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Research Article

Dolutegravir Reported Adverse Drug Reactions: A Systematic Review Protocol

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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 This regimen has been replaced by the Dolutegravir (DTG)-based regimen since DTG has a high genetic barrier to resistance.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: 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.

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

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ABBREVIATIONS

3TC: Lamivudine; ADR: Adverse Drug Reaction; ART: Anti-Retroviral 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

INTRODUCTION

Human Immunodeficiency Virus (HIV) remains a worldwide public health issue (UNIAIDS, 2021). 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. 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 (Be in the know, 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 (Be in the know, 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 (DoH, 2020). 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 (DoH, 2020). 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 (Venter WDF, *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-

• Identification and classification of DTG-associated ADRs.

• Establishment of the safety and efficacy of DTG in the therapy of HIV with an emphasis on pregnant women.

• Identification and categorization of the demographic factors associated with DTG ADRs.

MATERIALS AND 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 (Whiting P, *et al*., 2016). 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.

RESULTS AND DISCUSSION

Criteria for considering studies for this review

Study design: 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 M and McGann H, 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 JP, 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 1 and 2*) 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

S.No	Study characteristics
1	Lead author
2	Year
3	Study design
4	Sample size
5	Setting
6	Country of study conduct
7	Details of dolutegravir antiretroviral drugs regimen/combination/intervention
8	Duration of treatment
9	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)

S.No	Outcomes
1	ADRs/events recorded
2	Most common ADRs/events
3	ADRs/events requiring discontinuation
4	Number of ADRs/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

The following requirements should be met by studies to be considered in the review-

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 (Pannucci CJ and Wilkins EG, 2010). Assessment is arranged into several domains that bias may be introduced (Pannucci CJ and Wilkins EG, 2010). A judgement/conclusion of a high risk of bias in any domain consequently means the whole study has a high risk of bias (Pannucci CJ and Wilkins EG, 2010).

The Newcastle-Ottawa Scale will be used to assess the risk of bias for non-randomized 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 G, *et al*., 2014). 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 G, *et al*., 2014).

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 (e.g. 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 IR and Aronson JK, 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.

CONCLUSION

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 on-going medication safety monitoring for Dolutegravir regimens.

LIMITATIONS OF THE STUDY

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.

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AUTHORS' CONTRIBUTION

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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