centre
RNA	Ribonucleic acid
PMTCT	Prevention of Mother to child Transmission
NDOH	National Department of Health
HCT	HIV Counseling and Testing

PLHIV	People Living with HIV
ABC	Abacavir
AZT	Zidovudine
3TC	Lamivudine
RAL	Raltegravir
CNS	Central Nervous System
FDC	Fixed Dose Combination
ETR	Etravirine
NVP	Nevirapine
LPV	Lopinavir
ATV	Atazanavir
DRV	Darunavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
VL	Viral load
IPT	Isoniazid Preventative Therapy
OSF	Open Science Framework
CINALHL	The Cumulative Index to Nursing and Allied Health Literature
LDL	Low-density lipoprotein
NR	Not reported

CHAPTER 1

INTRODUCTION

1.1 Background information

Human Immunodeficiency Virus (HIV) according to World Health Organization (WHO) is a viral infection that attacks and destroys the body's immune system, particularly the white blood cells named CD4 cells (World Health Organization, 2022). This virus is generally believed to have originated in Kinshasa, in the Democratic Republic of Congo around 1920 when it crossed from chimpanzees to humans. It is not known how many people were infected with HIV or developed Acquired Immune Deficiency Syndrome (AIDS) before then. HIV was unfamiliar and there were no noticeable signs or symptoms after transmission (Avert, 2022).

While erratic cases of AIDS were recognized earlier than 1970, the existing data suggests that this epidemic started in the mid to late 1970s. By 1980, HIV may have already spread to five continents (North America, South America, Europe, Africa and Australia). At least 100,000 people could have already been infected in that period (Avert, 2022).

HIV remains a world-wide public health issue (Global HIV and AIDS statistics, 2020) and although HIV treatment and access has been successfully implemented by the scientific community, WHO, governments, social organizations, and local society, its global incidence was at a staggering 38 million in 2019 (Pandey and Galvani, 2019). Globally in 2020, at least 1.5 million people were newly infected with HIV. In 2020, 84% of the people living with HIV knew their status, 73% were on treatment and 66% were virally suppressed (UNAIDS, 2021). Current data suggests that 30% of all the recent HIV infections in the southernmost region of the African continent comprising of 10 countries, have been reported to be in South Africa (HIV and AIDS in South Africa, 2020). Although, the number of new infections are reducing we still see concerning numbers in SA. The total amount of people with HIV in South Africa increased from 7.4 million in 2016 to 7.7million in 2018 (HIV and AIDS in South Africa, 2020).

To curb the morbidity and mortality of HIV, treatment has shown to be the beacon of light in the HIV crisis. The quick advances in the discovery of drugs and antiretroviral therapy development

is exceptional. Consequently the death rate from HIV has reduced significantly. HIV has thus changed from a nearly universally fatal illness to a manageable chronic illness (Delaney, 2006)

Even though there has been impressing discoveries of drugs for the treatment of HIV, response to Highly Active Antiretroviral Therapy (*HAART*) is often affected by the incidence of toxicity. Antiretroviral treatment (ART) is characterized by differing rates of adverse events (Tozzi, 2010). Adverse Drug Reactions have been attributed to most cases of poor adherence to ART (Blake et al., 2000).

Until recently, the regimen recommended for the first-line combination treatment of HIV was Tenofovir (TDF)-Emtricitabine (FTC) and Efavirenz (EFV) also known as (TEE) (National Department of Health, 2019). However, the consistent use of EFV due to its adverse neurosensory effects and low genetic barrier from the drug-resistance mutations has become a limitation for its use (The NAMSAL ANRS 12313 Study Group, 2019). According to the latest antiretroviral therapy (ART) clinical guidelines, the EFV-based regimen has been replaced by the DTG-based regimen due to its favourable profile of maintained viral suppression and immunological recovery (Walmsley et al., 2013).

The regimen now recommended for primary treatment of HIV is now Tenofovir (TDF)-lamivudine (3TC)-dolutegravir (DTG) also known as TLD (National Department of Health, 2019). DTG is cheap, has an increased genetic barrier to resistance, and is accessible as a fixed-combination pill, and hence was introduced as the preferred first-line treatment for HIV by WHO in 2018 (WHO, 2018).

However, the administration of DTG at conception could result in neural-tube defects in infants and must therefore be used with caution in pregnant women. The drug is also known to increase the risk of insomnia and obesity (WHO, 2019). There is more evidence that the risks of weight gain, insomnia, Immune Reconstitution Inflammatory Syndrome (IRIS), and neural tube defects amongst patients receiving DTG are increased (Batista et al., 2019). These adverse drug reactions (ADRs) are common and easily identifiable. These adverse effects have thus resulted in the WHO making its use conditional and recommending that DTG patients be closely monitored. A global investigation into DTG ADRs is important in understanding how South Africa can manage a relatively new drug on the HIV regimen.

1.2 Justification of the study

While there has been research done on DTG , most of the primary studies and reviews have focused on its overall safety (including efficacy and pharmacology) in comparison with other agents. A cross sectional analysis done in Brazil reported that the prevalence of self-reported ADRs to first-line antiretroviral regimens was high and patients using DTG/TDF/3TC had a smaller number of ADRs as compared to other regimens (Llibre et al., 2015).There are a few reviews on its safety in pregnant women. One of the reviews concluded that continued pharmacovigilance is essential, but it is reassuring that no clear safety signals have been detected, to date, for pregnant women treated with DTG in terms of birth outcomes or congenital anomalies (Hill et al., 2018). Although there are studies summarizing overall DTG use in HIV we could not find any systematic review on the ADRs of DTG. This means there is a gap in literature. A review of existing studies, focusing mainly on ADRs will aid in further establishing the safety profile of this drug.

This study will assist in creating awareness of DTG known, unknown and rare adverse drug reactions, adverse drug reactions associated with use of other drugs and the effects of demographic factors on adverse drug reactions. This study will provide insight into better prescribing practices in HIV patients that will inevitably improve healthcare costs and improve patient's quality of life.

1.3 Aim of the study

This review aimed to assess the adverse drug reactions (ADRs) of DTG globally.

1.4 Objectives

- To identify and classify DTG associated adverse drug reactions.
- To classify ADRs according to the system organ affected.
- To establish the safety and efficacy of DTG in the treatment of HIV in pregnant women.

1.5 Research Question

This systematic review will answer the following question:

What are the reported adverse drug reactions to DTG?

1.6 Thesis overview

This dissertation comprises of five chapters. Chapter 1 consists of background and justification for the study. It also includes aims, objectives and the research question. Chapter 2 reviews literature pertaining to HIV , pharmacovigilance and DTG. Chapter 3 outlines the method used in this study. Chapter 4 presents the results and a discussion by means of a manuscript. Finally, Chapter 5 is the conclusion chapter and consists of the limitations of the study, recommendations for possible future studies and a conclusion.

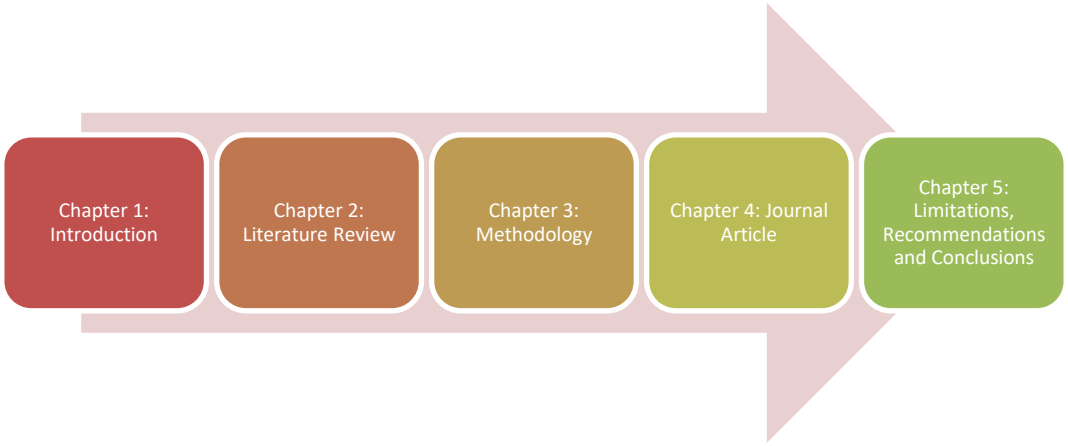


Figure 1.1 Illustration of the layout of the dissertation

CHAPTER 2

LITERATURE REVIEW

2.1.1 Introduction

The literature in this chapter covers a discussion of pharmacovigilance and reporting of ADRs. It also includes the overview of HIV, how it's transmitted, risk factors, its diagnosis and the replication cycle. It further elaborates on HIV treatment regimens and the drugs that target the replication cycle.

2.1.2 Pharmacovigilance

Adverse drug reaction according to the World Health Organization is a response that is harmful and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function. An adverse drug reaction, in contrast to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the event: that is, assessed as being at least possibly related to treatment by the reporting or reviewing health care professional (World Health Organization, 2018). WHO describes pharmacovigilance as the science and activities relating to detecting, assessing, understanding and preventing adverse effects or any other drug-related problem (WHO, 2018).

The disaster caused by thalidomide in 1961 resulted in the initiation of first systematic international efforts to address drug safety issues. Many thousands of babies at that time were born with congenital abnormalities due to exposure in utero to an unsafe medicine promoted for use by pregnant mothers. The Sixteenth World Health Assembly (1963) adopted a resolution that confirmed the need for quick action in terms of rapid reporting and distribution of information on adverse drug reactions. This later led to the formation of the WHO Pilot Research Project for International Drug Monitoring in 1968. The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines (WHO, 2002). This is how pharmacovigilance started.

South Africa has been engaged in pharmacovigilance (PV) activities to evaluate the effect of adverse drug reactions on public safety and health for over 40 years (Mehta*et al.,* 2017). The

Medicines and Related Substances Control Act 101 was put into effect in South Africa in 1965 (Mehta*et al.,* 2017).

In order to prevent adverse effects in patients because of deficient health products, an Adverse Drug Reaction (ADR) monitoring system was established in South Africa in 1987. This system is coordinated by the Regulatory Pharmacovigilance unit of SAHPRA, which consists of the main office in Pretoria and a satellite office, National Adverse Event Drug Monitoring Centre (NADEMC), situated in Cape Town's Groote-Schuur Hospital and attached to University of Cape Town's Clinical Pharmacology Division. The regulatory pharmacovigilance unit work in collaboration with programmatic units based at NDoH head office in Pretoria. The programmatic units are: the Extended Programme for Immunisation (EPI) unit , the Department of Health Pharmacovigilance Centre for Public Health Programmes (DoH-PvPHP) (SAHPRA, 2022).

It is important to monitor ADRs because the frequency and severity of side-effects may be very different in the post-marketing phase when a medicine is used for longer periods of time in a mixed patient population with a range of co-morbidities and concomitant medication, and for off-label indications (Mehta*et al.,* 2017). Detection of rare side-effects requires large sample sizes, so medicines must be monitored for performance throughout their use (Mehta*et al.,* 2017).

All healthcare professionals, including doctors, dentists, pharmacists, nurses and other healthcare professionals are requested to report all suspected adverse reactions to medicines (including vaccines and complementary medicines) , particularly serious ADRs and those related to new medicines. Consumers should be encouraged to report all suspected adverse drug reactions to their healthcare provider. It is vital to report an adverse drug reaction to the SAHPRA's Pharmacovigilance unit (SAHPRA, 2022).

In passive surveillance, health-care professionals or patients send spontaneous reports describing an adverse drug reaction after one or more medicinal products are administered to the marketing authorization holder or regulatory authority. Sometimes such first case reports are published, which may stimulate subsequent reporting (WHO, 2018).

Active surveillance involves enhanced or targeted monitoring for certain events or drugs and seeks to ascertain completely the number of adverse drug reactions through a pre-planned process. Active surveillance is also commonly known as toxicity monitoring (such as the WHO ARV programme) or safety monitoring (WHO, 2018).

ADRs have considerable economic as well as clinical costs as they often lead to hospital admission, prolongation of hospital stay and emergency department visits. In addition ADRs may trigger prescription cascades when new medications are prescribed for conditions that are a consequence of another medication, which is often an unrecognized ADR (Sultana *et al*., 2013)

2.2.1 HIV and Epidemiology

HIV (Human Immunodeficiency Virus) is a virus that attacks the body's immune system (HIV/AIDS information booklet, 2005). HIV infection results from 1 of 2 related retroviruses (HIV-1 and HIV-2) that destroy CD4+ lymphocytes and impair cell-mediated immunity, increasing risk of certain infections and cancers (Edward R, 2021). Even though human HIV-1 infection is the cause for most of the global AIDS pandemic, HIV-2 is a significant cause of disease in a number of regions of the world (Omobolaji et al., 2019). HIV-2 was first discovered in West Africa but has spread to other parts of Africa, Europe, India, and the United States (Omobolaji et al., 2019).

HIV was first discovered in the early 1980's (HIV/AIDS information booklet, 2005). Ever since, there has been a surge in the number of HIV infected people (HIV/AIDS information booklet, 2005). In 2019 its global incidence was at 38 million (Pandey and Galvani, 2019). The Joint United Nations Programme on HIV/AIDS (UNAIDS) frequently reports on the estimated burden of HIV infection in each country.Globally in 2020, at least 1.5 million people were newly infected with HIV (UNAIDS, 2021). In 2020, 84% of the people living with HIV globally knew their status while 73% were on treatment and 66% were virally suppressed (UNAIDS, 2021).

East and Southern Africa remains the region most affected by HIV in the world. It is home to around 6.2% of the world's population but over half (54%) of the total number of people living with HIV in the world (20.6 million people) (Global HIV and AIDS statistics, 2021).

South Africa accounted for more than a quarter (240,000) of the region's new infections in 2018 (Global HIV and AIDS statistics, 2021). Recent data shows that 30% of all HIV infections in Southern Africa have been reported to be in South Africa (HIV and AIDS in South Africa, 2020). The total amount of people with HIV in South Africa has since increased from 7.4 million in 2016 to 7.7 million in 2018 (HIV and AIDS in South Africa, 2020).

Seven other countries accounted for more than 50% of new infections: Mozambique (150,000), Tanzania (72,000), Uganda (53,000), Zambia (48,000), Kenya (46,000), Malawi (38,000), and Zimbabwe (38,000) (Global HIV and AIDS statistics, 2021).

In low-income and middle-income countries, most of the people living with HIV infection are women (Deeks et al., 2015). Every week, around 5000 young women aged 15–24 years become infected with HIV. In sub-Saharan Africa, six in seven new HIV infections among adolescents aged 15–19 years are among girls. Young women aged 15–24 years are twice as likely to be living with HIV as men. In some regions, women who have experienced physical or sexual intimate partner violence are 1.5 times more likely to acquire HIV than women who have not experienced such violence. In sub-Saharan Africa, women and girls accounted for 63% of all new HIV infections in 2020 (UNAIDS, 2021).Violence against women, and lack of access to care and education are key factors that contribute to this epidemic (Deeks et al., 2015).

2.2.2 Pathophysiology and Pathogenesis of HIV and AIDS

HIV attaches to and enters host T cells, it then releases HIV RNA and enzymes into the host cell. HIV reverse transcriptase copies viral RNA as proviral DNA (Edward R, 2021). Proviral DNA enters the host cell's nucleus, and HIV integrase facilitates the proviral DNA's integration into the host's DNA (Edward R, 2021). The host cell then produces HIV RNA and HIV proteins. HIV proteins are assembled into HIV virions and budded from the cell surface. HIV protease cleaves viral proteins, converting the immature virion to a mature, infectious virus, see figure 2.1 (Edward R, 2021).

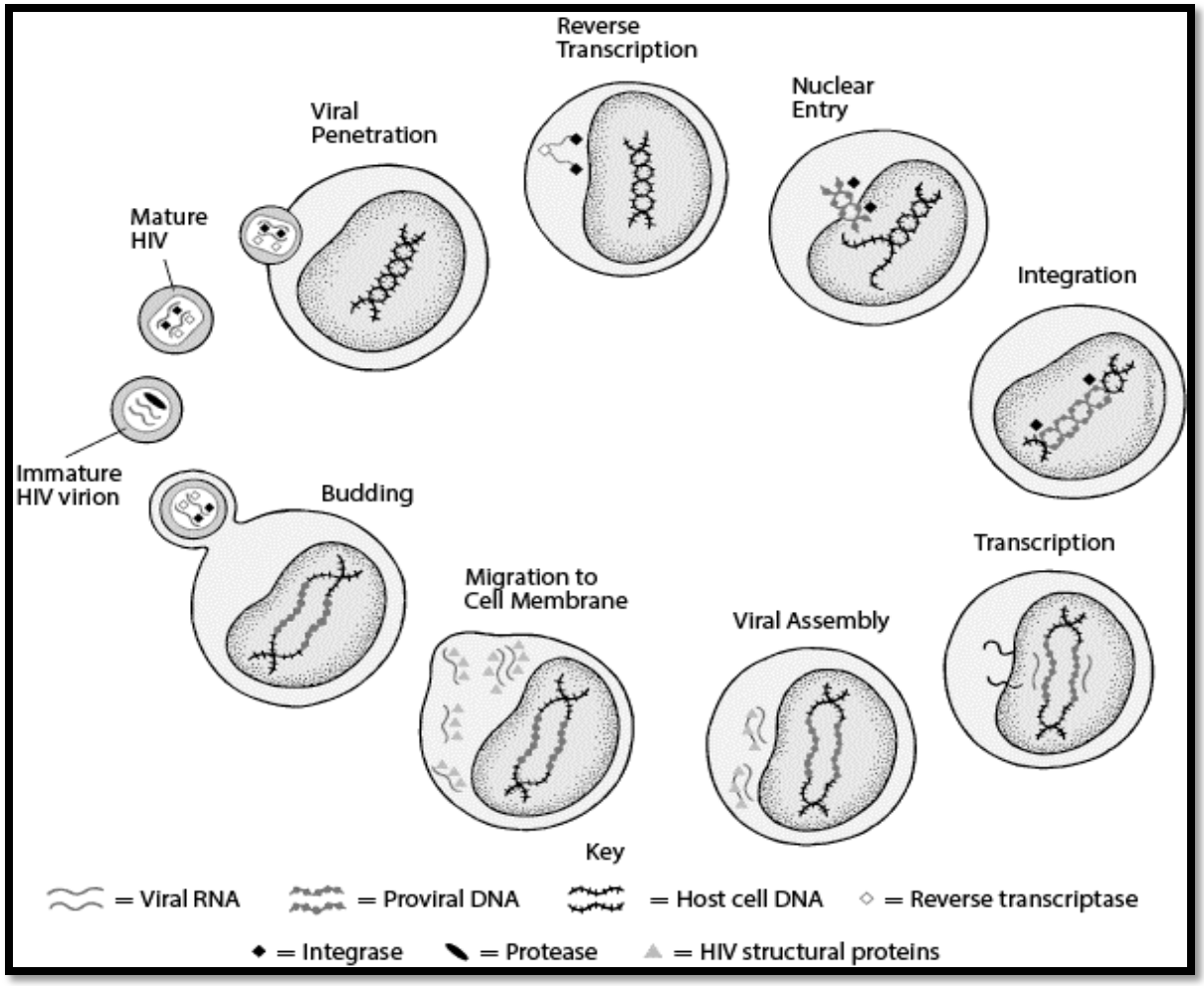


Figure 2.1 –HIV life cycle (Vijayan et al., 2017).

CD4+ T-cells are the central mediators of immune response in humans. HIV selectively infects CD4+ T-cells and destroys them. Upon infection with HIV, infection of CD4+ T-cells takes place and leads to either cell death or giant cell/syncytia formation, in which both infected and uninfected cells fuse, leading to spread of infection. Severe reduction of CD4+ T-cells occurs in the gut-associated lymphoid tissue (GALT), which is the major producer of CD4+ T-cells in the body. Absolute CD4+T-cell count and percentage have been shown to be associated with the disease progression (Vijayan et al., 2017)

Infected CD4+ cells have a half-life of about 2 days. This is much shorter than that of uninfected CD4+ cells. During the initial primary infection, HIV levels are highest (> 106 copies/mL), and the CD4 count drops rapidly. The normal CD4 count is about 750/mcL, and the immune system

is nominally affected if the count is > 350/mcL. Opportunistic diseases occur if the count drops below about 200/mcL (Edward R, 2021).

Plasma HIV virion levels (number of HIV RNA copies/mL) stabilize after about 6 months and averages 30,000 to 100,000/mL (4.2 to 5 log10/mL). The higher the viral load, the more quickly the CD4 count decreases to a level that seriously impairs immunity .This results in opportunistic infections and cancers that define Acquired Immune Deficiency Syndrome (AIDS). If the CD4 count drops below 200/mcL there is increased risk of Pneumocystis jirovecii pneumonia , toxoplasmic encephalitis, and cryptococcal meningitis. If it drops below 50/mcL there is increased risk of cytomegalovirus (CMV) and Mycobacterium avium complex (MAC) infections. Increase in plasma HIV RNA in untreated patients results in risk of progression to AIDS or death (Edward R, 2021).

2.2.3 Signs and Symptoms of HIV

As depicted in Fig 2.2, during the initial HIV infection, the transmitted virus first infects target cells in mucosal tissues and then spreads through the lymphoid system (eclipse phase). HIV RNA levels first become detectable after several days (acute phase) and then increase exponentially, reaching a peak a few weeks later, at which point the adaptive immune response results in partial control. HIV antibody responses are largely ineffective owing to rapid viral escape. The detection of virus in the blood (typically measured as viral RNA levels) is often associated with a short symptomatic phase marked by fever, generalized lymphadenopathy, a nonspecific rash, myalgias and/or malaise. More-severe complications — including meningitis — can occur, but many people are asymptomatic. During this period of primary or acute infection, the plasma levels of HIV RNA are typically at their peak (approximately 106 –107 copies per ml). The severity of symptoms is strongly correlated with peak viral load during this phase of the infection. Once the immune response develops the levels of virus decrease by about 100-fold to a steady-state level that is often referred to as the viral set point. This level can range from very few copies per ml of blood to approximately 106 copies per ml and tends to be higher in infants than adults (Deeks et al., 2015).

HIV-mediated destruction of CD4+ T cells leads to immunodeficiency and chronic inflammation (chronic phase) (Deeks et al., 2015). Higher levels of inflammation consequently lead to AIDS. It manifests as recurrent, severe, and occasionally life-threatening infections and/or opportunistic

infections. The signs and symptoms are those of the presenting illness, meaning that HIV infection should be suspected as an underlying illness when unusual infections present in apparently healthy individuals (Gilroy and Faragon, 2021).

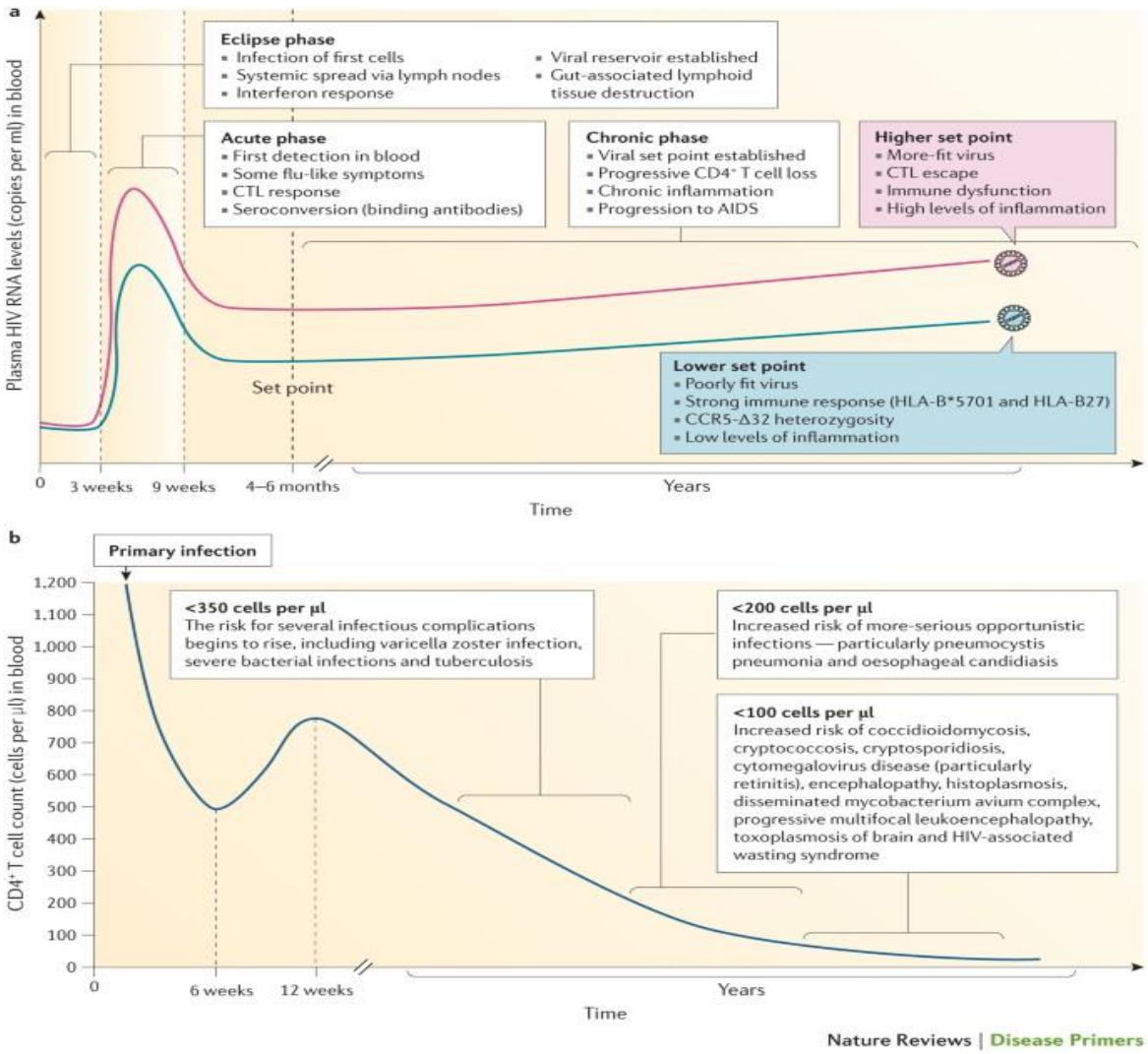


Figure 2.2- HIV Cascade (Vijayan et al., 2017)

2.2.4 Transmission and Risk factors for HIV

Transmission of HIV requires contact with body fluids. HIV is transmitted through blood, semen, vaginal secretions, breast milk, saliva, or exudates from wounds or skin and mucosal lesions

that contain free HIV virions or infected cells. Transmission is more likely with the high levels of the virus that are typical during primary infection, even when such infections are asymptomatic. Transmission by saliva or droplets produced by coughing or sneezing is highly unlikely (Edward R, 2021).

Risk factors include the following:

- Unprotected sexual intercourse, anal intercourse (Gilroy and Faragon, 2021)
- A large number of sexual partners (Gilroy and Faragon, 2021)
- Prior or current sexually transmitted diseases (STDs): Gonorrhea and chlamydia infections increase the HIV transmission risk 3-fold, syphilis raises the transmission risk 7-fold, and herpes genitalis raises the transmission risk up to 25-fold during an outbreak (Gilroy and Faragon, 2021)
- Sharing of blood contaminated needles –with drug users (Gilroy and Faragon, 2021)
- Receipt of blood products (Gilroy and Faragon, 2021)
- Mucosal contact with infected blood or needle-stick injuries (Gilroy and Faragon, 2021)
- Maternal HIV infection (for newborns, infants, and children): Steps taken to reduce the risk of transmission at birth include cesarean delivery and prenatal antiretroviral therapy in the mother and antiretroviral therapy in the newborn immediately after birth (Gilroy and Faragon, 2021)

In most countries HIV is spread through men who have sex with men, contact with infected blood and heterosexual intercourse (Edward R, 2021). In developed countries it is mainly spread through men who have sex with men (Edward R, 2021). Contact with infected blood is the common way it is spread in Africa, South America, and southern Asia (Edward R, 2021).

2.2.5 Diagnosis of HIV

Human immunodeficiency virus (HIV) infection should be considered in any patient with unusual or recurrent serious infections without another cause, especially in those with risk factors for HIV infection (Gilroy and Faragon, 2021).

There are many different circumstances where a patient may be tested for HIV, for example, for individuals and couples; pregnant mothers for PMTCT as part of clinical care and screening; in cases of sexual assault or domestic violence; for abandoned babies; in response to a court order; and as part of medical male circumcision (NDOH, 2015).

In all instances, HIV Counseling and Testing (HCT) must be ethical, confidential, based on human rights, conducted within a supportive environment, and be performed where there is relevant and adequate healthcare infrastructure. All forms of HCT should be voluntary and adhere to the five C's: consent, confidentiality, counseling, correct test results and connections to care, treatment and prevention services. People who are tested for HIV after counseling must give informed consent to be tested and be informed of their right to decline testing (NDOH, 2015).

HCT should be done according to the Department of Health testing algorithm (Figure 2.1). All patients tested for HIV should be recorded in the HCT register, regardless of where the HCT is done. Those who test positive for HIV should be further recorded in the pre-ART register to ensure tracking of linkage to care (NDOH, 2015).

For those who test HIV-positive, a second confirmatory HIV test is mandatory. All patients must receive post-test counseling, regardless of their HIV results. This includes risks for HIV transmission; safe sex and the use of condoms (even during pregnancy); contraception and fertility planning; HIV testing for sexual partners and children; repeat HIV testing for those who are HIV-negative; and PMTCT including safe infant feeding and infant prophylaxis (NDOH, 2015).

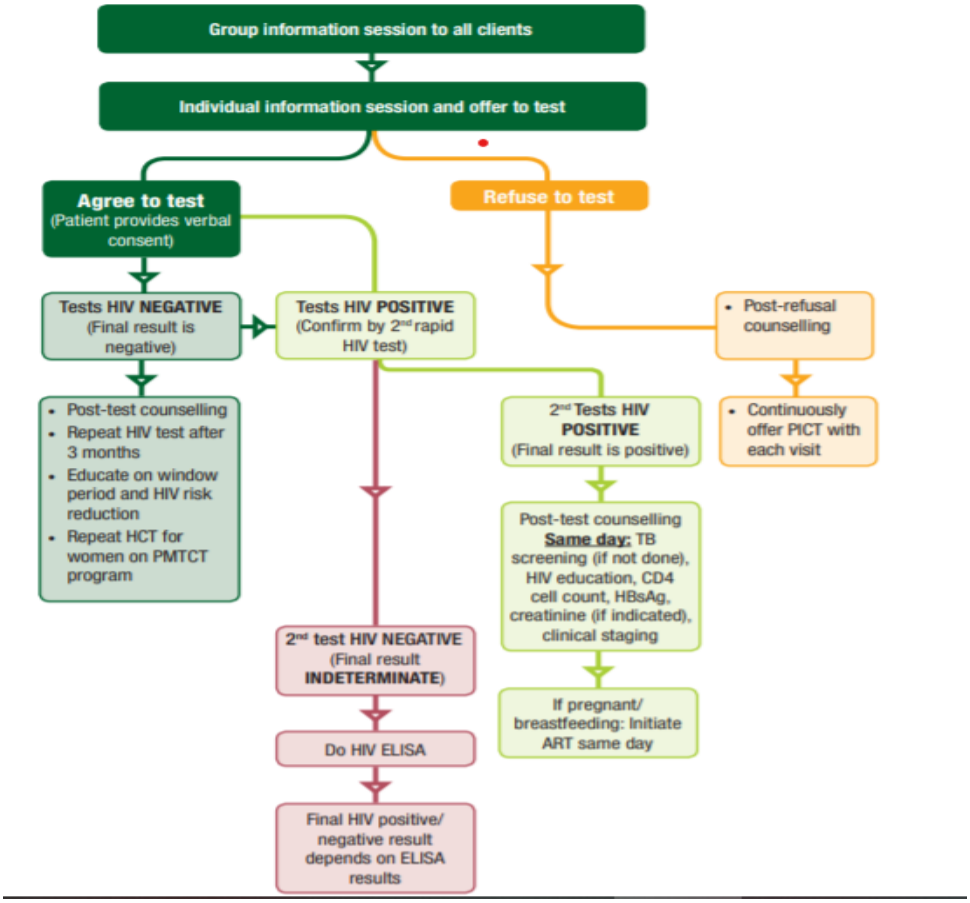


Figure 2.3- HIV testing algorithm (NDOH, 2015)

HIV Tests available include

- HIV antibody testing with or without HIV P24 antigen tests
- Nucleic acid amplification assays to determine HIV RNA level (viral load)

Detection of antibodies to HIV is sensitive and specific except during the first few weeks after infection (termed the "window period" of acute HIV infection). However, the HIV p24 antigen (a core protein of the virus) is already present in the blood during most of this time and can be detected by assays. Currently, a 4th-generation antigen/antibody combination immunoassay is recommended; it detects antibodies to both HIV-1 and HIV-2 as well as the p24 HIV antigen. The laboratory version is probably preferred over the point-of-care one for diagnosing early infection, but both can be done quickly (within 30 minutes). If the test result is positive, an assay to differentiate HIV-1 and HIV-2 and an HIV RNA assay are done (Cachay, 2021).

Earlier-generation enzyme-linked immunosorbent assay (ELISA) antibody assays are highly sensitive, but because they do not test for antigen, they are not positive as early as the 4th-generation combination test. Also, results are rarely false-positive. Positive ELISA results are therefore confirmed with a more specific test such as Western blot (Cachay, 2021).

Newer point-of-care tests using blood or saliva (eg, particle agglutination, immunoconcentration, immunochromatography) can be done quickly (in 15 minutes) and simply, allowing testing in a variety of settings and immediate reporting to patients. Positive results of these rapid tests should be confirmed by standard blood tests (eg, ELISA with or without Western blot) in developed countries and repetition with one or more other rapid tests in developing countries (Cachay, 2021).

If HIV infection is suspected despite negative antibody test results (eg, during the first few weeks after infection), the plasma HIV RNA level may be measured. The nucleic acid amplification assays used are highly sensitive and specific. HIV RNA assays require advanced technology, such as reverse transcription–polymerase chain reaction (RT-PCR), which is sensitive to extremely low HIV RNA levels. Measuring p24 HIV antigen by ELISA is less sensitive and less specific than directly detecting HIV RNA in blood (Cachay, 2021).

When HIV is diagnosed, the following should be determined:

- CD4 count
- Plasma HIV RNA level

Both are useful for determining prognosis and monitoring treatment (Cachay, 2021).

CD4 count

The CD4 count is calculated as the product of the following:

- White blood cell count (eg, 4000 cells/mcL)
- Percentage of white blood cells that are lymphocytes (eg, 30%)
- Percentage of lymphocytes that are CD4+ (eg, 20%)

Using the numbers above, the CD4 count (4000 x 0.3 x 0.2) is 240 cells/mcL, or about 1/3 of the normal CD4 count in adults, which is about 750 ± 250/mcL (Cachay, 2021).

HIV Viral Load

Plasma HIV RNA level (viral load) reflects HIV replication rates. The higher the set point (the relatively stable virus levels that occur after primary infection), the more quickly the CD4 count decreases and the greater the risk of opportunistic infection, even in patients without symptoms (Cachay, 2021)

2.3 Management of HIV

2.3.1 Treatment of HIV

In general, the goal of treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely. Highly active antiretroviral therapy (HAART) is the principal method for preventing immune deterioration. In addition, prophylaxis for specific opportunistic infections is indicated in particular cases (Gilroy and Faragon, 2021).

Successful long-term HAART results in a gradual recovery of CD4 T-cell numbers and an improvement of immune responses (Gilroy and Faragon, 2021). All people living with HIV (PLHIV) are eligible to start ART regardless of age, CD4 cell count and clinical stage. For all clients without contra-indications, ART should be initiated within 7 days, and on the same day if possible. Pregnant women, infants and children under five years, and clients with advanced HIV disease should be prioritised for rapid initiation. Certain clients (including pregnant women) may be able to initiate ART on the same day as their HIV diagnosis, provided that they are clinically well, and are motivated to start ART. While rapid, and same-day where possible, initiation is encouraged, all clients, particularly those with advanced HIV disease, should be carefully assessed for opportunistic infections that may necessitate ART deferral (NDOH, 2019).

Table 2.1 Medical Reasons to Defer ART (NDOH, 2019

Indication	Action

Tuberculosis (TB) symptoms cough night sweats fever weight loss	Investigate for TB before initiating ART. If TB is excluded, proceed with ART initiation and TB preventive therapy (after excluding contra-indications to TPT). If TB is diagnosed, initiate TB treatment and defer ART. The timing of ART initiation will be determined by the site of TB infection and the client's CD4 cell count
Diagnosis of drug-sensitive (DS) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	Defer ART initiation as follows: • If CD4 < 50 cells/μL – initiate ART within 2 weeks of starting TB treatment, when the client's symptoms are improving, and TB treatment is tolerated • If CD4 ≥ 50 cells/μL – initiate ART 8 weeks after starting TB treatment
Diagnosis of drug-resistant (DR) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	Initiate ART after 2 weeks of TB treatment, when the client's symptoms are improving, and TB treatment is tolerated
Diagnosis of DS-TB or DR-TB at a neurological site (e.g. TB meningitis or tuberculoma)	Defer ART until 4-8 weeks after start of TB treatment
Signs and symptoms of meningitis	Before initiating ART , test for meningitis
Cryptococcal antigen (CrAg) positive without symptoms or signs of meningitis	Delay treatment until the first 2 weeks of fluconazole prophylaxis is finished.
Confirmed cryptococcal meningitis	Delay ART until 4-6 weeks of treatment has been completed
Other infections Pneumocystis jirovecii pneumonia (PJP) / bacterial pneumonia	Defer ART for 1-2 weeks after commencing treatment for the infection

Clinical symptoms or signs of liver disease	Confirm liver injury using ALT and total bilirubin levels. ALT elevations > 120 IU/L with symptoms of hepatitis, and/or total serum bilirubin concentrations > 40 µmol/L are significant. Investigate and manage possible causes including hepatitis B, druginduced liver injury (DILI), or alcohol abuse
Note: Clients who are already on ART should NOT have their treatment interrupted upon diagnosis of the above conditions	

2.3.1.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitor drug class.

Nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) block the enzyme reverse transcriptase. HIV uses that enzyme to convert its RNA into DNA. Blocking reverse transcriptase prevents HIV from replication.

They work by acting as nucleotide base analogues. Following incorporation into the DNA chain by HIV's reverse transcriptase enzyme, they block further chain elongation (Nel et al., 2020).

Table 2.2: The nucleoside/nucleotide reverse transcriptase inhibitors available in South Africa.

Drug	Dose	Adverse drug reactions
Tenofovir disoproxil fumarate (TDF) NtRTI	300 mg per day	Renal failure Tubular wasting syndrome Decreased bone mineral density Nausea
Lamivudine (3TC) NRTI	300 mg per day	Anaemia
Emtricitabine (FTC) NRTI	200 mg per day	Anaemia (pure red cell aplasia) (rare), palmar hyperpigmentation

Abacavir (ABC) NRTI	600 mg per day	Hypersensitivity
Zidovudine (AZT) NRTI	300 mg 12-hourly	Anaemia GI upset Headache

TDF with either 3TC or FTC is the recommended NRTI drugs for first-line therapy. Patients with low creatinine clearance rate (CrCl) below 50 mL/min should be started on Abacavir (ABC) instead of TDF for first-line therapy. TDF sometimes causes renal failure. Creatinine should be checked at regular intervals. AZT may cause anaemia and neutropenia thus regular checking of haemoglobin (Hb) is essential for the first 6 months (Nel et al., 2020).

2.3.1.2 Integrase Strand Transfer Inhibitor drug class of antiretroviral drugs

Integrase strand transfer inhibitors (InSTIs) – often simply termed 'integrase inhibitors' – work by preventing the transfer of proviral DNA strands into the host chromosomal DNA. Currently, two InSTIs are available in southern Africa: Dolutegravir (DTG) and Raltegravir (RAL) (Nel et al., 2020).

Table 2.3– The Integrase strand transfer inhibitors available in South Africa

Drug	Dose	Adverse drug reactions
RAL	400 mg per 12 hours	Headache ,GI upset, Weight gain
DTG	50 mg per day	Insomnia, weight gain headache, GI upset.

DTG is preferred because it has a high barrier to resistance. It is also favored because it is available in combination and can be taken once a day. Weight gain has been a side-effect being reported recently, more in DTG than with RAL, and more in black women and in patients with lower baseline CD4+ counts as well as higher VLs (Nel et al., 2020).

Other benefits of DTG include

- Provides rapid viral suppression
- High genetic barrier to resistance
- No interaction with hormonal contraceptives
- Side-effects are mild and uncommon (NDOH, 2019).

2.3.1.3 Non-Nucleoside Reverse Transcriptase Inhibitor drug Class of antiretroviral drugs

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind non-competitively to HIV-1's reverse transcriptase and prevents viral RNA conversion to DNA.The four NNRTIs currently on the market in South Africa are Efavirenz (EFV), Nevirapine (NVP), Rilpivirine (RPV) and Etravirine (ETR) (Nel et al., 2020).

Table 2.4 The Non-Nucleoside Reverse Transcriptase Inhibitors available in South Africa

Drug	Dose	adverse drug reactions
EFV	600 mg per day 400 mg in < 40 kg	vivid dreams, dizziness, psychosis, rash, hepatitis, gynaecomastia
NVP	200 mg per 12 hours	Rash, hepatitis
RPV	25 mg per day	Rash, hepatitis
ETR‡	200 mg per 12 hours	Rash, hepatitis

Efavirenz (EFV) is recommended for first-line for patients who cannot tolerate DTG, or where DTG is contraindicated. Rilpivirine (RPV) is another good first-line contender, but it is not available in FDC and it cannot be given to patients on RIF-based TB treatment. It also can't be started in patients with a VL > 100 000 copies/mL (Nel et al., 2020).

2.3.1.4 Protease Inhibitor drug Class Of antiretroviral drugs

Protease inhibitors (PIs) are a class of agents that inhibit the action of HIV-1 protease, an enzyme that cleaves two precursor proteins into the final protein products that permit the production of infectious viral particles. Inhibition of the above, results in immature non-infectious virions.

The PI's available for use in South Africa are Lopinavir (LPV), Atazanavir (ATV) and Darunavir (DRV). They are given with low-dose Ritonavir (RTV; indicated as /r) which is used as a pharmacokinetic 'booster'. RTV is a potent inhibitor of CYP3A4 and thus its use results in higher drug levels. This allows for less frequent PI dosing, and reduces the chance of viral resistance developing (Nel et al., 2020).

Table 2.5 The Protease Inhibitors available in South Africa

Drug	Dose	adverse drug reactions
ATV/r	ATV/r 300 mg/100 mg per day	Dyslipidaemia Renal stones Hepatitis
LPV/r	400 mg/100 mg per 12 hours	GI upset, hepatitis dyslipidaemia
DRV/r	600 mg/100 mg per 12 hours	GI upset, hepatitis, rash, dyslipidaemia

2.3.2 Regimens in South Africa

2.3.2.1 Management of patients being initiated on first-line therapy (ART naïve patients)

ART should be initiated as soon as possible in all patients who are diagnosed with HIV except if they present with CM or tuberculosis meningitis TBM as mentioned above in section 2.2.1. In patients initiating ART (ART-naïve patients), the recommended regimen is TDF (300 mg) + 3TC (300 mg) (or FTC 200 mg) + DTG (50 mg) daily (Nel et al., 2020).

Initial antiretroviral therapy regimens for ART naïve patients are

1. TDF + 3TC (or FTC) + EFV
2. TDF + 3TC (OR FTC) + RPV
3. ABC + 3TC + DTG

2.3.2.2 Management of patients currently receiving first-line therapy

Patients who are virologically suppressed on NNRTI-based first-line therapy should be considered for a switch from an NNRTI to DTG in combination with the same two-drug NRTI backbone.

2.3.2.3 Management of patients starting or currently receiving second-line therapy

If the patient is failing an NNRTI regimen of 3TC/FTC + either TDF or ABC, then AZT + 3TC + DTG is the recommended second-line regimen. Resistance testing is indicated if the patient is failing other first-line regimens.

2.3.3 Opportunistic Infections treatment/Prophylaxis

In patients receiving ART , the use of appropriate prophylaxis is essential. Once the CD4+ count has increased to > 200 cells/μL prophylaxis can be discontinued, but certain minimal durations of prophylaxis apply for secondary prophylaxis (Nel et al., 2020).

Prophylactic cotrimoxazole (CTX) is recommended for HIV-positive patients with a CD4+ count < 200 cells/μL, or with WHO stage 3 or 4 conditions. It offers protection against Pneumocystis jirovecii, toxoplasmosis, isosporiasis and certain bacterial infections.

Isoniazid preventive therapy (IPT) should be commenced at initiation of ART. IPT should not be started in pregnancy, except in pregnant women where the CD4+ count is < 350 cells/μL and who are at high risk of death from TB. Active TB infection should always be excluded before commencing IPT (Nel et al., 2020).

2.4 Vaccination Efforts and New variant

The initial hope of an effective vaccine against HIV has not been fulfilled. Aside from the virus being able to rapidly mutate antigenic portions of key surface proteins, HIV infection progresses despite the host's humoral and cellular immune responses; therefore, any vaccination effect needs to surpass the normal host response to HIV (Gilroy and Faragon, 2021).

Wymant and colleagues discovered a highly virulent variant of subtype-B HIV-1 in the Netherlands. Patients with this variant had an increase in viral load and exhibited CD4 cell decline twice as fast as, compared with, individuals with other subtype-B strains. This increased virulence is attributable to the viral strain. Genetic sequence analysis suggests that this variant arose in the 1990s (Wymant *et al*., 2022). Although this virus more virulent the mutations found in the new variant don't make it resistant to existing HIV drugs, says Joel Wertheim, an evolutionary biologist and molecular epidemiologist at the University of California San Diego. "All of the tools in our arsenal should still work," he says (Wymant *et al*., 2022).

2.5 Chapter summary

Pharmacovigilance started after the disaster caused by thalidomide in 1961 when thousands of babies were born with congenital abnormalities. HIV is an infection that causes depletion of cells needed for normal immune function. This chapter has extensively discussed what is currently known in the literature regarding HIV and its management (including DTG). It presented an overview of the literature on the virus, how it affects our immune system , the role of ART and more importantly how DTG plays its role. In the following chapter, the steps taken to obtain the results of this study are discussed.

Dolutegravir Reported Adverse Drug Reactions: A Systematic Review Protocol

Authors

1. Lesley Wadesango

2. Ebenezer Wiafe

3. Kofi Boamah Mensah

4. Varsha Bangalee

5. Neelaveni Padayachee

Author Affiliations

Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road. Parktown, 2193, Johannesburg, South Africa (1,5)

Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa (2,3,4)

Clinical Pharmacy Services Unit, Directorate of Pharmacy, Ho Teaching Hospital, Ho, Ghana (2)

Department of Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Science, Kwame Nkrumah University of Science & Technology, Ghana (3)

Author email addresses

1. lwadesango@gmail.com

2. weben38@gmail.com

3. kofimensah227@yahoo.co.uk

4. bangalee@ukzn.ac.za

5. neelaveni.Padayachee@wits.ac.za

Dolutegravir Reported Adverse Drug Reactions: A Systematic Review Protocol

ABSTRACT

Background: Until recently, the first-line regimen for the management of Human Immunodeficiency Virus (HIV) was Tenofovir (TDF)-Emtricitabine (FTC) and Efavirenz (EFV). However, the use of EFV has now been limited due to adverse neurosensory effects and a low genetic barrier to resistance. This regimen has been replaced by the Dolutegravir (DTG)-based regimen since DTG has a high genetic barrier to resistance. Studies have reported a higher risk of Immune Reconstitution Inflammatory Syndrome (IRIS), weight gain, insomnia, and neural tube defects amongst people who received DTG. This review aims to assess the adverse drug reaction (ADR) profile of Dolutegravir by identifying and classifying Dolutegravir-associated adverse drug reactions.

Methods: Studies will be identified from an electronic database search. Studies that are potentially eligible will be selected through screening. Two team members will independently screen all citations, full-text articles, and abstract data; conflicts will be resolved through discussion. The (PRISMA-P) flow diagram that outlines all phases of screening and reasons for exclusion will be used during the selection process. After the selection of the final study sample, a data extraction form will be used as a collection tool. The data will be entered into Cochrane Collaboration Review Manager (RevMan 5.2) for storage and management. All the evidence gathered will be assessed for bias through the use of the Risk of Bias tool RoB 2.0 of Cochrane Collaboration. Reported ADRs will then be classified. We will also provide data for the effect of different demographic factors on ADRs as well as the effects of co-administration of DTG with other drugs on ADRs. We will additionally provide information on how Dolutegravir use in different regimens affects the ADRs. Results from the review will be summarized quantitatively through meta-analysis. A forest plot will be used to present results from the meta-analysis.

Conclusion: A review of existing studies will aid in establishing the safety profile of this drug. This review will make significant contributions to healthcare practice. It will aid in improving prescribers' and dispensers' knowledge of the drug. Additionally, it will also aid in patient education of the potential ADRs to DTG.

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Keywords: Adverse drug reactions, Antiretroviral safety, Dolutegravir, Human Immunodeficiency Virus, Pharmacovigilance.

Background

Human Immunodeficiency Virus (HIV) remains a worldwide public health issue (Global HIV and AIDS statistics, 2020). Although HIV management and access have been successfully implemented by the scientific community, the World Health Organization (WHO), governments, social organizations, and local societies, its global incidence was at 38 million in 2019 (Pandey and Galvani, 2019). Globally in 2020, at least 1.5 million people were newly infected with HIV (UNAIDS, 2021). In 2020, 84% of the people living with HIV knew their status, 73% were on treatment and 66% were virally suppressed (UNAIDS, 2021).

Current data suggests that 30% of all HIV infections in Southern Africa have been reported to be in South Africa (HIV and AIDS in South Africa, 2020). The total amount of people with HIV in South Africa has since increased from 7.4 million in 2016 to 7.7 million in 2018 (HIV and AIDS in South Africa, 2020).

Until recently, the regimen recommended for the first-line combination treatment of HIV was Tenofovir (TDF)-Emtricitabine (FTC) and Efavirenz (EFV) also known as TEE (National Department of Health, 2019). However, the consistent use of EFV due to its adverse neurosensory effects and low genetic barrier from the drug-resistance mutations has become a limitation for its use (The NAMSAL ANRS 12313 Study Group, 2019). According to the latest antiretroviral therapy (ART) clinical guidelines, the Efavirenz-based regimen has been replaced by the Dolutegravir (DTG)-based regimen due to its favourable profile of maintained viral suppression and immunological recovery (Walmsley *et al.,* 2013).

The recommended regimen for the primary management of HIV is Tenofovir (TDF)-Lamivudine (3TC)-Dolutegravir (DTG) also known as TLD (National Department of Health, 2019). DTG is cheap, has an increased genetic barrier to resistance, and is accessible as a fixed-combination pill, and hence was introduced as the preferred first-line therapy for HIV by the WHO in 2018 (WHO, 2018). However, the administration of DTG at conception could result in neural-tube defects in infants and must therefore be used with caution in pregnant women. The drug is also known to increase the risk of insomnia and obesity (Hill *et al*., 2018; Hill *et al*., 2019). There is more evidence that the risks of weight gain, insomnia, Immune Reconstitution Inflammatory Syndrome (IRIS), and neural tube defects amongst patients receiving DTG are increased (Batista *et al*., 2019). These adverse drug reactions (ADRs) are common and easily identifiable. A global investigation into DTG ADRs is important in understanding how South Africa can

manage a relatively new drug on the HIV regimen. These adverse effects have thus resulted in the WHO making its use conditional and recommended that DTG patients be closely monitored.

A review of the evidence from existing studies that evaluated the safety profile of DTG is relevant in promoting pharmacovigilance activities. Therefore, this proposed review aims to assess the global ADRs profile of DTG through:

1. Identification and classification of DTG-associated ADRs.
2. Establishment of the safety and efficacy of DTG in the therapy of HIV with an emphasis on pregnant women.
3. Identification and categorization of the demographic factors associated with DTG ADRs.

Methods

Protocol and Registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines were followed in the design of this review protocol (Higgins *et al*., 2011). The review protocol was registered with the Open Science Framework (OSF) on the 2nd of December 2020 (doi.org/10.17605/OSF.IO/Z9YAF). If there are any protocol amendments, a description of the change and the rationale will be presented in the main review.

Data Source and Search Strategy

The following databases will be explored from January 2010 to date for studies: Scopus, Web of Science, PubMed, Embase, Vigiacess, Cochrane Clinical trials registry, National institutes for health Clinical Trials Registry, and Cochrane Library.

A manual search will be also done for additional articles that may not be included on the aforementioned platforms. The following search terms will be used: ‘‘Dolutegravir’’, ‘‘Antiretroviral’’, ‘‘Safety’’, ‘‘Adverse events’’, ‘‘Human Immunodeficiency Virus’’, ‘‘Adverse effects’’, ‘‘Acquired Immunodeficiency Syndrome’’, ‘‘Adverse drug reactions’’, and ‘‘Adolescent’’. These terms will be used in different combinations with boolean operators for the listed databases.

Criteria for Considering Studies for this Review

Study Designs

Studies that will be included in the review will not be limited to randomized clinical trials (RCTs), non-RCTs, cohorts, and case-controls. Systematic reviews and other forms of reviews will be excluded.

Patients (Population)

Studies that reported on DTG ADRs in males and females aged ≥18 years will be included. There will be no restrictions regarding ethnicity, participants' language, country of origin, and other socio-demographics.

Interventions

We will include studies that investigated the safety of DTG either alone or in combination with other ARVs. Of particular interest is TLD, which was introduced by the WHO in 2018 as it is currently the only regimen with DTG being prescribed for first-line treatment of HIV.

Comparators

The team of reviewers will include studies that compared the DTG-containing regimens with previously recommended regimens. Of particular interest is the combination that was just downgraded: TEE.

Outcomes

Studies that reported on DTG ADR outcomes not limited to physical symptoms, hospitalizations, deterioration in organ function (hepatic or renal function), Immune Reconstitution Inflammatory Syndrome (IRIS), deaths, and the discontinuation of therapy.

The outlines outcomes will be assessed for all included studies. They will be grouped according to treatment periods. This will assist in assessing the short and long-term effects of DTG.

Exclusion Criteria

- Studies exclusively in children less than 18 years.

- Studies that were conducted in patients who were co-infected with tuberculosis and were being managed with rifampicin. This exclusion is because DTG is a substrate for Cytochrome-P450-3A4 (CYP3A4) and Uridine-diphosphate-glucuronosyltransferase-1A1 (UGT1A1). These enzymes are induced by rifampicin. The co-administration of DTG and rifampicin consequently leads to a reduction of DTG levels in the blood. Doubling the required daily dose of DTG is recommended for appropriate clinical efficacy (Cevik *et al*., 2018). This may affect the ADR profile of DTG.

- Studies that recruited patients with severe hepatic impairment. Hepatic toxicity has been reported without previous hepatic disease in some patients (Cunha, 2020). Therefore, studies conducted on these patients would potentially have biased outcomes regarding the DTG ADR profile.

- Animal studies will be excluded because the reviewers are interested in clinically relevant study findings regarding DTG ADRs.

- Studies that were not reported in the English language.

Selection of Studies

Two reviewers/authors will identify studies from the electronic database search and evaluate their eligibility for inclusion in the review. The potentially eligible studies will be identified through the screening of titles and abstracts after duplicated studies have been identified and removed. Another set of two reviewers will independently perform full-text screening and data extraction. Any disagreements that may arise between the reviewers, during the titles and abstracts screening, and the full-text screening, will be resolved through a discussion with a third reviewer. The agreement between each reviewer pair will be measured and reported by Kappa statistics. A PRISMA flow diagram illustrating the various stages of the review, and results obtained will be presented.

Data Extraction and Management

After the selection of the final study sample, two (2) data extraction forms (Tables) will be used to extract data. The form will contain the following sections:

- Table 1: Study Characteristics - Lead author, year, study design, sample size, study setting/country, details of DTG/antiretroviral drug regimen/combination/intervention, duration of treatment, comparator, and funding source.

- Table 2: Summary of Findings - Outcomes (any adverse drug reactions/events, most common ADRs/events, ADRs/events requiring discontinuation, number of ADRs/adverse events leading to death).

The data extraction forms will be tested to determine their validity and reliability. In the event of unclear or missing information in the selected studies, the corresponding authors of those studies will be contacted via email for clarification and to provide adequate information. Two independent reviewers will screen the contents of the data extraction forms to check for the accuracy and completeness of data. Any observed differences will be resolved by discussion.

Quality assessment and risk of bias

To assess the risk of bias for randomized control studies, the Cochrane Risk of Bias tool will be used. The tool offers a basis for assessing the risk of bias in the outcomes of any randomized trial (Sterne *et al*., 2019). Assessment is arranged into several domains that bias may be introduced (Sterne *et al*., 2019). A judgement/conclusion of a high risk of bias in any domain consequently means the whole study has a high risk of bias (Sterne *et al*., 2019).

The Newcastle-Ottawa Scale will be used to assess the risk of bias for nonrandomized studies. Each study will be judged on eight items, categorized into three groups: the selection of the study groups, the comparability of the groups, and the determination of the exposure or outcome of interest for case-control or cohort studies (Wells *et al*., 2019). A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars can be given for Comparability (Wells *et al*., 2019).

Two reviewers will independently assess the methodological quality of eligible studies and avoid the exclusion of studies based on the methodological quality assessment outcomes. For studies that employed other study designs, the reviewers would adopt an appropriate methodological

quality appraisal tool. A third reviewer would serve as an arbiter in instances of disagreement between the independent reviewers.

Data Synthesis

Adverse drug reactions will be classified into six types. Dose-related reactions (ARRs at normal or overdose), non-dose-related reactions (eg allergy or anaphylaxis), dose and time-related (due to dose accumulation), time-related (due to prolonged use), withdrawal (effects after stopping the drug), and failure of therapy (Edwards *et al*., 2000).

We will further group reported ADRs as;

- The patient/participant was hospitalized due to the reaction.
- The patient/participant's life was threatened by the reaction.
- The patient/participant's hospitalization time was prolonged due to the reaction.
- The reaction caused long-term patient/participant disability.
- The reaction did not lead to any of the above but was severe.
- The reaction was not severe.

The sociodemographic data of participants of included studies will be synthesized and presented as part of the study findings. Also, findings on the co-administration of DTG with other drugs, and how DTG use in different regimens affects adverse drug reactions will be presented. The findings from the review will be summarized quantitatively, unless otherwise. Homogenous studies will be analysed statistically through a meta-analysis. The lead author will make the entry into Cochrane Collaboration Review Manager (RevMan 5.2), and the second author will check for data entry errors and manage them appropriately.

Results from the meta-analysis will be presented in a forest plot. Where possible, a sensitivity and sub-group analysis will be performed.

Discussion and conclusions

Globally, more than 38 million people are infected by HIV. Effective antiretroviral therapy with the DTG regimen is available, yet there are safety concerns about the risks of weight gain, insomnia, Immune Reconstitution Inflammatory Syndrome (IRIS), and neural tube defects.

Our findings regarding the overall safety of DTG will be of great significance to policy-makers, healthcare providers, and patients. Additionally, we hope to identify gaps in research that may form the basis for future studies of DTG in ART regimens. The results of this study will provide a basis for ongoing medication safety monitoring for Dolutegravir regimens.

Limitations of the review

The reporting quality of some studies may be poor thus affecting the results. Studies may fail to provide a clear definition of ADRs or report on ADR incidence data. Additionally, studies might not use the same classification when reporting ADRs.This might make it difficult to draw an accurate conclusion.

List of abbreviations

3TC: Lamivudine; ADR: Adverse drug reaction; ART: Antiretroviral therapy; CYP3A4: Cytochrome-P450-3A4; DTG: Dolutegravir; EFV: Efavirenz; FTC: Emtricitabine; HIV: Human Immunodeficiency Virus; IRIS: Immune Reconstitution Inflammatory Syndrome; OSF: Open Science Framework; PRISMA-P: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol; RCTs: Randomized clinical trials; TDF: Tenofovir; UGT1A1: Uridine-diphosphate-glucuronosyltransferase-1A1; WHO: World Health Organization

Declarations

Ethics approval and consent to participate

None.

Consent for publication

None.

Availability of data and materials

None.

Competing interests

None.

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Authors' contributions

All the authors contributed significantly to the conception and development of the manuscript. The listed authors have read the manuscript for scientific content and have approved the manuscript for publication.

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The authors acknowledge the Department of Pharmacy and Pharmacology, Faculty of Health Sciences at the University of the Witwatersrand.

ORCID identifiers

Lesley Wadesango: https://orcid.org/0000-0002-2737-7102

Ebenezer Wiafe: http://orcid.org/0000-0002-0496-5737

Neelaveni Padayachee: https://orcid.org/0000-0002-6146-8702

Kofi Boamah Mensah: https://orcid.org/0000-0002-7971-4270

Varsha Bangalee: https://orcid.org/0000-0002-9613-1501

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CHAPTER 3

METHODOLOGY

3.1 Introduction

This chapter includes a full description of the methodology used for the study. The study design is described. The search strategy and types of outcomes are discussed. The inclusion and exclusion criteria are outlined here. The data extraction and data synthesis are discussed towards the end of this chapter. The chapter is concluded by a description of the risk of bias as well as assessment of publication bias.

3.2 Study Design

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines were followed in the design of this review protocol. The review protocol was registered with the Open Science Framework (OSF) on the 2nd of December 2020 (doi.org/10.17605/OSF.IO/Z9YAF).

3.3 Search Strategy for Identification of Studies

3.3.1 Data sources

A search of the published literature for studies reporting adverse drug reactions to DTG was conducted using the specified terms listed below.

3.3.2 Electronic searches

Electronic databases, PubMed/MEDLINE, Web of Science and CINAHL were searched for information relevant to the objective of this study as optimal searches in these databases guarantees adequate and efficient coverage for systematic reviews.

The following search terms were used as they are keywords and helped us to narrow our search to the most relevant studies. they were used in various combinations and adapted for each database:

‘‘Dolutegravir’’, ‘‘Antiretroviral’’, “Highly active antiretroviral”, ‘‘combination’’, ‘‘regimen’’, ‘‘Human Immunodeficiency Virus’’, ‘‘Adverse effects’’, ‘‘Acquired Immunodeficiency Syndrome’’, ‘‘Adverse drug reactions’’, “pharmacovigilance” and ‘‘Adolescent’’

The search strategy was developed by two reviewers and applied to identify published articles in a three-phase approach. First, a limited search of Pubmed (Medline) was carried out. The text words and index terms contained in the titles and abstract of the articles obtained were analyzed. Secondly, all related keywords and index terms identified were used in all the included databases. Thirdly, the reference section of selected articles was checked for additional related studies. The search strategy will be included as Appendix 1.

3.3.3 Inclusion criteria

Types of studies: The systematic review included:

- randomized clinical trials (RCTs),
- non-RCTs
- and observational studies (prospective/retrospective cohort and case-control),

published from 2010 to January 2022. Studies that investigated the safety of DTG either alone or in combination with other ARVs were included. Additionally, studies that reported on DTG ADR outcomes not limited to physical symptoms, hospitalizations, deterioration in organ function (hepatic or renal function), Immune Reconstitution Inflammatory Syndrome (IRIS), deaths, and the discontinuation of therapy were also included. Studies that compared the DTG-containing regimens with previously recommended regimens also formed part of the inclusion criteria.

Study participants: Studies were included in the review if participants were aged ≥18 years. There were no restrictions regarding sex, ethnicity, participants’ language, country of origin, and other socio-demographics.

3.3.4 Exclusion criteria

The following were excluded

- Studies done exclusively in children less than 18 years.

- Studies that were conducted in patients who were co-infected with tuberculosis and were being managed with rifampicin. This exclusion is because DTG is a substrate for Cytochrome-P450-3A4 (CYP3A4) and Uridine-diphosphate-glucuronosyltransferase-1A1 (UGT1A1). These enzymes are induced by rifampicin. The co-administration of DTG and rifampicin consequently leads to a reduction of DTG levels in the blood. Doubling the required daily dose of DTG is recommended for appropriate clinical efficacy. However this may affect the ADR profile of DTG.

- Studies that recruited patients with severe hepatic impairment. Hepatic toxicity has been reported without previous hepatic disease in some patients. Therefore, studies conducted on these patients would potentially have biased outcomes regarding the DTG ADR profile.

- Animal studies were excluded because the reviewers are interested in clinically relevant study findings regarding DTG ADRs.

- Studies that were not reported in the English language.

- Duplicate publications.

- All form of reviews/meta-analysis, pilot studies and case reports.

3.4 Risk of Bias

The risk of bias for each study was assessed using the Hoy 2012 tool (Hoy *et al*., 2012). Each study was measured using the Hoy 2012 tool with ten parameters addressing internal and external validity (Hoy et al., 2012). These ten parameters address four areas of bias and the last provides the summary of the risk of bias assessment. Each parameter was weighed as low, moderate or high risk of bias (Table 3.1). Studies were classified as having a low risk of bias when eight or more of the ten questions were answered as ‘‘yes (low risk)’’, a moderate risk of bias when six to seven of the questions were answered as ‘‘yes (low risk)’’ and a high risk of bias when five or fewer questions were answered as ‘‘yes (low risk)’’.

Table 3.1 Risk of bias assessment tool.

Name of author(s): Year of publication: Study title:		
Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	Yes (LOW RISK): The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	Yes (LOW RISK): The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	Yes (LOW RISK): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1

5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes (LOW RISK): All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	Yes (LOW RISK): An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	Yes (LOW RISK): The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate	Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	**0-3**
	MODERATE RISK	**4-6**
	HIGH RISK	**7-9**

3.5 Data Extraction and Management

Citations of the search results from the databases and websites using the search terms mentioned above were imported into Endnote and duplicates were removed. Articles whose titles and/or abstracts were not related to the study were then excluded, and the remaining eligible articles based on the inclusion criteria were retrieved.

After the selection of the final study sample, a data extraction form was used (see Appendix 2) to extract data. The form contains the following sections:

- **Table 1**: Study Characteristics - Lead author, year, study design, sample size, study setting/country, details of DTG/antiretroviral drug regimen/combination/intervention, duration of treatment, comparator, and funding source.

- **Table 2**: Summary of Findings - Outcomes (any adverse drug reactions/events, most common ADRs/events, ADRs/events requiring discontinuation, number of ADRs/adverse events leading to death).

3.6 Data Synthesis and Analysis

The findings from the review were summarized quantitatively. They were categorized and summarized our data into tables including gastrointestinal (GI) ADRs, central nervous system (CNS) ADRs, neuropsychiatric ADRs and ADRs related to the skin. ADRs causing discontinuation, ADRs in Pregnancy, ADRs and Demographics as well as Dose and Dose and time –related ADRs were also included.A narrative synthesis was done to describe and discuss the outcomes.

A data entry into Cochrane Collaboration Review Manager (RevMan 5.2) was made and data entry errors were checked and managed appropriately.

3.7 Ethics

This study used data from published studies and did not use data from individual participants. Therefore, ethics review and informed consent from participants was not necessary.

3.8 Chapter Summary

In this chapter, all the sections have discussed the methodological process that was undertaken in the study. The study design was described as well as the search strategy for identification of studies. The Risk of Bias as well as how the quality of the studies included was assessed was discussed. Finally the data extraction and synthesis processes were presented. The next chapter will present the results obtained through the process outlined above.

CHAPTER 4

RESULTS

4.1 Introduction

This chapter describes the literature search, summarizes the collected data and presents the findings of the study.

4.2 Description of the literature search

An electronic search of the following databases (PubMed/MEDLINE, Web of Science and CINAHL) using the search terms ‘‘Dolutegravir’’, ‘‘Antiretroviral’’, “Highly active antiretroviral”, ‘‘combination’’, ‘‘regimen’’, ‘‘Human Immunodeficiency Virus’’, ‘‘Adverse effects’’, ‘‘Acquired Immunodeficiency Syndrome’’, ‘‘Adverse drug reactions’’, “pharmacovigilance” and ‘‘Adolescent’’ was conducted, and it resulted in the identification of 501 publications. Following the removal of duplicate publications 445 publications were retrieved for a preliminary assessment. Preliminary screening of titles and abstracts of the 445 publications yielded 42 potential publications. Of these 42 publications using our inclusion criteria, 33 were found eligible, and were included in the meta-analysis. Figure 4.1 presents a flowchart of the process of identification of eligible publications and Table 4.1 presents characteristics of included publications. The list of excluded articles with reasons for exclusion is presented in Appendix 3.

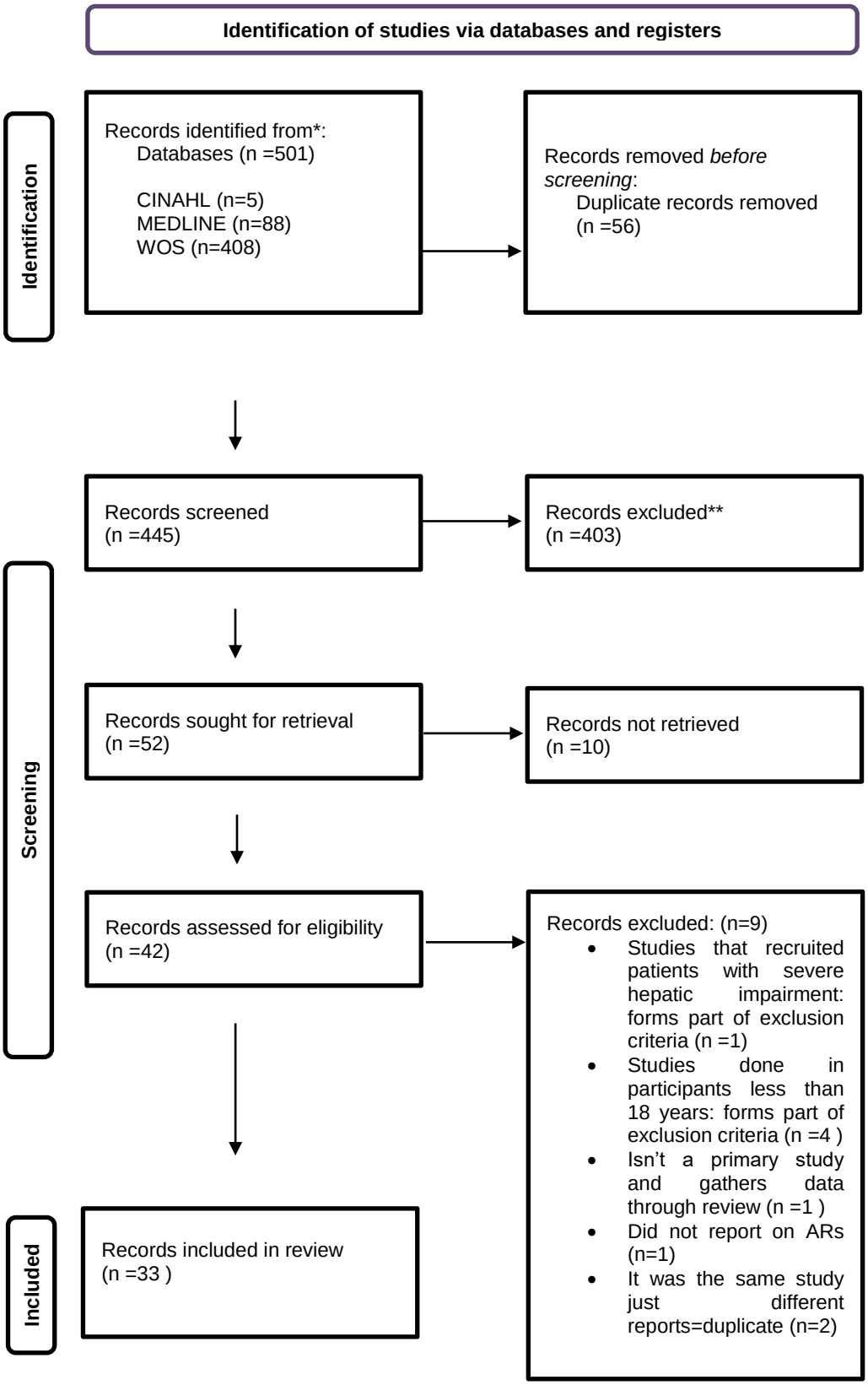

Identification of studies via databases and registers
Identification
Records identified from*:
Databases (n =501)
CINAHL (n=5)
MEDLINE (n=88)
WOS (n=408)
Records removed *before screening*:
Duplicate records removed (n =56)
Screening
Records screened (n =445)
Records excluded** (n =403)
Records sought for retrieval (n =52)
Records not retrieved (n =10)
Records assessed for eligibility (n =42)
Records excluded: (n=9)
Studies that recruited patients with severe hepatic impairment: forms part of exclusion criteria (n =1)
Studies done in participants less than 18 years: forms part of exclusion criteria (n =4)
Isn't a primary study and gathers data through review (n =1)
Did not report on ARs (n=1)
It was the same study just different reports=duplicate (n=2)
Included
Records included in review (n =33)

Figure 4.1 PRISMA flow diagram of selection of publications.

4.3 Characteristics of included studies

Of the 33 included publications, 19 were retrospective cohort studies, 13 were prospective cohort studies and one was a case control study. The included publications were published between 2010 and 2022 January with a total sample of 138 466 people who received a DTG dose at least 13 in countries. One study each was performed in the United States of America (Zash *et al*.,2021), Belgium (Nasreddine *et al*.,2020), German (Hoffman *et al*., 2017), and Thailand (Goh *et al*., 2019) , Netherlands (de Boer *et al*., 2016) , Spain (Cid-Silva *et al*., 2017), Korea (Chin *et al*., 2020).

One study was performed simultaneously in 21 countries (Chan *et al*., 2020) , while another one was performed in 9 african countries (Lockman *et al*., 2021). One study was performed in both the USA and Canada (Bourgi *et al*., 2020). Another study was conducted predominately in high-income countries (i.e. United States and Western Europe) while another was conducted in Europe, Latin America and North America. Two studies were performed in both South Africa and Uganda (Kintu *et al*., 2020, Trottier *et al*., 2017) and Cameroon (Group *et al*., 2019, Calmy *et al*., 2020).

Three studies each were performed in France (Cuzin *et al*.,2019, Ursenbach *et al*.,2020, Hocqueloux *et al*.,2019). Three Studies were performed in Brazil (Perreira *et al*., 2019, Batista *et al*., 2019, Correa *et al*., 2020). Five studies each were conducted in Italy (Floridia *et al*.,2020 Rossetti *et al*., 2019, d'Arminio Monforte *et al*., 2019, Ciccullo *et al*., 2019, Ciccullo *et al*., 2021).The rest were not specified.

While most of the included studies did focus on all the ADRs reported by patients, some only reported on specific ADRs like weight gain and neurotoxicity related effects. Some studies only reported on adverse effects that caused discontinuation. A few studies also specifically investigated DTG safety concerns in Pregnancy. Most studies reported a higher percentage of male and Caucasian participants. Table 4.1 represents all the study characteristics

Table 4.1 Study Characteristics

Study citation	Study characteristics			ADRS reported (number) [percentage]					ADRS resulting in discontinuation (number) [percentage]					
	Country and study design	Total number of DTG participants*	Ethnicity and Gender	GI	CNS	Neuropsychiatric	Skin	Other	GI	CNS	Neuropsychiatric	Skin	Other	Resulting in Death
(Batista *et al*., 2019)	Case control Brazil	72032		Nausea (425)[13.34%] Diarrhea (313)[9.83%] Vomiting(82)[2.57%] Abdominal pain (52)[1.63%]	Headache (294)[9.23%] Dizziness (215)[6.75%] Drowsiness (125)[3.92%]	Insomnia (190)[5.97%]	Itching (73)[2.29%]	Alopecia (35)[1.1%]						
(Bourgi *et al*., 2020)	Prospective USA , Canada	929	87% male 41% white					At two and five years, persons on INSTI-based regimens gained an estimated mean of 4.9 and 5.9kg						
(Cahn *et al*., 2020)	Retrospective 21 countries	1433	69% white 85% males	Diarrhea (182) Nausea	Headache (166) Arthralgia	Insomnia (90)		Nasopharyngitis (215) Upper			(15)		Renal-related (9)	

				(87)	(58)			respiratory tract infection (126) Syphilis (101) Pharyngitis (95) Increased weight (23)					Osteoporosis (2)	
(Calmy *et al*., 2020)	Prospective study Cameroon	310				(1)[0.5%]	[5%]	General disorders (43) Infections (30) Nervous system disorders (6)						Death (8)
(Calza *et al*., 2020)	Retrospective Italy	59	93.2% white 72.9 % male	diarrhoea with abdominal discomfort (15) Nausea (7)	Headache (18) Asthenia (3)	Sleep disturbances (13) Depression (6)		High ALT (2) High CK (4) Myalgias (3)	diarrhoea with abdominal discomfort (2)		sleep disturbance(3)			
(Castagna et al., 2014)	Prospective study USA,Canada, Europe	183	71% white 77% males	Diarrhea (4)[2%] Nausea (3)[2%]	Headache (3)[2%]			IRIS (5) Hypersensitivity (1)				rash, pruritus, paresthesia (1),	hepatitis (3), cholelithiasis (1)	

(Chan *et al*., 2020)	Prospective study	254	99% Thai 95% Male										No participants discontinued DTG because NP-AEs	
(Chin *et al*., 2020)	Retrospective Korea	153							(3)	Dizziness (2) headache (1)	Sleep disorder (1)		Renal (1) CK elevaltion (1)	
(Ciccullo *et al*., 2019)	Retrospective study Italy	416	75% males						(5)[1.2%]		(8)[3.5%]		Pregancy (1) Drug to drug interactions (1) Hypersensiivity [0.4%]	
(Ciccullo *et al*., 2021)	Retrospective study Italy	2282	72.4% males						42	76		Rash (21)	Dyslipidameia (3) Drug to drug interactions (9) Pregancy (4) Osteop	(23)

													orosis (1)	
(Cid-Silva *et al*., 2017)	Retrospective study Spain	275	92 % white 73% males						GI discomfort [22.2%]	Headache Dizziness	[70.4%] Abnormal dreams Insomnia Anxiety Depressive symptomes Suicidal ideation		Alterations of renal function [3.7%] Haematology toxicity [3.7%]	
(Correa *et al*., 2020)	Retrospective study Brazil	222	72.5% males	diarrhea(10) nausea (4) vomiting (3) heartburn (3) stomach pains (4)	Headache (1) Dizziness (2)	Insomnia (3)	Skin blemishes Itching	Fever Cough						
(Cuzin *et al*., 2019)	Prospective France	6274	28.5% females								(1374) [21,9%]			
(d'Arminio Monforte *et al*., 2019)	Prospective Italy	994	88% Italian 16% females								13 cases (1.3%)			
(de Boer *et al*., 2016)	Retrospective study Netherlands	556							[4.3%]		Insomnia and sleep disturbance [5.6%]		Intolerability (76)[13.7%]	

											and anxiety,psychosis depression [4.3%]			
(Floridia *et al*., 2020)	Retrospective Italy							No significant differences in abosolute weight change or occurenece of excessive weight gain were found among pregnant women						
(Gallant *et al*., 2017)	Prospective study Europe, Latin America , North America	315	57% white 10% females	Nausea (72)[23%] diarrhea (41)[13%]	headache (43) [14%]			URTI (29)[9%]						
(Goh *et al*., 2019)	Prospective study Thailand	313	96% male	Nausea (3) [1%]vomittin g (1)[0.3%] dyspepsi a (1) [0.3%]	Dizziness (11)[3.5%] Headache (3)[1%] Fatigue (1)[0.3%] Hot flushes (2)[0.6%]	Insomnia (10)[3%] Bipolor (1)[0.3%]	Rash (1)[0.3%] Dry skin (1)[0.3%]	High ALT (14)[[4.5%] Low CrCl (1)[0.3%] High LDL (1)[0.3%]					High ALT (1)	

					Palpitations (1) [0.3%]									
(Group *et al*., 2019)	Prospective study Cameroon	310	63.5 % females					Mean weight gain of 5kg						
(Hocqueloux *et al*., 2019)	Prospective study France	158	72% males								grade 2 mood disturbance			
(Hoffmann *et al*., 2017)	Retrospective study German	1073	90% Caucasian 93% males		Dizziness (13) Headache (16)	Insomnia (36) Depression (7) Poor concetration (8)			[0.7%] (7)		(49) [5%]		Renal [0.2%] (2) Hepatic [0.1%](1) Skin [0.3 %](3) Other [0.5%] (5)	
(Kintu *et al*., 2020)	Prospective South Africa and Uganda	125	All female					3 Mother to child Transmissions No NTDs detected						
(Lockman *et al*., 2021)	Prospective 9 countries	432	All female					Pregnacy infections Pre-emclapsia						

								Gestational diabetes						
(Min *et al*., 2011)	Prospective study	35	Above 60% Caucasian and 100% males	Diarrhea				hypertriglyceridemia (10 mg), lipase increase (10 mg), migraine (50 mg)						
(Mondi *et al*., 2019)	Retrospective study Italy	1679	57.7% Caucasian 32.7% female								Insomnia (11) Depression (5) Anxiety (5) Headache (5)		IRIS (5)	
(Nasreddine *et al*., 2020)	Retrospective study Belgium	4101	32.7 % females						[1.4%]		[5.2%]		Median weight gain 2kg	
(Pereira *et al*., 2021)	Retrospective Brazil	382	37% white 41% mixed					Average weight gain per week was 0.3kg						
(Rossetti *et al*., 2019)	Retrospective study Italy	132	80% Caucasian 69% males						(4)		(4)		Intolerance (5) IRIS (5)	
(Stellbrink *et al*., 2013)	Retrospective study United States and	155	80% Caucasian 80% males	Nausea (73)[47%] Diarrhea	Dizziness (5)[3%] Headache (11)[7%]	Insomnia (3)[2%]	Rash (2)[1%]							

	western Europe			(13)[8%]	Fatigue (5)[2%]									
(Trottier *et al*., 2017)	Retrospective study USA/CANADA	275 early switch	65% white 86% males	Nausea (27) [10%] Diarrhea (17)[6%]	Fatigue (19)[7%] Headache (13)[5%]	Total=35 [13%]								
(Ursenbach *et al*., 2020)	Restrospective study France	19462						265 cases of diabetes mellitus occurred						
(Walmsley *et al*., 2015)	Retrospective study North America, Europe, and Australia	419	76% Caucasian 10% females	Nausea[11%] Diarrhea [6 %]	Dizziness[7%] Fatigue [7%] Headache[6%]	Abnormal dreams [7%] Insomnia [10%]	Rash [≤1%]							
(Zash *et al*., 2021)	Retrospective	22,828						Duration of pre-pregnancy ART (years) was associated with higher baseline weight for DTG						

4.4 Risk of bias and quality assessment

The risk of bias for each study was assessed using the Hoy 2012 tool (Hoy *et al*., 2012). Each study was measured using the Hoy 2012 tool with ten parameters addressing internal and external validity (Hoy *et al*., 2012). These ten parameters address four areas of bias and the last provides the summary of the risk of bias assessment. If it was unclear the question was rated as high risk. Each parameter was weighed as low, moderate or high risk of bias then a final score provided a summary. A study was classified as low risk if the final score was between 0-3 , moderate risk if it scored between 4-6 and high risk if it was 7 and above.

A low risk study scored between 0-3 : Walmsley *et al*., 2015 , Trottier *et al*., 2017, Min *et al*., 2011, Group *et al*., 2019, Gallant *et al*., 2017, Ciccullo *et al*., 2019, Calza *et al*., 2020 , Calmy *et al*., 2020), Cahn *et al*., 2020 , Batista *et al*., 2019, Bourgi *et al*., 2020, Kintu *et al*., 2020. Hocqueloux *et al*., 2019.

A moderate risk study scored between 4-6 : Ursenbach *et al*., 2020 , Stellbrink *et al*., 2013, Rossetti *et al*., 2019 , Nasreddine *et al*., 2020 , Mondi *et al*., 2019 , Hoffmann *et al*., 2017, Goh *et al*., 2019 , de Boer *et al*., 2016, d'Arminio Monforte *et al*., 2019, Correa *et al*., 2020, Cid-Silva *et al*., 2017, Ciccullo *et al*., 2021 , Chin *et al*., 2020, Castagna *et al*., 2014, Cuzin *et al*., 2019, Chan *et al*., 2020, Floridia *et al*., 2020 , Zash *et al*., 2021, Pereira *et al*., 2021, Lockman *et al*., 2021.A high risk study scored from 7-9 : None of the studies included were of high risk of bias

The results are shown in Table 4.2

Table 4.2 Risk of bias assessment of included studies using the Hoy 2012 tool.

Citation	Representation	Sampling	Random Selection	Non-Response Bias	Data Collection	Case Definition	Reliabilty of tool	Method of data collection	Numerators and denominators	Summary assesment	Summary Assesment
(Batista et al., 2019)	0	0	1	1	0	0	0	0	1	3	Low risk
(Bourgi et al., 2020)	0	0	1	1	0	0	0	0	1	3	Low risk
(Cahn et al., 2020)	0	0	1	1	0	0	0	0	1	3	Low risk
(Calmy et al., 2020)	0	0	1	1	0	0	0	0	1	3	Low risk
(Calza et al., 2020)	0	1	0	1	0	0	0	0	1	3	Low risk
(Castagna et al., 2014)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Chan et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Chin et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Ciccullo et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Ciccullo et al.,	0	1	0	1	0	0	0	0	1	3	Low risk

2021)											
(Cid-Silva et al., 2017)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Correa et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Cuzin et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(d'Arminio Monforte et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(de Boer et al., 2016)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Floridia et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Gallant et al., 2017)	0	1	0	1	0	0	0	0	1	3	Low risk
(Goh et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Group et al., 2019)	0	0	0	1	0	0	0	0	1	2	Low risk
(Hocquelo ux et al., 2019)	0	1	0	1	0	0	0	0	1	3	Low risk
(Hoffmann et al., 2017)	0	1	1	1	0	0	0	0	1	4	Moderate risk

(Kintu et al., 2020)	0	0	1	1	0	0	0	0	1	3	Low risk
(Lockman et al., 2021)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Min et al., 2011)	0	1	0	1	0	0	0	0	1	3	Low risk
(Mondi et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Nasreddine et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Pereira et al., 2021)	0	1	1	1	0	0	1	0	1	5	Moderate risk
(Rossetti et al., 2019)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Stellbrink et al., 2013)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Trottier et al., 2017)	0	1	0	1	0	0	0	0	1	3	Low risk
(Ursenbach et al., 2020)	0	1	1	1	0	0	0	0	1	4	Moderate risk
(Walmsley et al., 2015)	0	1	0	1	0	0	0	0	1	3	Low risk

(Zash et al., 2021)	0	1	1	1	0	0	1	0	1	5	Moderate risk
YES=LOW RISK=0 NO=HIGH RISK=1											

4.5 Adverse Drug Reactions Reported

4.5.1 Gastrointestinal ADRs

Gastrointestinal ADRs were reported by 11 of all 33 studies (33%). In the study by Batista *et al.*, conducted in Brazil the reported GI ADRs were nausea (425 of 3185 reported ADRs)[13.34%], diarrhea (313)[9.83%], vomiting(82)[2.57%] and abdominal pain (52)[1.63%]. Out of all the 11 studies reporting on GI ADRs 10 studies each reported on nausea and diarrhea. A total of at least 1531 GI ADRs were reported across all the studies. Nausea was the most reported ADR with 48 % while diarrhea was competing with 40.7%. After nausea and diarrhea, vomiting (5.6%) and abdominal pain (4.6%) were also dominant. Heartburn and dyspepsia only made up 0.26% of the reported GI ADRs across all studies. Table 4.3.

Table 4.3 Studies reporting on Gastrointestinal ADRs

Number and Percentage recorded	(Batista *et al*., 2019) Total=3185	(Cahn *et al*., 2020) Total=1433	(Calza *et al*., 2020) Total=59	(Castagna et al., 2014) Total=183	(Correa *et al*., 2020) Total=222	(Gallant *et al*., 2017) Total=315	(Goh *et al*., 2019) Total=313	(Min *et al*., 2011) Total=35	(Stellbrink *et al*., 2013) Total=155	(Trottier *et al*., 2017) Total=275	(Walmsley *et al*., 2015) Total=419
Nausea	425 13.34%	87 6%	7 11.9%	3 1.6%	4 1.8%	72 22.9%	3 0.96%		73 47%	27 9.8%	46 11%
Diarrhea	313 9.83%	182 12.7%	15 25.4%	4 2.1%	10 4.5%	41 13%		3 8.6%	13 8%	17 6%	25 6%
Vomiting	82 2.57%				3 1.35%		1 0.3%				
Abdominal pain/discomfort	52 1.63%		15 25.4%		4 1.8%						
Heartburn /Dypepsia					3 1.35%		0.3%				

4.5.2 Central Nervous System ADRs

CNS ADRs were reported by 11 of all 33 studies (33%). Out of all the 11 studies reporting on CNS ADRs all of them reported patients experiencing headache. Dizziness was reported in 6

studies while fatigue was reported in 5 studies. A total of at least 1111 CNS ADRs were reported across all the studies. Across all the studies, headache was the most reported ADR with 53.3% and dizziness followed with 24.8%. After headache and dizziness, fatigue (5.1%) was also dominant. Table 4.4.

Table 4.4 Studies reporting on CNS ADRs

Number and percentage recorded	(Batista *et al*., 2019) Total=3185	(Cahn *et al*., 2020) Total=1433	(Calza *et al*., 2020) Total=59	(Castagna et al., 2014) Total=183	(Correa *et al*., 2020) Total=22	(Gallant *et al*., 2017) Total=315	(Goh *et al*., 2019) Total=313	(Hoffmann *et al*., 2017) Total=1073	(Stellbrink *et al*., 2013) Total=155	(Trottier *et al*., 2017) Total=275	(Walmsley *et al*., 2015) Total=419
Headache	294 9.2%	166 11.6%	18 30%	3 1.6%	1 4.5%	43 14%	3 1%	16 1.5%	11 7%	13 5%	25 6%
Dizziness	215 6.8%				2 9%		11 3.5%	13 1.2%	5 3%		29 7%
Fatigue			3 5%				1 0.3%		5 3%	19 7%	29 7%
Drowsiness	125 3.9%										
Arthralgia		58 4%									
Hot flushes							2 0.6%				
Palpitations							1 0.3 %				

4.5.3 Neuropsychiatric ADRs

Neuropsychiatric ADRs were reported by 10 of all 33 studies (30%). Insomnia was reported in 8 of 10 studies. A total of at least 473 neuropsychiatric ADRs were reported across all the studies. Across all the studies, insomnia was the most reported ADR with 386 of 473 (81%). Depression , abnormal dreams, poor concentration and bipolar were also reported. Table 4.5.

Table 4.5 Studies reporting on neuropsychiatric ADRs

Number and percentage recorded	(Batista *et al*., 2019) Total=3185	(Cahn *et al*., 2020) Total=1433	(Calmy *et al*., 2020) Total=310	(Calza *et al*., 2020) Total=59	(Correa *et al*., 2020) Total=22	(Goh *et al*., 2019) Total=313	(Hoffman *et al*., 2017) Total=1073	(Stellbrink *et al*., 2013) Total=155	(Trottier *et al*., 2017) Total=275	(Walmsley *et al*., 2015) Total=419
Insomnia	190 6%	90 6.3%	1 (unspecified) 0.5%	13 22%	3 1.4%	10 3%	36 3.36%	3 2%	35 unspecified 13%	41 10%
Depression				6 10.2 %			7 0.7%			
Bipolar						1 0.3%				
Poor concentration							8 0.7%			
Abnormal dreams										29 7%

4.5.4 Dermatological ADRs

Skin ADRs were reported by 6 of all 33 studies (18%). Rash was reported in 4 of 6 studies. A total of at least 92 skin ADRs were reported across all the studies. Across all the studies, itching was the most reported (79%) ADR followed by rash.Table 4.6.

Table 4.6 Studies reporting on dermatological ADRs

Number and percentage recorded	(Batista *et al*., 2019) Total=3185	(Calmy *et al*., 2020) Total=310	(Correa *et al*., 2020) Total=22	(Goh *et al*., 2019) Total=313	(Stellbrink *et al*., 2013) Total=155	(Walmsley *et al*., 2015) Total=419
Itching	73 2.3%	15 (unspecified) 5%	Rash and itching Quanity unspecified			
Rash				1 0.3%	2 1.3%	4 1%
Dry skin				1 0.3%		

4.5.5 Other

Other ADRs recorded are included in Table 4.1 of study characteristics but of particular interest is weight gain (Bourgi *et al*., 2020, Cahn *et al*., 2020, Group *et al*., 2019, Pereira *et al*., 2021), High ALT (Calza *et al*., 2020, Goh *et al*., 2019), IRIS (Castagna et al., 2014).

4.5.6 Adverse Drug Reactions causing discontinuation

Nine studies recorded GI ADRs leading to discontinuation. Diarrhea was the most reported leading cause of DTG withdrawal/discontinuation. Across all studies reporting on discontinuation due to GI ADRs at least 2.3% of the participants had discontinued DTG. CNS ADRs causing drug discontinuation were headache and dizziness representing at least 3% across studies reporting discontinuation due to CNS ADRs. Insomnia was the leading cause of discontinuation. Other causes of discontinuation included renal function alteration (Cahn *et al*., 2020, Chin *et al*., 2020, Cid-Silva *et al*., 2017, Goh *et al*., 2019, Hoffmann *et al*., 2017), hepatitis (Castagna et al., 2014, Hoffmann *et al*., 2017), pregnancy (Ciccullo *et al*., 2019, Ciccullo *et al*., 2021), drug to drug interactions (Ciccullo *et al*., 2019, Ciccullo *et al*., 2021) , osteoporosis (Chan et al., 2020, Ciccullo et al., 2021) and IRIS (Mondi et al., 2019, Rossetti et al., 2019) .Although (Calmy et al., 2020) and (Ciccullo et al., 2021) reported ADRs causing death none of them were attributed to DTG.

4.5.7 Adverse Drug Reactions in Pregnancy

In a study conducted in SA and Uganda there were three Mother to child transmissions and no NTDs detected (Kintu et al., 2020). Calmy et al., 2020 also observed no NTDS due to DTG. Lockman and his colleagues reported pregnancy infections, pre-emclapsia and gestational diabetes due to DTG administration (Lockman *et al*., 2021). According to Zash et al., 2021 the duration of pre-pregnancy ART (years) was associated with higher baseline weight for DTG. Among women on ART at conception, low baseline weight in pregnancy was associated with increased risk of severe birth outcomes while high baseline weight was associated with increased risk of macrosomia and maternal hypertension (Zash et al., 2021).

All the publications included in this systematic review were observational studies. The sample sizes for most of the studies in this review were small, and only 15 publications were used. The lowest number of participants was 83, whereas the largest group size was 25,543 participants. Only the prevalence of foetal outcomes from mothers diagnosed with either WHO 2013 criteria or the IADPSG 2010 guideline was evaluated and the review found that the pooled prevalence of the foetal outcomes ranged from 2% to 11%. The subsequent chapter contains a detailed discussion of the findings in the current chapter.

4.6 Chapter Summary

Literature search was done through electronic search of online databases using search terms and a search strategy. Characteristics of included studies were described, the results from the search were reported and the risk of bias results were presented. The subsequent chapter contains a detailed discussion of the findings in the current chapter.

CHAPTER 5

DISCUSSION

5.1 Introduction

The regimen now recommended for primary treatment of HIV is now a DTG-based regimen. DTG is cheap, has an increased genetic barrier to resistance, and is accessible as a fixed-combination pill, and hence was introduced as the preferred first-line treatment for HIV by WHO in 2018 (WHO, 2018). This systematic review was carried out to assess and report the adverse drug reactions (ADRs) reported by patients taking DTG.Thirty three studies, with a total sample of 138 466 people received a DTG dose in at least 13 in countries. There was a wide variation across the studies. Studies were unevenly distributed with only a few studies representing Africa. This is the final chapter of this systematic review and it presents a discussion of the findings along with the limitations of the study and recommendations thereof.

For this study, only the risk of bias assessment was used in assessing the quality of the included studies. Each of the ten parameters in the risk of bias tool was allocated an equal weight and all the included studies in the final review were of either moderate or high quality. The overall assessment of bias was dependent on the number of high-risk parameters out of the ten parameters.

5.2 Adverse Drug Reactions Reported

A total sample of 138 466 people received a DTG dose in at least 13 in countries .Italy was the country with the highest rate of use of DTG. Most of the studies were conducted outside Africa in Europe. Only one study was conducted in South Africa (Kintu *et al*., 2020). The main objectives of all the included studies were indicative of the evaluation of the safety of DTG as monotherapy or even as part of a regimen. The mean age for all included studies was 38 years. The mean percentage for the race group which accounted for the highest population of patients who were administered DTG were Whites (72 %). Males (78%) accounted for the greater proportion of patients who received DTG. One study even reported 100% of the participants

being male (Min *et al*., 2011).This could be because DTG was cautioned in women of child bearing age because of the possibility of NTDs (WHO, 2019).

As previously mentioned, nausea and diarrhea were the most reported GI ADRs. Vomiting and abdominal pain were also dominant. Headache, dizziness and fatigue were reported in most studies reporting on CNS ADRs. Insomnia was the most neuropsychiatric ADR. Rash was reported in most studies reporting on skin ADRs. Of all the other ADRs recorded of particular interest is weight gain, high ALT and IRIS. The ADRs mentioned above are similar to the reactions described in most of the package inserts.

Other ADRs reported are: alopecia, nasopharyngitis, upper respiratory tract infection, syphilis , pharyngitis, general disorders, infections, nervous system disorders, myalgias, hypersensitivity, fever, cough and cases of diabetes mellitus

Nausea and diarrhea were the most reported GI leading cause of DTG withdrawal/discontinuation. CNS ADRs causing drug discontinuation were headache and dizziness. Insomnia was the leading neuropsychiatric cause of discontinuation. Other causes of discontinuation included renal function alteration, hepatitis, pregnancy , drug to drug interactions, osteoporosis and IRIS .

In relation to the number of people who substituted DTG in ART due to adverse reactions, it is important to note that, based on the data collected, nausea, diarrhea, and headaches (adverse reactions presented as reasons for changing the therapeutic regimen) are described as very common side effects in most drug package inserts.

In pregnant women on DTG the following were reported: mother to child transmissions , pregnancy infections, pre-emclapsia and gestational diabetes.

5.3 Implication for clinical practice

This study has demonstrated that the prevalence of adverse drug reactions can affect treatment continuity and thus cause treatment resistance. These findings can be employed by physicians to identify ADRs as early as possible to target and support earlier interventions for patients to be able to continue their treatment even after experiencing ADRs.

5.4 Implication for public health practice

Knowledge about the prevalence of ADRs to DTG may be of substantial public health relevance. Education to patients on the ADRs to expect as well as regular monitoring is imperative to ensure that patients continue their medication without any breaks. Also, monitoring the prevalence of ADRs is essential to plan and organize health and social services.

5.5 Implication for research

This review fills an important gap in the literature and highlights the need for continued research of DTG safety outcomes especially in pregnant women.

5.6 Limitations

The main limitation of this study is the diverse findings of the published studies. Data was widespread and not all the demographics were represented by the participants. Relevant publications were obtained using a search strategy that was based on the combination of various search terms adapted for each database. However, there may be a possibility of omitting certain publications that were not indexed properly under these terms.

This systematic review was limited in its selection of databases and its restriction to English publications. Also due to the heterogeneity in the data, it was not possible to undertake a meta-analysis.

Among some discontinuation cases, the reason of DTG discontinuation was unavailable in some cases.

5.7 Conclusion

This systematic review has demonstrated that the ADRs reported are similar to the reactions described in most of the package inserts as expected. The findings of this systematic review postulate that DTG has similar ADRs as those documented in published clinical trials. However the study is a reminder for health care professionals to be vigilant in monitoring and reporting adverse drug reactions in the HIV population.

Health care professionals should adopt tools to regularly monitor ADRs upon the initiation and withdrawal of DTG. Patients should be warned that the possible ADRs and prescribers should also be more aware of the ADRs to help make prescribing decisions more rational and effective.

It should be kept in mind that all medications present risks associated with their usage. Since adverse reactions are part of the risks associated with the consumption of a drug, it is not normally possible to anticipate situations where the use of a drug is advisable or not, based on only adverse reactions. In principle, an adverse reaction does not necessarily mean that there is a problem with a specific drug.

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Appendix 1

Draft Search Strategy using PubMed/Medline

SN	SEARCH TERMS
S1	Dolutegravir* OR Antiretroviral* OR Highly active antiretroviral OR Human immunodeficiency virus OR Acquired immunodeficiency syndrome
S2	Combination OR Regimen OR Therapy OR Therapeutic options OR Management options
S3	Adverse drug OR Adverse OR Unintended OR Unintentional OR Unwanted OR Unexpected OR Undesirable OR Toxic*
S4	Reaction* OR Effect* OR Event* OR Toxicity OR toxicities OR Harm*
S5	Pharmacovigilance OR Drug surveillance OR product surveillance" OR complication OR complications OR safety OR safe)*
S6	S1 AND S2
S7	S3 AND S4
S8	S6 AND S7
S9	S5 AND S6
S10	S8 OR S9

Appendix 2

Data extraction form

Table 1: Study Characteristics

Study characteristics	
Lead author	
Year	
Study design	
Sample size	
Setting	
Country of study conduct	
Details of Dolutegravir antiretroviral drugs regimen/combination/intervention	
Duration of treatment	
Comparator and funding source	

Table 2: Summary of Findings

Summary of findings	
Outcomes	
ADRs/events recorded	
Most common ADRs/events	

ADRs/ events requiring discontinuation	
Number of ADRs/ leading to death	

APPENDIX 3

Excluded Full Text articles with reasons for exclusion

Study	Reasons for exclusion
(Casado et al., 2019)	Study was done in people with hepatic disease which forms part of our exclusion criteria.
(Elzi et al., 2017)	Study participant criteria did not match our inclusion criteria
(Hongo et al., 2021)	Study participant criteria did not match our inclusion criteria
(Llibre et al., 2019)	Study participant criteria did not match our inclusion criteria
(J et al., 2016)	Study design did not match our inclusion criteria
(Olliges et al., 2021)	Study did not report on any ADRs
(Venter et al., 2020)	Study participant criteria did not match our inclusion criteria
(Waitt et al., 2019)	Study is a report of a study that we already included
(Walmsley et al., 2013)	Study is a report of a study that we already included

Appendix 4 – Acceptance letter

Dear Authors

March 30, 2022

SRP-2022-57811-Regular

1

2Department of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa

3Department of Pharmacy, Ho Teaching Hospital, Ho, Ghana

4

***Correspondence to:**

We would like to inform you that your manuscript ID SRP-2022-57811-Regular has been accepted for publication in **SYSTEMATIC REVIEWS IN PHARMACY (ISSN 0975-8453).**

TITLE: **Dolutegravir Reported Adverse Drug Reactions: A Systematic Review Protocol (SRP-2022-57811-Regular)**

Thanks for submission of your work with us.

Regards,

Professor Dr. Lucius,

Associate Editor

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Lesley Wadesango1*, Ebenez er Wiafe2,3, Kofi B oamah Mensah2,4, Varsha B angalee2 , Neelaveni Padayachee1

Department of Pharmacy and Pharmacology, U niv ersity of the Witwatersrand,

Johannesburg, South Africa

Department of Pharmacy Practice, K wame Nkrumah U niv ersity of Science and Technology,

Ghana

Lesley Wadesango, Department of Pharmacy and Pharmacology,

University of the Witwatersrand, Johannesburg, South Africa, E-mail: lwadesango@gmail.com