Review Article
Volume 14:5, 2023

Journal of AIDS & Clinical Research

ISSN: 2155-6113 Open Access

The Incidences of Metabolic Syndrome Complications during Chronic HIV-Antiretroviral Treatment, a Focus on Selected Regimens: A Systematic Review and Meta-Analysis Protocol

Mlindeli Gamede[1*], Mbulelo Aubrey Sosibo[2] and Mluleki Luvuno[2]

[1]*Department of Physiology, University of Pretoria, Gauteng, South Africa*

[2]*Department of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa*

Abstract

Introduction: Metabolic syndrome complications are the leading causes of morbidity and mortality among non-communicable diseases in the world. The onset of these diseases can be attributed to factors such as genetic susceptibility, poor diets, and chronic medications. Antiretroviral (ARVs) for Human Immunity Immunodeficiency Virus (HIV) have been previously associated with complications such as central obesity which is a risk factor for the onset of the metabolic syndrome. This protocol outlines the process for conducting a systematic review to investigate the association between chronic ARVs 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, Science direct, and Embase Database. Articles will be screened against inclusion and exclusion criteria in two stages, first by the title and abstract, and second by the full article. The articles that remained after full article screening will be assessed for bias and the data will be extracted. The heterogeneity test will be conducted using both x^2 and I^2 tests, meta-analysis and data will be presented in forest plots, odds of ratio, and standard error of a mean.

Dissemination and registration: The current protocol paper narrates the methods that will be followed when conducting a systematic review and meta-analysis about the risks of ARVs in the development of metabolic diseases, focusing on ARV regimen one and regimen two. The results intend to give an insight about the ARVs as one of the risk factors of 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 # CRD42022316038

Keywords: Metabolic disease • Metabolic syndrome • Diabetes mellitus • Antiretroviral therapy • HIV antiretroviral regimens • CD4 count and viral load

Introduction

Metabolic Syndrome (MS) is a group of disorders that are associated with metabolisms such as Insulin Resistance (IR), central obesity, hypertension, dyslipidemia, non-alcoholic fatty liver diseases, and Type Two Diabetes Mellitus (T2DM) [1]. The pathogenesis of these conditions can be attributed to factors such as unhealthy lifestyles, genetic susceptibility, and chronic drug treatments (drug-induced metabolic disorders) [2-4]. Sub-Saharan Africa is the region with the highest burden of HIV infections in the African continent and across the world [5]. During the year 2017, Sub-Saharan Africa had about 75% of the world's HIV related deaths, 65% of the world's new infections, and 71% of people living with HIV. Globally, above 60% of people that are living with HIV are in Antiretroviral Treatment (ART), and the Eastern and Southern African regions had about 67% of those individuals on ART [6,7]. This makes the sub-Saharan African region to be the one with the highest population on ART. The global response to the HIV pandemic includes encouraging all individuals with HIV infection to take ART regardless of their viral load or CD4

***Address for Correspondence:** Mlindeli Gamede, Department of Physiology, University of Pretoria, Gauteng, South Africa, Tel: 782075704; E-mail: mlindeli.gamede@up.ac.za*

Received: 28 April, 2023, Manuscript No. JAR-23-97364**; Editor assigned:** 01 May, 2023, PreQC No. JAR-23-97364 (PQ); **Reviewed:** 16 May, 2023, QC No. JAR-23-97364; **Revised:** 17 September, 2023, Manuscript No. JAR-23-97364 (R); **Published:** 25 September, 2023, DOI: 10.37421/2155-6113.2023.14.964

count. Hence, South Africa has recently adopted the "test and treat" strategy [8]. This strategy aims to identify at least 90% of all infected individuals, 90% in enrolling diagnosed individuals in ART, and 90% in HIV viral suppression in all ART receiving patients [9]. However, some ART regimes such as Highly Active Antiretroviral Therapy (HAART) have been previously associated with metabolic complications including hyperlipidemia and reduction in circulating adipokines [10]. Hence, the recent guidelines for ART initiation involve the screening of non-communicable diseases including diabetes, hypertension, and epilepsy [11]. The dispensation of ART can be done in any 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 remain unclear. This review is aimed at compiling the data about metabolic syndrome complications associated with recently approved ART. Furthermore, this review will also compare the prevalence of these complications between the first-line and second-line Antiretroviral (ARV) regimens [12]. The findings of this review may indicate if the newly formulated ART is associated with the onset of metabolic syndrome complication. This will be determined by the prevalence of these complications in patients that have been chronically receiving ART in the revised formulations. This information might alert the clinicians to recommend lifestyle modification for patients that are initiated in the regimes. Lifestyle modifications include increasing physical activity, quitting alcohol, and healthy eating habits. These interventions might improve the quality of life for the patients on ART and reduce the risks of the development of other complications such as kidney and heart conditions.

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

Note: TDF: Tenofovir Disoproxil Fumarate; 3TC: Lamivudine; FTC: Emtricitabine; EFV: Efavirenz; LPV: Lopinavir/ritonavir; ATV/r: Atazanavir/ritonavir; AZT: Azidothymidine; DTG: Dolutegravir

Table 1. Drugs in ART regimen one and regimen two recommended by a world health organization.

Review questions

The purpose of this protocol is to elaborate on the design and the procedures that will be used in the proposed systematic review to answer the following research questions:

Primary: What is the association between chronic ARV regimens and the onset of metabolic syndrome complications?

Secondary: Which ART regimen that most associated with metabolic syndrome complication between regimen one and two.

Literature Review

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.

Eligibility criteria

The studies that are reporting the presence of metabolic and cardiometabolic complications in patients that are on ART, particularly the first and second regimens will be eligible for selection and the criteria for metabolic syndrome is narrated in Table 2.

Metabolic syndrome criteria		
Metabolic syndrome complications	**Diagnostic ranges**	
Insulin resistance	FBG (100-125 mg/dl), IGT (140-199 mg/dl), RBG (<200 mg/dl)	At least 3 of 5 of the complications
Hypertension	SBP: ≤ 130 mmHg; DBP: ≤80 mmHg	
Obesity	BMI: 30kg/m^2 or more	
Dyslipidemia	Non-HDL-C: <100 (mg/dl), LDL-C: <70 (mg/dl)	
HBA1c	<6.5%	

Note: FBG: Fasting Blood Glucose; IGT: Impaired Glucose Tolerance; RBG: Random Blood Glucose; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Metabolic Index; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol

Table 2. Criteria for metabolic syndrome that is going to be used in the envisage systematic review.

Study design eligible

Primary epidemiological observational study designs such as cross-sectional cohort and case control studies. The intervention studies will also be eligible for selection due to the availability of the data from non-treated control. Animal research studies will not be eligible for selection due to the uncertainty of chronic exposure to ARV medication.

Participants eligible

Population from the region of sub-Saharan Africa aged 18 years and, that have been on ARV medication for more than five years. The participants that have reported a history of metabolic syndrome complications will be excluded due to increased risk of bias.

Exposures eligible

ARV medication for HIV, regimen one and regimen two.

Outcome measures eligible

The outcome reports on the effects of any of the drugs used in the making of regimen one and regimen two on the metabolic and cardiovascular systems. 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.

Data representation

The forest plots, odds of ratio, and Standard Error of a Mean (SEM) will be used to present data.

Patient and public involvement

This study does not involves the patients and public.

Information sources

Search engines or database: PubMed, Google Scholar, Medline, Science direct, and Embase Database.

Website: clinical info.hiv.gov.

Organizations: World health organization, UNAIDS, center for aids research, UC San Diego treatment action campaign, centers for disease control and prevention, governments department of health reports

Search strategy

Keywords/phrases: ART regimen one, ART regimen two, ARV fixe dose combination, ARV induced metabolic syndrome, ARV induced metabolic syndrome, ARV induced glucose intolerance, ARV induced cardiometabolic diseases, and ARV induce energy dysregulation

Selection process

The selection process show in Table 3.

Criteria components	Inclusion	Exclusion
Study design	A meta-analysis, systematic review, randomized controlled Trial, cohort study, and test-tube lab research.	Animal studies.
Types of participants	This review will consider all studies that involve human subjects that are between the age 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 No history of cardiovascular and 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 cardio metabolic complications and dysregulation of energy homeostasis before commencing ARV medication; human subject on ARV medication for less than 5 years human subjects on any regimen other than regimes one and two.
Type of intervention	The interventions will include chronic HIV ART, demarcated on regimens one and two.	Interventions without the chronic ART regimens one and two.
Type of outcome measure	The primary outcome of interest will be the prevalence of metabolic syndrome complications in people on chronic ARV treatment either first or second regimens.	Any outcome they do not include metabolic syndrome related abnormalities.
Types of studies	For both review questions, this review will consider published research studies (Clinical practice guidelines, narrative reviews, and observational studies), government reports, health organization reports, case reports, and unpublished research studies.	Animal experimental studies.
Sample size	A minimum of 10 reported participants.	Participants less than 10.
Publication date	This review will consider studies conducted in the past ten years.	Publications older than ten years.
Language	The studies are written in English and those translated will be considered.	Publications in another language besides English.
Location	Global	N/A

Table 3. Inclusion and exclusion criteria.

Results and Discussion

Data extraction process

The criteria that will be used to extract data will include the study identifiers, study design, exposure, and outcome information. Study identifiers will include the author names, study title, publication type and date, publication details (journal name, volume, issue, and page numbers), and the location where the research was being conducted, identified by the address of the corresponding authors. 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 either metabolic or cardiovascular complications post chronic exposure to the drug. At least one of the targeted parameters must be present in the publication for the data to be extracted.

Two reviewers will independently review every record and report retrieved by the search strategy independently, while the third reviewer will serve as arbitrator where there are disagreements between the two reviewers. The publications that will be selected for the screening process will have to qualify through the criteria. The selection of eligible studies will be done in two folds, the first being the screening of the record and reports using the titles and abstracts using the questions in Table 4. The records that will meet the inclusion criteria will be taken forward to the second fold. The second fold will be a full article screening; this will be based on the questions in Table 5.

Screening domain	Selection		
	Yes-include	No-exclude	Unsure-include
Study design	Yes-meta-analysis, systematic review, randomized controlled trial, cohort study, and test-tube lab research.	No-the study is an animal study, commentary or editorial.	Unclear-the title or the abstract has the keywords but it doesn't show the study design.
Publication type	Yes-the study is a scholarly journal, WHO report, ADA reports, governmental reports or accredited non-governmental reports, higher education institution thesis. The publication has 500 words in length.	No-the publication is not a scholarly journal, WHO report, ADA reports, governmental report or accredited non-governmental report, higher education institution thesis, the publication has less than 500 words in length.	Unclear-the title and abstract do not show if the study is a scholarly journal, WHO report, ADA reports, governmental report or accredited non-governmental report, or higher educational institution thesis.
Population	Yes-The study population represents both patients on ART and those who are not on ART.	No-the study population represents only patients on ART.	Unclear-the title and the abstract don't have a clear narrative of the population but have the keywords required.
Exposure	Yes-the exposure is ARV drugs on both regimens one and two.	No-the exposure is ARV drugs not in regimens one and two.	Unclear-the tittle and abstract do not show the type of exposure.
Outcome	Yes–the outcome of interest is the metabolic syndrome complication associated with ART.	No-the outcome does not have metabolic syndrome complication.	Unclear-the title and abstract do not have a clear outcome.

Table 4. The screening process, assessing the articles one by one, pre-analysis.

Screening domain and question	Yes-include	No-exclude
Comparator: Does the research compare the development of metabolic disease between the population on chronic ART and those who are not be it HIV positive or negative or unknown.	Yes-the research compares the development of metabolic diseases in the population on ART with the population, not ART.	No-the research does not compare the development of metabolic diseases in the population on ART with the population, not ART.
Duplicate: Does the research use the different data set from the data set that is already included.	Yes-the research uses the new dataset for analysis.	No-the research used the dataset that has been previously used for analysis.

Table 5. The final step of screening the articles.

Data collection process

Selection-the research team will select studies and extract data following this process:

- Studies title screening of database search results by the primary investigator.
- Abstract screening of listed eligible studies for the study's population, exposure, comparator, and outcome settings using a designed Google form screening tool checklist. Any unresolved screening will be resolvedby the third reviewer.
- Eligible abstract screened studies will be screened for full article screening by two reviewers.
- Data extraction will be done for eligible full articles by two reviewers independently, one person for data extraction, and the

second person will verify at least 50% of studies for general characteristics information and 100% of studies regarding outcomes data.

Comparator, control: The population within the same age group, HIV positive or negative but not on ARV treatment and without a history of metabolic syndrome complications. However, data from HIV positive patients will be specified in the review.

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 Hoy, et al. tool.
- The study will include studies that are published in English and French language, this will improve the robustness of the study and will allow for the inclusion of francophone African countries. The French study publications that are eligible for the study will be translated to English by a Google translator.
- The minimum sample size for included studies will be calculated to differentiate estimates with good precision using the Clapper-Pearson confidence interval formula.
- **Publication bias:** If there are >=10 studies in the meta-analysis, we will further investigate publication bias using funnel plots and Eggerֹs 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.

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 me.

A random effects meta-analysis estimate will be used to analyze the estimated prevalence data that will be pooled, to estimate the mean of the distribution of effects. A forest plot will be generated displaying prevalence with the corresponding confidence interval for each included study and the overall random effects pooled estimate with its confidence interval.

Conclusion

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 population) will be extracted as separate studies and treated as separate datasets in the analysis.

Conflicts of Interest

None.

Author Contribution

Dr. Mlindeli Gamede was involved in conceptualizing, designing of the work, the acquisition, analysis, interpretation of data, drafted the manuscript and substantively revised the manuscript. Mr. Aubrey Sosibo was involved in the conception, design of the work, the acquisition of data Dr. Mluleki Luvuno was involved in conceptualizing, design of the work, analysis, interpretation of data, and substantively revised the manuscript. The whole team is involved in writing the actual systematic review and meta-analysis.

References

1. Md, Anna-Kaisa Niemi. "Neonatal presentations of metabolic disorders." *Neo Reviews* 21 (2020): e649-e662.
2. Di Marzo, Vincenzo, and Cristoforo Silvestri. "Lifestyle and metabolic syndrome: Contribution of the endocannabinoidome." *Nutrients* 11 (2019): 1956.
3. Botta, Margherita, Matteo Audano, Amirhossein Sahebkar, and Cesare R Sirtori, et al. "PPAR agonists and metabolic syndrome: An established role?." *Int J Mol Sci* 19 (2018): 1197.
4. Ebrahimi-Fakhari, Darius, Clara Van Karnebeek, and Alexander Munchau. "Movement disorders in treatable inborn errors of metabolism." *Mov Disord* 34 (2019): 598-613.
5. Dwyer-Lindgren, Laura, Michael A Cork, Amber Sligar, and Krista M Steuben, et al. "Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017." *Nature* 570 (2019): 189-193.
6. Baral, Stefan, Amrita Rao, Patrick Sullivan, Nancy Phaswana-Mafuya, and Daouda Diouf, et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment." *Lancet HIV* 6 (2019): e632-e638.
7. Ndung'u, Thumbi, Joseph M McCune, and Steven G Deeks. "Why and where an HIV cure is needed and how it might be achieved." *Nature* 576 (2019): 397-405.
8. Phanuphak, Nittaya, Pich Seekaew, and Praphan Phanuphak. "Optimising treatment in the test-and-treat strategy: What are we waiting for?." *Lancet HIV* 6 (2019): e715-e722.
9. Sohail, Maira, Emily Bess Levitan, Aadia Iftikhar Rana, and Sonya Lynn Heath, et al. "Estimating the first 90 of the UNAIDS 90-90-90 goal: A review." *J Int Assoc Provid AIDS Care* 19 (2020).
10. Meena, Durga S, Madhukar Rai, Surya K Singh, and Jaya Tapadar, et al. "Metabolic changes in the patients on second-line highly active antiretroviral therapy (HAART): A prospective cohort study from north India." *J Family Med Prim Care* 9 (2020): 1550.
11. Hopkins, Kathryn L, Khuthadzo Hlongwane, Kennedy Otwombe, and Janan Dietrich, et al. "Demographics and health profile on precursors of non-communicable diseases in adults testing for HIV in Soweto, South Africa: A cross-sectional study." *BMJ Open* 9 (2019): e030701.
12. Dobrowolski, Piotr, Aleksander Prejbisz, Alina Kurylowicz, and Alicja Baska, et al. "Metabolic syndrome-a new definition and management guidelines." *Arch Med Sci* 26 (2022): 99-121.

How to cite this article: Gamede, Mlindeli, Mbulelo Aubrey Sosibo and Mluleki Luvuno. "The Incidences of Metabolic Syndrome Complications during Chronic HIV-Antiretroviral Treatment, a Focus on Selected Regimens: A Systematic Review and Meta-Analysis Protocol." *J AIDS Clin Res* 14 (2023): 964.