Health Science Reports

WILEY

Health Science Reports
Open Access

METHODS AND PROTOCOLS OPEN ACCESS

The Prevalence of Cardiovascular Disease Risk Factors on Diabetic Human Immunodeficiency Virus-Infected Individuals on Antiretroviral Treatment: A Systematic Review and Meta-Analysis Protocol

Khanyisa Maswanganyi[1] | Amogelang Sedibe[1] | Nomusa Christina Mzimela[2] | Mlindeli Gamede[1]

[1]Department of Physiology, Faculty of Health Sciences, University of Pretoria, Gauteng, South Africa | [2]School of Laboratory Medicine and Medical Science, College of Health Sciences, University of Kwa-Zulu Natal, Durban, South Africa

Correspondence: Khanyisa Maswanganyi (u19167572@tuks.co.za)

Received: 16 August 2024 | **Revised:** 8 July 2025 | **Accepted:** 17 July 2025

Funding: Research reported in this systematic review and meta-analysis protocol was supported by the South African National Research Foundation (NRF) under a Thuthuka Grant TTK220324671.

Keywords: cardiovascular disease and ART | dyslipidaemia and HIV/ARVs | glycated hemoglobin and ART | hypercholesterolemia and HIV/ARVs | hypertension and ART | hypertriglyceridemia and ART | impaired fasting glucose and ART | obesity and ART | T2DM and ART

ABSTRACT

Background and Aims: People with human immunodeficiency virus (PLWHIV) have a higher prevalence of non-communicable diseases (NCDs) such as obesity, diabetes mellitus and cardiovascular diseases (CVDs). Previous studies have depicted that PLWHIV have these NCDs due to the predisposing risk factors of CVDs including dyslipidaemia, impaired fasting glucose, hypertension, obesity, and elevated glycated hemoglobin. Understanding the cumulative consequences of these disorders is critical in this population. Hence, the aim of this protocol is to narrate the methods and techniques that will be used to perform a systematic review and meta-analysis of the prevalence of various CVD risk factors among diabetic individuals receiving antiretroviral therapy. Furthermore, this review will explore the extent to which traditional and HIV-specific risk factors contribute to the beginning and progression of CVD in the HIV-positive population by merging available data.

Methods: Literature search will be conducted using selected keywords on databases such as PubMed, Google Scholar, Scopus, and Web of science to identify eligible publications according to the eligibility criteria. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines will be used for reporting and risk of bias will be assessed using the Cochrane Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I tool). Data synthesis and sensitivity analysis will be performed using RevMan software and strength of evidence will be assessed using the grading of recommendations assessment, development, and evaluation approach (GRADE) pro tool.

Ethical Considerations and Registration: This systematic review protocol is registered with PROSPERO (CRD42024524396) and it doesn't require any ethical clearance as it will use data from published reports.

Abbreviations: ART, antiretroviral therapy; CVDs, cardiovascular diseases; DM, diabetes mellitus; GRADE, grading of recommendations assessment, development, and evaluation approach; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NCDs, non-communicable diseases; PLWHIV, people living with human immunodeficiency virus; PRISMA, preferred reporting items for systematic reviews and meta-analysis; ROBINS-I, risk of bias in non-randomized studies of interventions; SAMRC, South African medical research council; SOF, summary of findings; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

1 | Introduction

Type 2 diabetes mellitus (T2DM) related complications including cardiovascular diseases (CVDs) are among the prominent causes of morbidity and mortality globally [1]. People living with human immunodeficiency virus (PLWHIV) have an increased prevalence of metabolic disorders [2]. These metabolic disorders may arise a result of the virus or might be due to chronic antiretroviral treatments [3]. According to the World Health Organization (WHO), the quantity of PLWHIV is estimated to be 38.4 million and approximately 75% of these individuals are given antiretroviral therapy (ART) [4]. Previous studies have indicated that approximately 10.3% of the adult population living with HIV have T2DM [5]. This prevalence is 3.8% higher in comparison to the general population [5]. Approximately 33.2% of people with T2DM have been diagnosed with CVDs [6]. The most common causes of death in diabetic individuals are cardiovascular-related complications [7]. Various risk factors of CVDs such as obesity, dyslipidaemia, hypertension, and hyperglycemia are often prevalent in diabetic individuals [8]. These factors also contribute to the development of atherosclerotic plaque thus increasing the risk of developing CVDs [9]. The use of chronic medication has been associated with side effects that lead to the development of various metabolic derangements [10]. Moreover, ART has been previously associated with metabolic complications including weight gain, dyslipidaemia, elevated cholesterol, and insulin resistance [11, 12]. Previous clinical studies have alluded that Highly active antiretroviral therapy (HAART) contributes to the prevalence of diabetes mellitus (DM) amongst PLWHIV [13]. Furthermore, nucleoside reverse transcriptase inhibitor (NRTI) based antiviral regimens have been associated with complications such as hyperglycemia, hypercholesterolemia, and elevated triglycerides which are the risk factors of CVDs [11, 14]. The global prevalence of HIV and T2DM is on an upward trajectory, therefore it is essential to investigate the potential interaction between these two conditions and how this interaction contributes towards the development of severe CVDs in PLWHIV [15, 16]. The correlations between CVDs and DM are widely documented in the general population, however, the prevalence of CVDs risks factors in HIV-positive and diabetic population receiving ART requires further investigations. Hence this protocol aims to narrate the methods and techniques that will be used to conduct a systematic review and meta-analysis to extensively to assess the prevalence of certain CVD risk factors on diabetic individuals who use antiretroviral treatment. This review aims to clarify the extent to which traditional and HIV-specific risk factors contribute to the onset and progression of CVD in the HIV-positive population by combining the existing data. The findings of this study will assist healthcare professionals with early cardiovascular disease risk identification through quantifying the prevalence of risk factors. Additionally, this will enhance the treatment strategies through personalized treatment strategies that target the risk factors identified to minimize or prevent cardiovascular disease development in diabetic individuals using ART.

TABLE 1 | Eligibility criteria (inclusion and exclusion).

Criteria components	Inclusion	Exclusion
Study design	Cross-sectional studies, registry studies, retrospective cohort studies, observational, case control studies, systematic reviews, and meta-analysis.	Animal studies, randomized controlled trials, ecological studies, prospective cohort studies.
Participants	Age: 18–50 Gender: Both male and female Diagnosis: T2DM Medical History: No history of pre-existing cardiovascular diseases before HIV-treatment ARV treatment: On chronic ARV treatment	Age: < 18, > 50 Diagnosis: Type 1 Diabetes Mellitus and gestational diabetes Medical History: history of pre-existing cardiovascular disease before HIV-treatment ARV treatment: On acute ARV treatment and/or other HIV unrelated treatment
Study intervention	The use of HIV-treatment drugs of interest and/or their respective components	Any treatment unrelated to HIV-treatment, HIV-treatment drugs outside of those of interest
Study outcomes	The presence of risk factors such as: obesity, hypertension, dyslipidaemia (hypercholesterolemia and hypertriglyceridemia), impaired fasting glucose, glycated hemoglobin	Studies that do not include assessment of the listed risk factors.
Sample size	A minimum of 100 participants involved in the study	Participants less than 100
Year of publication	2000–2024	Publications before 2000
Language	English	Any language outside of English
Location	Globally	N/A

2 | 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 prevalence of the risk factors of CVD in diabetic HIV-infected patients on ART?

Secondary: What is the most prevalent risk factor of CVD in diabetic HIV-infected patients on ART?

2.1 | Study Design

Participants: The systematic review will include studies that involve a minimum of 100 study participants, of all genders and reporting on HIV-infected adult (18–45) patients on HIV treatment.

Intervention: The use of HIV-treatment drugs of interest and/or their respective components

Comparators: Adult (18–45) HIV-infected patients on treatment will be compared to the control population within the same age group, HIV-positive or negative but not on ARV treatment and without a history of cardiovascular complications.

Outcomes: The study outcomes of this systematic review are expected to include the following: obesity, hypertension, dyslipidaemia, hypercholesterolemia, and hypertriglyceridemia.

3 | Methods

This systematic review protocol will be following the preferred reporting items for systematic reviews and meta-analysis for protocols (PRISMA-P) 2015 guidelines for reporting protocols (please refer to the additional files for review but not for publication for the completed PRISMA-P 2015 guidelines checklist).

3.1 | Criteria for the Selection of Studies for the Review

Identification of eligible studies for this review will be performed in accordance with the eligibility criteria outlined in Table 1.

3.2 | Search Strategy

The search strategy includes the implementation of a multiple search engine search, and the use of keywords to identify eligible studies. The details are described in the following subsections below.

3.3 | Search Engines

The search strategy that will be implemented involves searching electronic databases such as PubMed, Google Scholar, Scopus and Web of science with a search duration covering articles from 2000 to 2024 to identify eligible publications.

3.4 | Keywords

The keywords that will be used to refine the search on the databases include the following: T2DM and ART, obesity and ART, hypertension and ART, dyslipidaemia and HIV/ARVs, hypercholesterolemia and HIV/ARVs, hypertriglyceridemia and ART, impaired fasting glucose and ART, glycated hemoglobin and ART, Cardiovascular disease and ART. The Boolean operators to be used in search refinement include “AND” and “NOT” to refine the search based on the eligibility criteria.

3.5 | Identification of Eligible Studies

Three independent reviewers (K.M., A.S., & N.C.M.) will perform the selection process by assessing the titles, abstracts, and full texts of all article results obtained from the database search and select studies that match the eligibility requirements. If the three reviewers have a dispute on the selection of a research article, a fourth reviewer (MG) will be the designated mediator. The outcomes from the selection procedure and report screening will be presented using the PRISMA 2020 flowchart for systematic reviews and study selection [17] (Please see Table 2 attached under the additional files for review but not for publication section). In the event where there is ambiguous information, the authors of the articles will be contacted for clarification of the problematic information.

3.6 | Patient and Public Involvement

The public and patients will not be involved.

3.7 | Ethical Considerations

This study will make use of information from published literature therefore it will not require any ethical approvals.

3.8 | Data Management

3.8.1 | Study Records and Data Extraction

The reviewers (K.M., A.S., & N.C.M.) will utilize a Microsoft Excel spreadsheet to document the data extracted from studies deemed eligible. The extracted data will be categorized into various sections encompassing study identifiers, methodology, and outcome particulars. The study identifiers procured from the eligible studies will encompass author names, study titles, publication years, publication types, countries, and study settings. The methodology sections of the reported studies will

be evaluated based on categories such as study design, sample size, gender distribution, age demographics, population type, treatment modalities, and treatment duration. Additionally, outcomes of interest, including obesity, hypertension, dyslipidaemia, hypercholesterolemia, hypertriglyceridemia, impaired fasting glucose and glycated hemoglobin will be assessed and extracted.

3.8.2 | Data Simplification

Studies featuring the same treatment regimens will be grouped together. Furthermore, studies that report similar effects of the treatment regimens will also be grouped together.

3.8.3 | Risk of Bias

Assessing the risk of bias is crucial, identification and assessment of biases that are large enough to misrepresent study results [18]. The Cochrane Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool will be used to assess the risk of bias. This tool asses the risk of bias using the following items: (1) Bias due to confounding, (2) Bias in selection of participants into the study, (3) Bias in classification of interventions, (4) Bias due to deviations from intended interventions, (5) Bias due to missing data, (6) Bias in measurement of outcomes, and (7) Bias in selection of reported result [19]. If there is a discrepancy between independent evaluations of the risk of bias according to the items of the ROBINS-I tool from the three reviewers (K.M., A.S., & N.C.M.), a fourth reviewer (MG) will be designated as the mediator.

3.8.4 | Data Synthesis

Data synthesis is a process in which the findings of individual studies are merged and evaluated [20]. The reported data extracted from studies will be synthesized and meta-analyzed using Review Manager version 5.4 software. To estimate the mean of the distribution of effects, the estimated prevalence data will be pooled and analyzed using a random-effects meta-analysis. A Forest plot will be created, illustrating the prevalence and confidence interval for each included study, as well as the overall random-effects pooled estimate and confidence interval. The forest plot will be generated using an odd ratio and a confidence interval, with solid lines indicating the 95% confidence interval. Each reported study will be represented on the y-axis by a horizontal line that includes the primary author's name and the year of study. The weight of the study results will be automatically obtained from RevMan software and included in the Forest plot.

3.8.5 | Sensitivity Analysis

Sensitivity analysis is a method used to evaluate the strength of an assessment by examining the degree of which results are affected by a difference in methods or assumptions to identify the results' dependence on assumptions [21]. The RevMan software forest plot will be used to automatically determine heterogeneity, which will then be analyzed using the I-squared statistic. An I^2 value of 50 or above but less than 75 will be classified as average heterogeneity, and research with such average I^2 values will be included. Studies with significant heterogeneity ($< 25\%$, > 75) will be eliminated due to high risk of bias.

3.8.6 | Assessment of Strength of Evidence

Strength of evidence is used to determine the confidence level of whether the evidence mirrors the true effect [22]. The strength of evidence in the included studies will then be evaluated using the GRADE (grading of recommendations assessment, development, and evaluation approach). The quality of the evidence will be assessed in terms of bias risk, consistency, directness, precision, and publication bias. Each outcome's evidence will be classified as high, moderate, low, or extremely low. Following the completion of selection of eligible studies, a summary of the findings (SOF) will synthesized using a GRADE pro tool.

3.8.7 | Systematic Review Registration

This systematic review protocol is registered with the International Prospective Registry of Systematic Reviews (PROSPERO) Registration number: CRD42024524396.

Author Contributions

Khanyisa Maswanganyi: conceptualization, investigation, writing – original draft, methodology, writing – review and editing, formal analysis, project administration, visualization, data curation. **Amogelang Sedibe:** methodology, investigation, writing – review and editing. **Nomusa Christina Mzimela:** conceptualization, methodology, supervision, investigation, writing – review and editing. **Mlindeli Gamede:** conceptualization, funding acquisition, validation, methodology, supervision, resources, writing – review and editing.

Acknowledgments

South African Medical Research Council: Research reported in this systematic review and meta-analysis protocol was supported by the South African Medical Research Council (SAMRC) under a Self-Initiated Research Grant. The views and opinions expressed are those of the authors and do not necessarily represent the official views of the SAMRC.

National research Foundation South Africa: Research reported in this systematic review and meta-analysis protocol was supported by the South African National Research Foundation (NRF) under a Thuthuka Grant. The views and opinions expressed are those of the authors and do not necessarily represent the official views of the NRF. Grant Number: TTK220324671.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Transparency Statement

The lead author Khanyisa Maswanganyi 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.

References

1. P. Balakumar, K. Maung-U, and G. Jagadeesh, "Prevalence and Prevention of Cardiovascular Disease and Diabetes Mellitus," *Pharmacological Research* 113 (2016): 600–609, https://doi.org/10.1016/j.phrs.2016.09.040.

2. J. Jumare, P. Dakum, N. Sam-Agudu, et al., "Prevalence and Characteristics of Metabolic Syndrome and Its Components Among Adults Living With and Without HIV in Nigeria: A Single-Center Study," *BMC Endocrine Disorders* 23, no. 1 (2023): 160, https://doi.org/10.1186/s12902-023-01419-x.

3. M. Moyo-Chilufya, K. Maluleke, K. Kgarosi, M. Muyoyeta, C. Hongoro, and A. Musekiwa, "The Burden of Non-Communicable Diseases Among People Living With HIV in Sub-Saharan Africa: A Systematic Review and Meta-Analysis," *Eclinicalmedicine* 65 (2023): 102255, https://doi.org/10.1016/j.eclinm.2023.102255.

4. Organisation WH [Internet], Global HIV/AIDS statistics (2021), https://www.who.int/hiv/data/global_hiv_epidemic_response/en/.

5. A. C. Hernandez-Romieu, S. Garg, E. S. Rosenberg, A. M. Thompson-Paul, and J. Skarbinski, "Is Diabetes Prevalence Higher Among HIV-Infected Individuals Compared With the General Population? Evidence From Mmp and NHANES 2009–2010," *BMJ Open Diabetes Research & Care* 5, no. 1 (2017): e000304, https://doi.org/10.1136/bmjdrc-2016-000304.

6. T. R. Einarson, A. Acs, C. Ludwig, and U. H. Panton, "Prevalence of Cardiovascular Disease in Type 2 Diabetes: A Systematic Literature Review of Scientific Evidence From Across the World in 2007–2017," *Cardiovascular Diabetology* 17, no. 1 (2018): 83, https://doi.org/10.1186/s12933-018-0728-6.

7. A. S. M. Matheus, L. R. M. Tannus, R. A. Cobas, C. C. S. Palma, C. A. Negrato, and M. B. Gomes, "Impact of Diabetes on Cardiovascular Disease: An Update," *International Journal of Hypertension* 2013 (2013): 1–15, https://doi.org/10.1155/2013/653789.

8. B. M. Leon, "Diabetes and Cardiovascular Disease: Epidemiology, Biological Mechanisms, Treatment Recommendations and Future Research," *World Journal of Diabetes* 6, no. 13 (2015): 1246–1258, https://doi.org/10.4239/wjd.v6.i13.1246.

9. J. J. Joseph, P. Deedwania, T. Acharya, et al., "Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association," *Circulation* 145, no. 9 (2022): e722–e759, https://doi.org/10.1161/CIR.0000000000001040.

10. A. A. Verhaegen and L. F. Van Gaal, "Drugs That Affect Body Weight, Body Fat Distribution, and Metabolism," *Endotext [Internet]* (2019), https://www.ncbi.nlm.nih.gov/books/NBK537590/.

11. D. Thet and T. Siritientong, "Antiretroviral Therapy-Associated Metabolic Complications: Review of the Recent Studies," *HIV/AIDS-Research and Palliative Care* 12 (2020): 507–524, https://doi.org/10.2147/HIV.S275314.

12. V. Honnapurmath and V. Patil, "Antiretroviral Therapy-Induced Insulin Resistance and Oxidative Deoxy Nucleic Acid Damage in Human Immunodeficiency Virus-1 Patients," *Indian Journal of Endocrinology and Metabolism* 21, no. 2 (2017): 316, https://doi.org/10.4103/2230-8210.202029.

13. S. P. Lin, C.-Y. Wu, C.-B. Wang, T.-C. Li, N.-Y. Ko, and Z.-Y. Shi, "Risk of Diabetes Mellitus in HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy: A Nationwide Population-Based Study," *Medicine* 97, no. 36 (2018): e12268, https://doi.org/10.1097/MD.0000000000012268.

14. I. Antony, V. Kannichamy, A. Banerjee, A. B. Gandhi, S. Valaiyaduppu Subas, and P. Hamid, "An Outlook on the Impact of HIV Infection and Highly Active Antiretroviral Therapy on the Cardiovascular System–A Review," *Cureus* 12, no. 11 (2020): 11539, https://doi.org/10.7759/cureus.11539.

15. N. H. Cho, J. E. Shaw, S. Karuranga, et al., "IDF Diabetes Atlas: Global Estimates of Diabetes Prevalence for 2017 and Projections for 2045," *Diabetes Research and Clinical Practice* 138 (2018): 271–281, https://doi.org/10.1016/j.diabres.2018.02.023.

16. S. Rehman, E. Rehman, M. Ikram, and Z. Jianglin, "Cardiovascular Disease (CVD): Assessment, Prediction and Policy Implications," *BMC Public Health* 21, no. 1 (2021): 1299, https://doi.org/10.1186/s12889-021-11334-2.

17. D. Moher, L. Shamseer, M. Clarke, et al., "Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement," *Systematic Reviews* 4, no. 1 (2015): 1, https://doi.org/10.1186/2046-4053-4-1.

18. J. A. Hayden, D. A. van der Windt, J. L. Cartwright, P. Côté, and C. Bombardier, "Assessing Bias in Studies of Prognostic Factors," *Annals of Internal Medicine* 158, no. 4 (2013): 280–286, https://doi.org/10.7326/0003-4819-158-4-201302190-00009.

19. J. A. Sterne, M. A. Hernán, B. C. Reeves, et al., "Robins-I: A Tool for Assessing Risk of Bias in Non-Randomised Studies of Interventions," *BMJ* 355 (2016): i4919, https://doi.org/10.1136/bmj.i4919.

20. T. van den Berg, M. W. Heymans, S. S. Leone, et al., "Overview of Data-Synthesis in Systematic Reviews of Studies on Outcome Prediction Models," *BMC Medical Research Methodology* 13, no. 1 (2013): 42, https://doi.org/10.1186/1471-2288-13-42.

21. L. Thabane, L. Mbuagbaw, S. Zhang, et al., "A Tutorial on Sensitivity Analyses in Clinical Trials: The What, Why, When and How," *BMC Medical Research Methodology* 13, no. 1 (2013): 92, https://doi.org/10.1186/1471-2288-13-92.

22. "Definition of Levels of Evidence (LoE) and Overall Strength of Evidence (SoE)," *Global Spine Journal* 5, no. 6 (2015): 539, https://doi.org/10.1055/s-0035-1570346.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Table 2: PRISMA-P checklist.