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Prevalence of metabolic syndrome, discrete or comorbid diabetes and hypertension in sub-Saharan Africa among people living with HIV versus HIV-negative populations: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Metabolic disorder and high blood pressure are common complications globally, and specifically among people living with HIV (PLHIV). Diabetes, metabolic syndrome and hypertension are major risk factors for cardiovascular diseases and their related complications. However, the burden of metabolic syndrome, discrete or comorbid diabetes and hypertension in PLHIV compared with HIV-negative population has not been quantified. This review and meta-analysis aims to compare and analyse the prevalence of these trio conditions between HIV-negative and HIV-positive populations in sub-Saharan Africa (SSA).

Methods and analysis The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guides the methods for this study. Eligibility criteria will be published original articles (English and French language) from SSA that present the prevalence of metabolic syndrome, discrete and/or comorbid diabetes, and hypertension comparisons between PLHIV and HIV-negative populations. The following databases will be searched from January 1990 to February 2017: PubMed/Medline, EBSCOhost, Web of Science, Google Scholar, Scopus, African Index Medicus and Cochrane Database of Systematic Reviews. Eligibility screening and data extraction will be conducted independently by two reviewers, and disagreements resolved by an independent reviewer. Methodological quality and risk of bias will be assessed for individual included studies, while meta-analysis will be used to estimate study outcomes prevalence according to subgroups. Sensitivity analysis will also be performed to further test the robustness of the findings.

Ethics and dissemination This proposed study does not require ethical approval. The results will be published as a scientific article in a peer-reviewed journal, and presented at conferences and to relevant health agencies.

Trial registration number PROSPERO registration number (CRD42016045727).

Strengths and limitations of this study

- Understanding the differences in the burden of metabolic syndrome (and its subcomponents), diabetes and hypertension between HIV-positive and HIV-negative populations.
- This review contributes to informing public health actions needed for non-communicable disease (NCD) comorbidities and population health.
- Stringent adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement guidelines.
- Inclusion of non-English-language (French) published studies and literature to increase the representativeness of the findings in the region.
- A limitation is the lack of single definition criteria of metabolic syndrome over the study period; thus, hypertension and diabetes are inclusive of the subcomponents.

INTRODUCTION/RATIONALE

The epidemiological transition model developed by Omran argued that infectious and parasitic diseases will decrease, while chronic and ageing-related conditions and diseases will increase, these changes being driven by social factors and lifestyles.[1 2] The generalisation of Omran's model to low-income and middle-income countries (LMICs) is not applicable due to the increased incidence of chronic diseases, an ageing population with related health conditions and a resurgence of infectious diseases among this population.[2 3] Frenk *et al*[3] envisioned the protracted epidemiological transition model as being able to describe the health inequality, morbidity and mortality by social class, this being applicable to LMICs that are faced with prolonged periods of both infectious and chronic diseases.[4] Sub-Saharan Africa (SSA) is also undergoing a demographic transition, with increased population size and growth,

changing age structures, inequality, urbanisation and rural exodus.[5] In addition, these countries now have the highest prevalence of HIV/AIDS, with many people being on antiretroviral treatment.[6] Within this context, the prevalence of non-communicable diseases (trio) is increasing and is projected to exceed that of communicable diseases by 2030,[7] due to epidemiological and demographic transitions.[8]

The leading non-communicable conditions are cardiovascular diseases (CVD) and diabetes, with hypertension being a major risk factor.[8] Diabetes is a metabolic condition that affects mainly adults around the world, specifically type 2, which is the most prevalent, accounting for approximately 95% of all cases.[9 10] Diabetes and hypertension are also major causes of increased morbidity, mortality and other health complications globally.[11 12] The global prevalence of hypertension is 20%–50%,[13] while estimates suggest that diabetes will affect approximately 642 million people by 2040, mostly among adults of age 20 years and above.[13–16] Patients with diabetes have an increased incidence of hypertension and other health risks,[10 17] the predisposing risk factors being obesity, high carbohydrate and sugar diets, physical inactivity and other related factors clustering into metabolic dysfunctions.[18 19]

Metabolic syndrome (Mets) is the clustering of risk factors for the development of type 2 diabetes and CVD,[20] which has an increasing prevalence in SSA.[21 22] This condition and its risk factor represents clinical concept used to indicate pre-diabetes and prehypertension.[23] Mets develops from clustering conditions and the risk factors of diabetes, hypertension and CVDs. The relationship between Mets, diabetes and hypertension is complex, as high glucose intolerance and blood pressure are criteria for Mets diagnosis, while diabetes and hypertension are discretely health conditions. Nevertheless, there are a variety of definitions for Mets, each with criteria that influence its diagnosis and complexity.[9 24] The influence of fat redistribution, such as visceral obesity, increased waist:hip ratio and adipose tissue, is an established presentation of cardiometabolic traits.[25] Obesity is a major contributor to increased glucose intolerance, high blood pressure and lipid disorders that result in metabolic dysfunction.[26] However, not all overweight and obese individuals are diabetic, and not all patients with diabetes are overweight or obese.[25] Abdominal obesity is a consistent marker of Mets diagnosis,[27] and the prevalence of Mets among patients with diabetes and hypertension rises with an increasingly ageing population.[28]

These trio conditions (diabetes, hypertension and Mets) are highly prevalent among the HIV-infected population as a result of their long-term dependence on antiretroviral therapy (ART) regimen,[29 30] which has been shown to be a contributing factor to developing metabolic complications, such as lipodystrophy, dyslipidemia and insulin resistance.[31 32] Modifiable lifestyle risk factors similar to the general population are also a major contributing factor to increasing metabolic disorders.[33] Hypertension is a common AIDS-unrelated condition among HIV-positive persons, with an estimated prevalence of between 4.7% and 54.4% in high-income countries and 8.7%–45.9% in LMICs.[34] These trio conditions have emerged as one of the contributors to non-AIDS-related causes of morbidity and mortality globally.[35] The causative and predisposing factors of developing these conditions are similar among all populations, regardless of HIV status, and include sociodemographic change, an aged population, globalisation, overweight, obesity and sedentary lifestyles.[16 36 37] Globally, non-communicable disease (NCD) comorbidities in people living with HIV (PLHIV) is high, and while its prevalence is similar to the general population that is not infected, those who are infected also have to contend with the dual burden of NCD and other infectious diseases.[38]

Studies have shown that metabolic conditions are more common among PLHIV due to the HIV infection itself and the ARV regimen; however, these have been done mainly in developed countries.[39–41] Empirical evidence about the differential cardiometabolic traits between people infected and uninfected with HIV is limited and conflicting, especially for SSA, and a consolidated estimate will assist in assessing the need for monitoring and managing metabolic dysfunction in HIV-infected populations.[42] A narrative systematic review indicated the difference in the prevalence of hypertension among HIV-positive populations in developed countries to be between 4.7% and 54.4%, and ranging between 8.7% and 45.9% in LMICs.[34] However, most of the studies included in the review were from developed countries, the focus being on PLHIV, with no comparative HIV-negative control groups. A review without a meta-analysis on the prevalence of Mets among PLHIV reported a 30% mean prevalence in Africa.[43] With only a few studies being from South America, Africa and Asia, the result could be an overestimation or underestimation.

Most reviews with or without meta-analysis that have explored the prevalence of diabetes, hypertension and/or Mets have focused on PLHIV, without a comparable HIV-negative baseline.[42 44–47] Moreover, data comparing the burden of NCD among the HIV-positive and HIV-negative populations (in the same setting) are limited, especially in the era of increasing longevity due to ART roll-out and the epidemiological transition taking place in SSA. The growing burden of chronic diseases (including chronic HIV) will further strain the region's weak healthcare infrastructure, resources and services, and increase healthcare expenditure in coming years.[48] Understanding the burden of Mets (and its individual components) among PLHIV is essential to maintaining the gains made against acute HIV morbidity and mortality.[38] This proposed review therefore attempts to unpack this multimorbidity aspect by HIV status, thereby increasing the accuracy of burden estimation, which is needed for effective healthcare system planning in HIV endemic settings.[49 50] This study will conduct a systematic review and meta-analysis specific to SSA, which bears a high dual burden due to a protracted epidemiological

transition. The risk of metabolic disorders in HIV-positive people, compared with HIV-negative populations, is an important research priority area,[51] as relevant data are limited, especially in the era of increasing access to ART in SSA. This review will attempt to highlight the unique contribution of understanding the burden of Mets (and its subcomponents) and discrete or comorbid diabetes and hypertension by comparing the prevalence between HIV-positive and HIV-negative populations in SSA, which has not been explored, to the best of our knowledge.

The aim of this study is to conduct a systematic review and meta-analysis of studies documented from 1990 to 2017 to determine the differential prevalence of Mets, discrete and/or comorbid diabetes and hypertension between HIV-positive and HIV-negative populations in SSA.

Research questions

The proposed review will seek to address the following research questions:

1. What is the prevalence of diabetes among adults in SSA with and without HIV infection?
2. What is the prevalence of hypertension among adults in SSA with and without HIV infection?
3. What is the prevalence of Mets among adults in SSA with and without HIV infection?
4. What is the prevalence of comorbid diabetes and hypertension among adults in SSA with and without HIV infection?

METHODS

Eligibility criteria (inclusion and exclusion)

Inclusion criteria

The review will include studies on the prevalence of Mets (and its subcomponents), type 2 diabetes and hypertension discretely or as comorbid conditions, and exclude those on other related cardiovascular and non-communicable diseases conditions. The following factors will apply:

1. Study designs: This review and meta-analysis will include randomised control trials, cross-sectional, case–control and cohort studies that assess the prevalence of Mets (and subcomponents), discrete and/or comorbid diabetes and hypertension among PLHIV and/or HIV-negative populations in SSA. Included studies will be those conducted with both or any of the study outcomes.
2. Study participants: Adult (age 18 years and older) human participants residing in SSA, regardless of their ethnic background.
3. Study outcome definition: Outcomes will be defined through self-report, use of antihypertensive and cholesterol-lowering and antidiabetic drugs. The WHO/IDF (International Diabetes Federation) recommendation on the definition and diagnosis of diabetes mellitus for diabetes will be used.[52] The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure will be used for hypertension diagnosis definition.[53] The diagnosis criteria for Mets will be that of the IDF,[54] National Cholesterol Education Program-Adult Treatment Panel III definition (NCEP ATP III),[55] European Group for Study of Insulin Resistance[56] and WHO criteria.[55] Refer to table 1 for outcome definitions.
4. Time-period: Published and grey literature and unpublished data reported between 1 January 1990 and 28 February 2017 will be included, taking into account changes in the definition of diabetes and Mets over this period.
5. Study settings: Community or population-based settings, health facilities settings within rural and urban areas of SSA will be included.
6. Study languages: All studies reported in English and French languages within any SSA country will be considered. The inclusion of French-language articles will increase the precision of combined estimates of effect size, study result generalisation and applicability,[57] and enhance the study coverage and robustness across SSA. A French-speaking person will assess studies published in French to ensure that the content and results are not over-rated or under-rated, after which they will be translated into English.
7. HIV status: Studies considering the outcome for PLHIVs who are on antiretroviral treatment and/or are treatment-naïve will be included, as well as those relating to HIV-negative populations.

Exclusion criteria

The following factors will apply:

1. Study design: case series/studies, reviews, commentaries and other publications without primary data.
2. Study participants: studies conducted among African populations residing in other continents.
3. Study outcome definition: studies with no Mets criteria or definition, and with different stages of hypertension progression will be excluded.
4. Study languages: studies published in languages other than English and French.
5. Study outcome results: studies lacking prevalence rates and data to compute it after consultation with the author. Duplicate publications from the same studies will be excluded, while those with outcome results published in more than one journal will be reviewed as one study, and relevant information will be collated comprehensively and authors will be contacted to validate data extracted.

Source of information and search strategies

This review will be guided and written by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement, as indicated in table 2.[58] Eligible published articles on the prevalence of diabetes, hypertension and/or/with Mets among

Table 1 Definition of review outcomes

Diseases/conditions	Definition
Diabetes mellitus (WHO/IDF) 2006	Fasting plasma glucose (≥7.0 mmol/L (126 mg/dL)) or 2-hour plasma glucose (≥11.1 mmol/L (200 mg/dL))
Hypertension or high blood pressure — JNC 7[53]	Hypertension (high blood pressure) defined as ≥140/90/90 mm Hg, systolic and diastolic pressure The following are the criteria for diagnosis: 1. Optimal blood pressure — <120/80 mm Hg, systolic and diastolic blood pressure 2. Prehypertension — 120–139/80–89 mm Hg, systolic and diastolic blood pressure 3. Stage 1 hypertension — 140–159/90–99 mm Hg, systolic and diastolic blood pressure 4. Stage 2 hypertension — >160/100 mm Hg, systolic and diastolic blood pressure
Metabolic syndrome	Metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to increase the risk and directly promote the development of cardiovascular disease and type 2 diabetes mellitus.[75] The diagnostic criteria for identifying metabolic syndrome for this study include[55 75]: •NCEP/ATP III criteria — Diagnosis of 3 out of 5: abdominal obesity, given as waist circumference (men 102 cm (40 inches), women 88 cm (35 inches)), triglycerides ≥150 mg/dL, HDL cholesterol (men <40 mg/dL, women <50 mg/dL), blood pressure ≥130/≥85 mm Hg, fasting glucose ≥110 mg/dL •WHO criteria — Diagnosis of insulin resistance (either, type 2 diabetes, impaired fasting glucose, impaired glucose tolerance, normal fasting glucose levels (110 mg/dL) or glucose uptake below the lowest quartile). In addition, diagnosis of 2 other risk factors is sufficient. 1. Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) 2. Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L) 3. HDL cholesterol (men 35 mg/dL (0.9 mmol/L), women 39 mg/dL (1.0 mmol/L)) 4. Body mass index 30 kg/m^2 and/or waist:hip ratio (men >0.9, women >0.85) 5. Urinary albumin excretion rate (≥20 g/min) or albumin:creatinine ratio (≥30 mg/g) •EGIR criteria — A plasma insulin >75th percentile with any 2 risk factors: waist circumference (men ≥94 cm, women ≥80 cm), triglyceride (≥150 mg/dL) and/or HDL-C (<39 mg/dL) in men or women, ≥140 mm Hg or on antihypertensive medication, impaired glucose tolerance or impaired fasting glucose but not diabetes •IDF criteria — A central obesity and any 2 or 4 additional risk factors: raised triglyceride (≥1.7 mmol/L (150 mg/dL), reduced HDL-cholesterol (male <1.03 mmol/L (40 mg/dL), women <1.29 mmol/L (50 mg/dL)), raised blood pressure (≥130/≥85 mm Hg) or antihypertensive drug, raised fasting plasma glucose (≥5.6 mmol/L (100 mg/dL)) or diagnosed type 2 diabetes

EGIR, European Group for Study of Insulin Resistance; IDF, International Diabetes Federation; JNC 7, Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; NCEP/ATP III, National Cholesterol Education Program-Adult Treatment Panel III definition; HDL, high-density lipoprotein.

Table 2 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist

Section/topic	Item #	Checklist item	Page no reference	Line no. reference
Administrative information				
Title			1	3–5
Identification	1a	Identify the report as a protocol of a systematic review	1	5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable	
Registration	2	If registered, provide the name of the registry (eg, PROSPERO) and registration number	2	59
Authors			1	6, 12
Contact	3a	Provide name, institutional affiliation and email address of all protocol authors; provide physical mailing address of corresponding author	1	6–12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	19	671–681
Amendments	4	If protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable	
Support				
Sources	5a	Indicate sources of financial or other support for the review	19	675
Sponsor	5b	Provide name for the review funder and/or sponsor	19	675
Role of sponsor/ funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	19	676
Introduction				
Rationale	6	Describe the rationale for the review in the context of what is already known	4–6	105–202
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators and outcomes (PICO)	6–7	203–215
Methods				
Eligibility criteria	8	Specify the study characteristics (eg, PICO, study design, setting, time frame) and report characteristics (eg, years considered, language, publication status) to be used as criteria for eligibility for the review	7–8	217–266
Information sources	9	Describe all intended information sources (eg, electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8–9 8	267–282 244–246
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9 22	272–273 table 3
Study records				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9	283–287
Selection process	11b	State the process that will be used for selecting studies (eg, two independent reviewers) through each phase of the review (ie, screening, eligibility and inclusion in meta-analysis)	9	288–302
Data collection process	11c	Describe planned method of extracting data from reports (eg, piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10	312–316

Continued

Table 2 Continued

Section/topic	Item #	Checklist item	Page no reference	Line no. reference
Data items	12	List and define all variables for which data will be sought (eg, PICO items, funding sources), any preplanned data assumptions and simplifications	10	317–328
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	7 20	230–238 table 1
Risk of bias	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10–11 23	338–347 table 4
Data				
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11	349–371
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (eg, I^2, Kendall's tau)	11–12	373–381
	15c	Describe any proposed additional analyses (eg, sensitivity or subgroup analyses, meta-regression)	12	388–394
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11	351–352
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (eg, publication bias across studies, selective reporting within studies)	12	384–386
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (eg, GRADE)	12	396–399

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Table 3 Search strategy and terms guide

Search	Search terms	Number of hits
#1	Metabolic syndrome OR syndrome X OR insulin resistance syndrome	
#2	Hypertension OR high blood pressure	
#3	Type 2 diabetes mellitus OR type 2 diabetes OR diabetes Mellitus OR non-insulin dependent diabetes OR adult onset diabetes	
#4	Human Immunodeficiency Virus OR Acquired Immune Deficiency Syndrome Virus OR AIDS Virus OR HIV Seronegativities OR Seronegativity, HIV OR HIV Seropositivities OR Seropositivity, HIV	
#5	#1 OR #2 OR #3 AND #4	
#6	African filter((((Angola OR Benin OR Botswana OR 'Burkina Faso' OR Burundi OR Cameroon OR 'Cape Verde' OR 'Central African Republic' OR Chad OR Comoros OR Congo OR 'Democratic Republic of Congo' OR Djibouti OR 'Equatorial Guinea' OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR 'Guinea Bissau' OR 'Ivory Coast' OR 'Cote d'Ivoire' OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR 'Sao Tome' OR Senegal OR Seychelles OR 'Sierra Leone' OR Somalia OR 'South Africa' OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR 'Western Sahara' OR Zambia OR Zimbabwe OR 'Central Africa' OR 'Central African' OR 'West Africa' OR 'West African' OR 'Western Africa' OR 'Western African' OR 'East Africa' OR 'East African' OR 'Eastern Africa' OR 'Eastern African' OR 'South African' OR 'Southern Africa' OR 'Southern African' OR 'sub Saharan Africa' OR 'sub Saharan African' OR 'sub Saharan Africa' OR 'sub Saharan African' NOT 'guinea pig' NOT 'guinea pigs' NOT 'aspergillus niger'))))	
#7	# 5 AND # 6 Limits: 01/01/1990 to 28/02/2017 in English and French on humans	

HIV-infected and HIV-uninfected populations in SSA will be sought. The search retrieving will be broad, robust and precise using relevant medical subject headings (MeSH) terms in combination with the African search filter, as indicated in table 3.[59]

1. Electronic search: The following databases will be searched: PubMed/Medline, EBSCOhost, Web of Science, Google Scholar, Scopus, African Index Medicus and Cochrane Database of Systematic Reviews for eligible studies.
2. Reference lists search: The reference lists of relevant material will be searched to identify additional studies of interest.
3. Grey literature search: Authors, experts in the field and authors of conference proceedings will be contacted through emails for any relevant information, data and results. Studies will be excluded after three unsuccessful attempts to contact the author.
4. Search management: The records of retrieved articles will be managed using EndNote Reference Manager X.[60] The included and excluded articles at each screening stage will be stored as different files. Figure 1[61] indicates the prototype steps for managing the records and data for the review.

Study screening and selection

A screening criteria checklist will be developed using Google Forms, and tested for reliability and applicability to select relevant studies, and will involve three levels: title, abstract and full article screening.

1. Title screening: One investigator will independently select studies that meet the inclusion criteria by screening article titles for significance to the review focus and outcome, and duplicate citations will be excluded.
2. Abstract screening: Four investigators, two reviewers per language, will independently review abstracts of the included title-screened articles, being guided by the stated inclusion criteria.
3. Full article screening: This will be similar to the abstract screening and will further establish the eligibility of the identified studies. The first reviewer will assess for the articles' eligibility for meta-analysis, general characteristics and outcomes. The second reviewer will verify at least 50% of the studies for general characteristics information and 100% of studies for outcomes data.
4. Screening agreement and disagreement: Screening will establish the inter-rater reliability using Cohen's kappa coefficient, κ, which is a robust statistic used for inter-rater reliability testing,[62 63] and any disagreement will be resolved through consultation of the study coordinator, if necessary. Authors will be contacted if there are missing information and data from the published articles that are relevant to the study and for further reported result clarity where needed. The reasons for exclusion at all stages will be documented.

Data extraction

A Google Form will be designed, pretested and standardised to extract data from the reviewed and included studies. The data extraction and entry will also be conducted by two reviewers to establish an inter-rater reliability and avoid data entering errors,[63] with disagreement

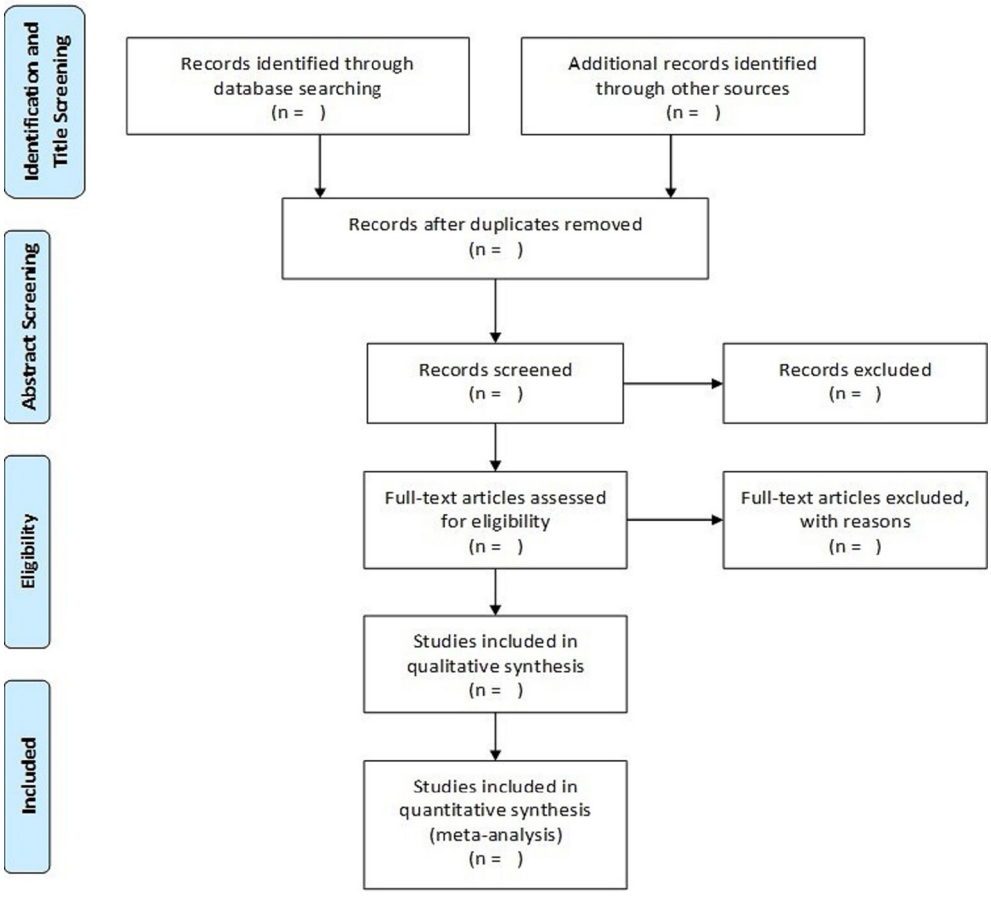

Figure 1 Search management flow chart for review.

resolved by the study coordinator. The following data items will be extracted:

1. Publication details: author(s) name, year of publication, year(s) of study, language, publication status.
2. Study characteristics and settings: rural or urban, study site, hospital or community/population-based country settings, study design, sample size, length of study duration of follow-up, source of funding, ethical approval.
3. Study participant's characteristics: sex proportion, mean age, HIV status, participants' number and proportion for single studies with multiple outcomes and/or population subgroups.
4. Study outcome: Mets, diabetes and hypertension, comorbid diabetes and hypertension.
5. Study target population: HIV-positive and/or HIV-negative study participants, number and proportion of participants with or comorbid study outcome (CI, p values).

Quality and risk of bias assessment

The quality assessment will be conducted by two reviewers using the Effective Public Health Practice Project/McMaster Evidence Review and Synthesis Centre Tool: Quality Assessment Tool for Quantitative Studies (see online supplementary appendix 1).[64] The tool was selected due to its use of summary scoring to determine the quality of studies, ranging from strong, moderate to weak, and its ability to assess all types of quantitative study methods. This is important, as scale or checklist tools are more likely to include criteria that do not directly relate to internal validity, resulting in unreliable validity assessment.[65] The summary scores for all the included studies will be documented and reported in the final review. The study's risk of bias will be performed using the risk of bias tool for prevalence studies by Hoy *et al*[66] and the Cochrane guidelines available in Review Manager V.5.3 (http://tech.cochrane.org/revman) (table 4). The quality and risk of bias assessment will be presented as part of the table of characteristics of the included studies. The inter-rater agreement will be calculated using the proportion of agreement and kappa statistics. The minimum sample size for included studies will be calculated to determine a good precision estimate, using the pooled estimate of study outcomes prevalence among PLHIV and HIV-negative populations. This calculation will use the Clopper-Pearson CI formula,[67] and a study with good precision for this meta-analysis will be defined as one whose sample size is greater than or equal to the calculated minimum sample size.

Table 4 Risk of bias tool (adapted from Hoy *et al*[66] tool for prevalence studies)

Study title: Name of author(s) Year of publication		
Risk of bias items	**Risk of bias level: low risk = yes, high risk = no**	**Score: yes=0, no=1**
External validity		
1. Was the study target population a close representation of the national population in relation to relevant variables, for example, age, sex?		
2. Was the sampling frame a true or close representation of the target population?		
3. Was some form of random selection used to select the sample, OR, was a census undertaken?		
4. Was the likelihood of non-participation bias minimal?		
Internal validity		
5. Was data collected directly from the participants (as opposed to proxy)?		
6. Were acceptable case definitions and diagnostic measures of metabolic syndrome, diabetes and hypertension used?		
7. Were the study instruments that measured the parameter of interest (eg, prevalence of diabetes) shown to have reliability and validity (if necessary)?		
8. Was the same mode of data collection used for all study participants?		
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?		
10. Were the numerator(s) and denominator(s) for the calculation of the prevalence of metabolic syndrome, diabetes and hypertension appropriate?		

Presentation of summary on the overall risk of study bias.
The total score ranged from 0 to 9, with the overall score categorised as follows:
1. Low risk of bias: 8 or more 'yes' answers, further research is very unlikely to change our confidence in the estimate.
2. Moderate risk of bias: 6–7 'yes' answers, further research is likely to have an important impact on our confidence and may change in the estimate.
3. High risk of bias: 5 or fewer 'yes' answers, further research is very likely to have an important impact on our confidence and likely change the estimate.

Data synthesis and analysis

The data will be systematically described, analysed and summarised to answer the four research questions, and the data will be narratively synthesised if meta-analysis cannot be performed.

Data analysis

The prevalence results of Mets (and its subcomponents), discrete and/or comorbid diabetes and hypertension will be stratified and compared by HIV status to establish any significant difference. As some definitions of Mets include diabetes and blood pressure as criteria, the prevalence of subcriteria in studies that assessed Mets across HIV-positive and HIV-negative populations will be included as a secondary objective. The prevalence estimate will be presented by country, geographical region and HIV status. Furthermore, given the international changes in the definition of diabetes, hypertension and Mets, the analysis will also be stratified by the period of definition used in the included/eligible studies. This study-specific prevalence estimates will be pooled using the random-effects meta-analysis model to present the mean of the distribution of effects between HIV-infected and HIV-negative populations.[68] The variance for the random meta-analysis estimate will be computed using the updated DerSimonian and Laird variance estimator method.[69] The random-effects model will be used in anticipation of substantial variation in Mets prevalence and on the different outcome definitions across the included studies/period. To minimise the effect of extreme prevalence on the overall estimates, single arcsine transformation will be performed on the raw prevalence before pooling the data.[70] CIs at 95% will be calculated for all reported study outcome prevalence measures using the Clopper-Pearson method.[67]

Heterogeneity

The statistical heterogeneity in the meta-analysis will be assessed using the I^2 statistic,[71] and if the I^2 value is greater than 50%, it will be regarded as substantial heterogeneity. Forest plots and the overall random-effects pooled estimate will be generated to display prevalence with the corresponding CI for each study. If asymmetry is present based on visual assessment, exploratory analyses will be performed to investigate and adjust this using trim and/or fill analysis. The prevalence of

the study outcomes between mean/median age and gender will be estimated. Meta-regression analysis will be explored among HIV-infected participants who are on antiretroviral treatment and are treatment-naïve, if adequate data are found.

Publication bias

If there are ≥10 studies in the meta-analysis, publication bias will be further investigated using funnel plots and Egger's test,[72] the data being analysed using Stata V.13.0.

Sensitivity analysis

A sensitivity analysis to assess the robustness of the individual study designs and data set of the observed outcomes to the analysis assumptions will also be undertaken to further reduce the risk of bias assessment. The primary analysis will be repeated with altered extracted data sets and statistical methods to determine any changes in the combined outcome estimate effect.[73] The data set and statistical model for the statistical analysis will be determined during the review process and reported in the final review.

Strength of evidence assessment

The quality and strength of evidence extracted from the included and analysed studies will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADEpro software will be used to assist in grading the evidence and presenting the summary of findings in the review and meta-analysis.[74]

Review reporting and dissemination

The proposed systematic review and meta-analysis will be guided by the PRISMA guidelines.[58] The final report and completed PRISMA checklist will be published as a scientific article in a peer-reviewed journal. In addition, the review findings will be presented at conferences and/or to relevant health agencies.

Potential amendments

While there are no planned amendments for this protocol, if any substantial amendments arise during the review itself, these will be documented and reported in the published findings.

Ethical consideration

As the present review and meta-analysis study will use aggregated published data and information for analysis, no ethical approval will be required.

CONCLUSION

This systematic review and meta-analysis will attempt to identify the distribution of Mets, diabetes and hypertension and their common related comorbidities between PLHIV and HIV-negative general populations across SSA. The rigorous methodology proposed for this review will ensure a robust knowledge synthesis and provide evidence-based knowledge of the prevalence of the study outcomes for stakeholders, researchers and policy makers. This will assist with indicating the research gaps and priorities for Mets, diabetes and hypertension in the whole of Africa.

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