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The Impact of Selected Regimens of Chronic HIV-Antiretroviral Treatment on Glycemic Control Markers and Correlates: A Systematic Review and Meta-Analysis Protocol

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ABSTRACT

Background and Aim: Diabetes mellitus is one of the leading causes of morbidity and mortality among non-communicable diseases worldwide. The etiology of diabetes can be mainly attributed to factors such as genetic susceptibility, unhealthy diets, and chronic medications. Chronic medications such as HIV-antiretrovirals (ARVs) have been previously associated with the risks of developing metabolic complications. Hence, this protocol outlines the process for conducting a systematic review to investigate the association between chronic ARV treatment and the onset of metabolic syndrome complications.

Methodology and Analysis: The studies included in the systematic review are selected according to the inclusion and exclusion criteria. These studies are searched using search engines or databases such as PUBMED, GOOGLE SCHOLAR, MEDLINE, ScienceDirect, and EMBASE DATABASE. The articles that remained after full article screening will be assessed for bias using the Downs and Black checklist, and the data will be extracted. Additionally, heterogeneity tests will be conducted using both X^2 and I^2 tests, meta-analysis will be conducted using the Review Manager version 5.4 software (RevMan), and data will be presented in forest plots. Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) will be used to assess the strength of evidence in eligible reports.

Dissemination and Registration: The findings intend to give an insight into the ARVs as a risk factor for metabolic diseases and further elaborate on the regimen that possesses a high risk between the first and second regimens. This protocol has been registered on PROSPERO Database #CRD42024521322.

1 | Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by impaired glucose tolerance [1]. The impairment of glucose tolerance can arise from cellular insulin resistance or reduced insulin secretion [2]. The DM resulting from reduced insulin secretion from the pancreas is known as type 1 diabetes mellitus (T1DM) [3]. The one that emanates from cellular insulin resistance is known as type 2 diabetes mellitus (T2DM), which accounts for approximately 90% of all diabetes cases globally [4,

5]. However, both T1DM and T2DM are characterized by dysglycemia and other correlated complications, as shown in Table 2. The etiology of DM can be attributed to factors such as unhealthy lifestyles, genetic susceptibility, and chronic drug treatments (drug-induced metabolic disorders) [6–8]. Observational studies have revealed that enhanced anti-HIV treatment distribution correlates with increased DM cases globally [9].

Sub-Saharan Africa is the region with the highest burden of HIV infections in the African continent and across the world [10]. In 2017, Sub-Saharan Africa accounted for about 71% of people living with HIV globally [10]. The global statistics indicate that approximately 60% of people that are living with HIV are in antiretroviral treatment (ART), and again, about 67% of that population comes from the Eastern and Southern African regions [11, 12]. As a result, the sub-Saharan African region has the highest population on ART globally. The global response to the HIV pandemic includes encouraging all individuals with HIV infection to take ART regardless of their viral load or CD4 count [12]. Hence, South Africa has recently adopted the "test and treat" strategy [13]. The strategy aims to identify at least 90% of all infected individuals, enroll the diagnosed individuals with ART, and achieve 90% HIV viral suppression in all ART-receiving patients [14]. However, some ART regimes such as highly active antiretroviral therapy (HAART) have been previously associated with metabolic complications including dysregulation of glucose metabolism [15]. The HIV infection induces chronic inflammation, which is one of the factors implicated in the pathogenesis of insulin resistance. Moreover, metabolic syndrome is also driven by the chronic inflammatory state that often stems from conditions including obesity. The comprehension of the metabolic syndrome and HIV infection medication relationship remains important in preventing metabolic diseases such as T2DM. Hence, the recent guidelines for ART initiation involve the screening of non-communicable diseases, including diabetes, hypertension, and epilepsy [16]. The dispensation of ART can be done in either of the three regimens, namely, first-, second-, and third-line regimens, respectively. This depends on the clinical scenario presented by the patient during enrolment or if the other lower regimen fails to suppress the viral load. Table 1 indicates the drugs and combinations of drugs that make up the first- and second-line ART regimens as per the World Health Organization (WHO). Among these ART regimens (first- and second-line), the profile of the risk factors and level of the risk of developing metabolic complications remains unclear. This systematic review and meta-analysis protocol intends to demonstrate how the investigators will systematically synthesize results from eligible studies to determine the pooled effect size of chronic first- and second-line ART on dysglycemia. The findings may validate whether the newly formulated ART is associated with the onset of DM and related complications. In turn, it will provide high-quality evidence for policymakers and clinicians, leading to a better quality of life for the patients on ART and reducing the risks of the development of other metabolic complications, kidney and heart conditions.

1.1 | Review Questions

Primary: What is the association between chronic ARV regimens and dysglycemia?

Secondary: is there any association between a specific ART regimen and dysglycemia?

1.2 | Population/Participants Eligible

Population from the region of sub-Saharan Africa, aged 18 years and who have been on ARV medication for more than 5 years. Studies that used participants who have reported a history of metabolic syndrome complications will be excluded due to the increased risk of bias (refer to Table 2).

1.3 | Exposures Eligible

ARV medication for HIV, Regimen 1 and Regimen 2.

1.4 | Comparator

Population of the same age but HIV positive but not on ART.

Population of the same age, HIV negative, and not on ART.

1.5 | Outcome Measures Eligible

The outcome of interest is the metabolic and cardiovascular abnormalities in the selected population including fasting plasma glucose; oral glucose tolerance test (OGTT); random plasma glucose; HOMA Index; body mass index; lipid profile (LDL-C, HDL-C, TGs); blood pressure.

TABLE 1 | Drugs in ART Regimens 1 and 2 recommended by the World Health Organization.

ART regimen	Regimen components	Recommended for adults and adolescents, including women and adolescent girls who are of childbearing potential
First-line regimen	TDF + 3TC + DTG	Yes
First-line regimen	EFV + FTC + TDF	Yes
Second-line regimen	AZT + 3TC + ATV/r	Yes
Second-line regimen	TDF + FTC + LPV/r	Yes

Abbreviations: 3TC, Lamivudine; ATV/r, Atazanavir/ritonavir; AZT, azidothymidine; DTG, Dolutegravir; EFV, Efavirenz; FTC, Emtricitabine; LPV, Lopinavir/ritonavir; TDF, Tenofovir disoproxil fumarate.

TABLE 2 | Criteria for dysglycemia that are used in the envisaged systematic review [17].

Dysglycemia criteria		
Dysglycemic complications	**Diagnostic ranges**	**At least 2 of 5 of the complications**
Fasting blood glucose (FBG)	100–125 mg/dL	
Postprandial glucose (2-h glucose)	140–199 mg/dL	
Random blood glucose	< 200 mg/dL	
Dyslipidemia	Non-HDL-C: < 100 (mg/dL)/LDL-C: < 70 (mg/dL)	
Glycated hemoglobin (HBA1c)	< 6.5%	

Abbreviations: FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDL-C, low density lipoprotein cholesterol; RBG, random blood glucose.

1.6 | Review Outcomes

1.6.1 | Primary

- The mean and standard deviation of the dysglycemia criteria markers (Table 2) in participants exposed to ARV regimens versus those without exposure or between baseline and end-line measurements.

1.6.2 | Secondary

The regimen that has the highest mean difference.

2 | Methods and Design

2.1 | Study Design

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were used to formulate this protocol, which outlines the methods that will be used for the proposed systematic review and meta-analysis. Furthermore, this protocol has been registered with PROSPERO.

2.2 | Eligibility Criteria

The PEOs framework was used as the basis of the eligibility criteria. The studies that report the presence of metabolic and cardiometabolic complications in patients who are on ART, particularly the first and second regimens will be eligible for selection as narrated in Table 1 and the criteria for dysglycemia is narrated in Table 2.

2.3 | Study Design Eligible

Primary epidemiological observational study designs such as cross-sectional cohort and case–control studies. Clinical trials will also be eligible for selection depending on the data availability from nontreated control. Animal research studies will not be eligible for selection due to the uncertainty of chronic exposure to ARV medication. The studies will be selected based on the inclusion and exclusion criteria in Table 3.

2.4 | Time

The study must have been conducted between 2005 and 2024 to be eligible. This is the period where most African countries began to access the ART.

2.5 | Search Strategy

KEYWORDS/PHRASES: “Metabolic disease and HIV”; “Impaired glucose tolerance and HIV”; “Diabetes mellitus”; “Antiretroviral therapy”; “HIV-antiretroviral regimens” “Dysglycaemia”; “Antiretroviral therapy and lipid profile”; “hyperlipidemia and HIV”; and “impaired glucose tolerance”.

We will employ the following search engines/databases: PUBMED, GOOGLE SCHOLAR, ScienceDirect, and SCOPUS DATABASES. The Pan African Clinical Trial Registry will also be searched for potential studies. Additionally, reference lists of eligible studies will be scrutinized to prevent any inadvertent omissions.

2.6 | Study Selection Process

- After executing the search strategy, articles retrieved from the designated databases were imported into EndNote, where duplicate articles were identified and removed.
- Subsequently, two independent authors (Dr. M.W. Gamede and Mr A. Sosibo) will conduct the initial screening of titles and abstracts.
- Selected articles will undergo further evaluation through full-text review by the same two authors. In cases where full texts are not openly accessible, efforts will be made to obtain them through the university librarian.
- A third and fourth reviewer, Dr. M. Luvunoand Dr. N. Gumede, respectively, will serve as arbitrators where there are disagreements between the two reviewers.

3 | Data Extraction and Collection Process

Data extraction will be done independently for eligible full articles by two reviewers, extracting the general characteristics information and study outcome data. The criteria utilized to extract data will include the study identifiers, study design,

TABLE 3 | Inclusion and exclusion criteria.

Criteria components	Inclusion	Exclusion
Types of participants	This review will consider all studies that involve human subjects that are between the ages of 18 and 40 years old, both males and females. The focus will be on the metabolic side effects of chronic exposure to ARV regimens for at least 5 years, with metabolic diseases before the enrollment in ARV treatment, restricted to only first and second regimens.	Human subjects of age younger than 18 years and older than 40 years. Human subjects that fall under the desired age interval but with a history of metabolic complications before commencing ARV medication. Human subjects on ARV medication for less than 5 years Human subjects on any regimen other than Regimens 1 and 2.
Type of intervention	The interventions will include chronic HIV ART, demarcated on Regimens 1 and 2.	Interventions without the chronic ART Regimens 1 and 2.
Type of outcome measure	The primary outcome of interest will be the prevalence of dysglycemia in people on chronic ARV treatment either first or second regimens.	Any outcome they do not include dysglycemia or impaired glucose tolerance syndrome-related abnormalities.
Types of studies	For both review questions, this review will consider published research studies (clinical practice guidelines, narrative reviews, observational studies), government reports, health organization reports, case reports, randomized controlled trials, and unpublished research studies.	Animal experimental studies.
Reporting guidelines for studies	RCTs-consolidated standard of reporting trial (CONSORT). Observational studies (cohort, crossectional, and case–control studies), strengthing the reporting of observational studies in epidemiology. Case report: consolidated clinical cases reporting (CARE). Clinical practice guidelines: Apprisal of guidelines research and evaluation (AGREE).	Studies that do not conform to the respective style of reporting.
Publication date	This review will consider studies conducted in the past 20 years when ARVs were introduced in Sub-Saharan Africa.	Publications older than 20 years.
Language	The studies must be written in English to be considered.	Publications in another language besides English.
Location	Sub-Saharan Africa	Population outside of the Sub-Saharan Africa.

exposure, and outcome information. Microsoft Excel will be used to store and arrange the extracted data. Study identifiers will include the author's name, study title, publication type and date, publication details (journal name, volume, issue, and page numbers), and the location of the research, identified by the corresponding author's address. The data extraction will also be guided by the details of the participants, i.e., the age and gender of the participants at the time of research. The exposure extracted will include the name of the drug studied, the size of the population, and the report about metabolic complications post-chronic exposure to the drug. The mean, standard deviation, sample size, and characteristics of study participants of at least one of the targeted parameters (fasting plasma glucose, oral glucose tolerance test [OGTT], random plasma glucose, HOMA Index, body mass index, lipid profile [LDL-C, HDL-C, TGs], blood pressure) must be present in the publication for the data to be extracted.

3.1 | Risk of Bias Assessment

The quality assessment of the review will involve

- The researchers will assess the potential of the studies to be included and the third reviewer will assess the appropriateness of methods and assess the risk of bias using the Downs and Black checklist. The scores will be rated as follows: excellent if the score is 25, good if between 20 and

TABLE 4 | The reporting template for statistical parameters in the systematic review.

Study/ publication	Outcome	Number of participants	Standard error of the mean	Standard deviation (SD)	Variances	*p*-value

24, moderate if between 14 and 19, and poor for a score of 11–13 and very poor if less than 10.

- Publication bias: If there are $>=10$ studies in the meta-analysis, we will further investigate publication bias using funnel plots and Egger's test. If asymmetry is presently based on visual assessment, we will perform exploratory analyses to investigate and adjust this using trim and/or fill analysis.
- Heterogeneity: We will assess statistical heterogeneity in our meta-analysis using the *I*-squared statistic. If the *I*-squared is greater than 50%, we will be regarded as substantial heterogeneity.

3.2 | Strategy for Data Synthesis

We will calculate 95% confidence intervals for all discrete and co-morbid metabolic syndrome, diabetes, and hypertension prevalence measures using the Clopper–Pearson method.

Test for heterogeneity will be conducted using X^2 and I^2 from Review Manager version 5.4 software. For I^2, values between 0% and 100% will be obtained to determine whether reports have strong homogeneity or strong heterogeneity. Furthermore, when a value obtained is less than 25%, it will indicate strong homogeneity, 50% will indicate an average and a value obtained greater than 75% will indicate substantial heterogeneity.

A random-effects meta-analysis estimate method will be used to generate a forest plot displaying the mean difference with the standard deviation for each included study and the overall random-effects pooled estimate.

Assessment of the strength of evidence of eligible studies: Two reviewers (M.W.G. and A.M.S.) will assess the strength of evidence for eligible studies, while the other two reviewers will confirm the strength of evidence (N.G. and M.L.). Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) will be used to evaluate the strength of evidence in eligible reports and the summary of the finding (SoF) table will be created.

3.3 | Analysis of Subgroups or Subsets

For studies with several risk estimates of these conditions, the multivariable regression model risk will be chosen. Data from any article providing multiple study outcome measures for different population subgroups (HIV-positive and negative populations) will be extracted as separate studies and treated as separate datasets in the analysis.

4 | Statistical Presentation of the Outcomes

The outcomes obtained from the studies will be presented in a table format using the following statistical parameters: nammber of participants (*n*) Standard error of the mean ($M \pm SD$), standard deviation (SD), variances and the *p*-value derived from mean (see Table 4 for template of data reporting).

Author Contributions

Mlindeli Gamede: conceptualization, methodology, investigation, validation, funding acquisition, writing–original draft. **Mbulelo Aubrey Sosibo:** conceptualization, investigation, writing–review and editing, methodology, validation, formal analysis. **Nontobeko Gumede:** conceptualization, investigation, writing–review and editing, methodology, formal analysis. **Mluleki Luvuno:** conceptualization, investigation, writing–review and editing, methodology, formal analysis.

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Disclosure

The lead author Mlindeli Gamede affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. All authors have read and approved the final version of the manuscript Dr. Mlindeli Gamede had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Statement

The data that will be analyzed will be the data that is published and there will be no data collection from subjects. The authors declare that there will be no informed consent required to be signed and therefore no ethics approval required for the systematic review and meta-analysis.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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