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METHODS AND PROTOCOLS

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Prevalence of metabolic dysfunction-associated steatotic liver disease in people living with HIV and on antiretroviral treatment: A systematic review and meta-analysis protocol

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Abstract

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common hepatic condition globally. The prevalence of MASLD continues to increase, paralleling the consistent rising rates of risk factors such as obesity and type 2 diabetes. Literature suggests that human immunodeficiency virus-infected (HIV-infected) individuals may have an increased risk of developing MASLD due to a complex interplay of factors including antiretroviral therapy. Since the development and widespread use of effective antiretroviral therapy (ART), HIV-induced liver disease has continued to be the predominant cause of liver-related morbidity and mortality. This protocol serves to narrate the methods that will be employed in conducting the published literature search for the systematic review and meta-analysis which will report on the global prevalence of MASLD on people living with HIV and on ARV treatment.

Methods: The search of literature will be done using search engines or electronic databases including PubMed, Google Scholar, African Journal Online, and ResearchGate. Specific keywords will be used to search literature that has reported on the prevalence of MASLD among HIV patients receiving antiretroviral treatment, this will ensure the reproducibility of the study. Cross-sectional and longitudinal observational studies, retrospective cohort studies, clinical trial studies, meta-analyses, and systematic reviews that were published in the English language from 1990 to 2024 will be included. Animal studies will be excluded. Three independent reviewers will conduct the selection process and select studies that meet the eligibility criteria. A quality assessment tool, Downs and Blacks will be used to assess the risk of bias of the selected studies. A review manager will be used for meta-analysis of collected data and the Grading of Recommendations Assessment, Development, and Evaluation tool will assess the strength of evidence.

Ethics, dissemination, and registration: The review will not require ethical clearance as it will only include data that is publicly available in published reports. The results

of this review will be disseminated through publications. This study is registered with PROSPERO (CRD42024516814).

KEYWORDS

dyslipidemia and ARVs, dyslipidemia and HIV, metaboli dysfunction-associatedsteatotic liver disease and ARVs, metabolic dysfunction-associated steatotic liver disease and HIV, metabolic syndrome and HIV

1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a liver condition that is primarily characterized by the accumulation of fat in the liver cells, not associated to the excessive consumption of alcohol (<20 g/day for women and 30 g/day for men).[1,2] The severity of MASLD may range from liver complications such as ranging from hepatosteatosis, steatohepatitis hepatic fibrosis, and hepatic carcinoma.[1] The prevalence of MASLD is estimated to be more than 30% of the global population.[3] However this prevalence is reported to be significantly higher in western countries due to the unhealthy lifestyle habits and sedentary behavior that increase the risk factors associated with the development of MASLD.[4] The prevalence of MASLD is also suggested to be affected by gender and age.[5] Moreover, the metabolic disorders such as obesity and diabetes mellitus have been associated with the onset of MASLD.[6,7] The pathogenesis of MASLD and its progression is not fully understood.[8] However, the accumulation of fats and activation of inflammatory responses in the liver has been associated with hepatic insulin resistance.[9] The hepatic insulin resistance is normally not isolated from the systemic insulin resistance.[10] Furthermore, metabolic disorders including obesity and diabetes mellitus have been on an upwards trajectory in the past decades globally.[11] These metabolic conditions are directly linked the adipose tissue dysfunctions and systemic insulin resistance, the precursors of hepatic steatosis and liver inflammation.[12-14] This might contribute to the future MASLD pandemic and exacerbate the burden caused by the noncommunicable diseases on the health system. Chronic treatments for communicable disease such as antiretroviral therapy (ART) have also been associated with the onset of metabolic disorders. Moreover, people living with HIV (PLWHIV) have been reported to have a high prevalence of liver-related morbidities.[15] These morbidities may be attributed to direct drug cytotoxicity, hypersensitivity reactions involving the liver, or mitochondrial toxicity of some drugs in the regimens of ART.[16] The development and effectiveness of highly active antiretroviral therapy (HAART) came with significantly increased life expectancy of PLWHIV.[17] However, HAART regimens have also been associated with the development of various metabolic complications, particularly in lipid and glucose metabolism such as insulin resistance, hypercholesterolemia, and hypertriglyceridemia, which are dysmetabolic states encompassed by the metabolic syndrome and can subsequently increase the risk of cardiovascular disease.[18,19] Modern ART is dispensed as single-tablet regimens comprising of a combination of at least three antiretroviral drugs from different classes. Currently recommended first-line single-tablet ART regimens consist of two nucleoside reverse transcriptase inhibitor (NRTI) drugs coformulated with a third non-nucleoside reverse transcriptase inhibitor (NNRTI), boosted protease inhibitor (PI) or integrase inhibitor (INSTI) drug. While modern antiretroviral drugs are generally well tolerated and with an improved drug safety profile, long-term use has been notably linked with adverse events often implicating the liver, thereby predisposing HIV patients to drug-induced liver injury.[20] The use of NRTIs is linked to mitochondrial toxicity resulting from the inhibition of mitochondrial DNA polymerase-γ, which can lead to the development of hepatic steatosis and lactic acidosis.[20,21] To varying degrees, the use of NNRTIs is associated with hepatotoxicity through hypersensitivity reactions involving the liver during the course of treatment. Nevirapine (NVR) and efavirenz (EFV), NNRTIs, have been found to account for a hepatotoxicity risk of approximately 18% and 8%, respectively.[22] Moreover, NVR is suggested to be the only NNRTI associated with the development and/or progression of liver fibrosis (LF), while the contributory role of other available NNRTIs as well as INSTIs remain inconclusive due to the lack of data.[21] However, published studies on the effects of NVR on LF are not consistent, one study found NVR-related severe LF while in contrast, another study demonstrated low risk of NVR-related significant LF and similarly another study suggested a protective function of NVR against LF progression.[23-25] There is also an inconsistency with regard to the effect of INSTIs on liver steatosis, while some studies suggested an increased risk, and other studies suggested a reduced risk of liver steatosis with the use of INSTIs.[21] The use of PIs has been markedly linked with hepatotoxicity, insulin resistance, dyslipidemia, and lipodystrophy, these are metabolic changes which can increase the risk of hepatic steatosis.[20] Similar to INSTIs, evidence linking PIs to LF is conflicting.[20] Taken together, more research is needed to clarify the relationship between some antiretroviral drug classes and the risk of hepatic steatosis and fibrosis, to curb the rising rates of liver disease. Considering that ARVs are administered in combination, the role or contribution of modern HIV combination therapy regimens on the development of MASLD has yet been correlated in a systematic review. Hence, this protocol aims to narrate the methods and techniques that will be used to systematically search and analyze the studies that reported on the prevalence and risk factors of MASLD in PLWHIV. The envisage systematic review and meta-analysis will provide the prevalence of overt MASLD and the occurrence of the selected risk factors of MASLD including markers of dyslipidemia and liver damage in

PLWHIV. Moreover, the envisage systematic review and meta-analysis will further report on the prevalence of MASLD in sub-Saharan Africa in the people living with HIV and on ARVs.

1.1 | Research question

1. What is the estimated global prevalence of MASLD in adult HIV-infected individuals receiving antiretroviral therapy?

1.2 | Objectives

1. To determine the global prevalence of overt MASLD and the occurrence of the risk factors of MASLD in HIV-infected individuals receiving ART.
2. To determine the estimated prevalence of MASLD in HIV-infected individuals receiving ART in sub-Saharan Africa.

2 | METHODS

This systematic review protocol will be prepared in line with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2015 guidelines for reporting protocols.[26]

2.1 | Systematic review protocol registration

This systematic review protocol has been registered with the International Prospective Registry of Systematic Reviews (PROSPERO) (CRD42024516814).

2.2 | Criteria for considering studies for the review

Identification of eligible studies for this review will be done following the eligibility criteria outlined in Table 1.

2.3 | Study design

2.3.1 | 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.

2.3.2 | Intervention

HIV treatment (ART).

TABLE 1 Eligibility criteria (inclusion and exclusion).

Criteria components	Inclusion	Exclusion
Study design	Cross-sectional and longitudinal observational studies, retrospective cohort studies, clinical trial studies, systematic reviews, and meta-analysis	Animal studies
Participants	Age: 18-45	Age: <18, >45
	Gender: Both male and female	Medical history: History of pre-existing metabolic conditions before HIV-treatment
	Medical history: No history of pre-existing metabolic conditions before HIV-treatment	ARV treatment: On treatment for less than 3 years and/or other HIV-unrelated treatment
	ARV treatment: On treatment for a least 3 years	
Study intervention	The use of HIV-treatment drugs of interest and/or their respective components	Any treatment unrelated to HIV-treatment and HIV-treatment drugs outside of those of interest
Study outcomes	MASLD prevalence, defined by the presence of markers of hepatic steatosis, steatohepatitis (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). The markers of dyslipidemia (triglycerides and cholesterol)	Outcomes that are not indicative of MASLD prevalence
Sample size	A minimum of 100 subjects involved in the study	Subjects less than 100
Year of publication	1990s–2023 (Present)	Publications older than 1990s
Language	English	Any language outside of English
Location	Globally	N/A

2.3.3 | Comparators

HIV positive/negative individuals not receiving ART, without any pre-existing liver disease.

2.3.4 | Outcomes

The study outcomes of this systematic review are expected to include the following:

1. Primary outcome: Prevalence of MASLD in PLWHIV and receiving ART.
2. Secondary outcomes: Selected metabolic complications defining MASLD including, macrovesicular and/or microvesicular hepatic steatosis, elevated liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST), markers of dyslipidemia (triglycerides and cholesterol).

2.4 | Search strategy

2.4.1 | Search engines

The search strategy will be used to find eligible publications by searching electronic databases such as PubMed, Google Scholar, African Journal Online, and Research Gate.

2.4.2 | Keywords

The keywords that will be used to filter out the available information are as follows: metabolic dysfunction-associated steatotic liver disease and HIV; metabolic dysfunction-associated steatotic liver disease and ARVs; metabolic syndrome and HIV; dyslipidemia and HIV; dyslipidemia and ARVs.

2.5 | Identification of eligible studies

Three independent reviewers (AS, KM, & NCM) will conduct the selection process by screening the titles, abstracts, and full texts of all the obtained article results retrieved by the search strategy and thereafter select studies that meet the eligibility criteria. Where there are disagreements between the three reviewers related to the selection of studies, a fourth reviewer (MWG) will be consulted as mediation. The results based on selection process and screening of reports will then be presented using the PRISMA flowchart for systematic reviews. In cases where information in a selected article remains unclear, the author will be contacted at least twice for clarification before the study is excluded.

2.6 | Patient and public involvement

The public and patients will not be involved.

2.7 | Data management

2.7.1 | Study records and data extraction

The three reviewers (AS, KM, & NCM) will utilize a Microsoft Excel file to record the extracted data from the studies that have been selected as eligible. The fourth reviewer (MWG) will serve as an arbitrator where there is a disagreement between the reviewers and confirm if all selected studies meet the inclusion criteria. The extracted data will be divided into different categories including the study identifiers, methodology, and outcome information. The study identifiers that will be obtained from the eligible studies will include the author names, study title, year of publication, publication type, country, and study setting. The methodology of the study reported will be considered with the categories including the study design, sample size, gender, age, population type, treatment used, and duration of treatment. The outcome of interest including the prevalence of MASLD defined by the presence of steatosis in the liver will be considered and extracted.

2.7.2 | Data simplification

If there is variation of prevalence due to the type of antiretroviral medicine used, studies that report on the same treatment regimen will be grouped together.

2.7.3 | Risk of bias

The Downs and Black checklist will be utilized to evaluate the potential risk of bias.[27] Three reviewers (AS, KM, & NCM) will analyze the eligible reports using the checklist tool, which is reporting bias (10 items), external validity (three items), internal validity (six items), and selection bias (seven items). The scores for each domain will be rated as excellent (25–26), good (20–24), moderate (14–19), poor (11–13), and very poor (<10). If disagreement arises between independently evaluation of the risk of bias according to the four domains of the Downs and Black, from the three reviewers (AS, KM, & NCM), a fourth reviewer (MWG) will be consulted as mediation.

2.7.4 | Data synthesis

A Review Manager version 5.4 software will be utilized for the meta-analysis of reported data. 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. An odd ratio and confidence interval will be utilized to generate the forest plot, with solid lines representing the 95% confidence interval. Each reported study will be represented on the y-axis by a horizontal line with the primary author and year of study listed. The weight of the study results, which will be obtained automatically using RevMan software, will also be included in the forest plot.

2.7.5 | Sensitivity analysis

The RevMan software forest plot will be used to automatically calculate heterogeneity and based on the I-squared statistic; the heterogeneity of individual studies will be assessed. An I^2 value equal to and greater than 50 but less than 75 will be considered as an average heterogeneity reading and studies with such average I^2 values will be included. Studies with strong heterogeneity (<25% and >75) will be excluded as they will be considered high risk based on the risk of bias.

2.7.6 | Assessment of strength of evidence

The strength of evidence on the included studies will then be assessed using the grading of recommendations assessment, development, and evaluation approach (GRADE).[28] The quality of evidence will be evaluated in terms of bias risk, consistency, directness, precision, and publication bias. Each outcome's evidence will be assessed as high, moderate, low, or extremely low. Furthermore, using a GRADE pro tool, a summary of the findings (SOF) table will then be created.

3 | DISCUSSION

In this systematic review and meta-analysis, publicly available and globally published studies that report on the prevalence of MASLD among HIV-infected individuals receiving ART will be examined. The findings of the review will then be used to focus particularly on Africa to determine the implications of the dramatic high rates of HIV infection and treatment, and the subsequent development of MASLD. This review will provide evidence-based knowledge of the link between HIV and MASLD, and further emphasize the need to screen for liver disease after an HIV diagnosis, and as well as encourage regular monitoring to prevent development and/or progression of liver disease.

AUTHOR CONTRIBUTIONS

Amogelang Sedibe: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing. **Khanyisa Maswanganyi**: Conceptualization; investigation; writing—review and editing; methodology. **Nomusa Christina Mzimela**: Conceptualization; investigation; writing—review and editing; methodology. **Mlindeli Gamede**: Conceptualization; investigation; funding acquisition; writing—review and editing; methodology; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data availability is not applicable to this article as no new data were created or analyzed in this study.

TRANSPARENCY STATEMENT

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.

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