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The association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa: A systematic review and meta-analysis protocol

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Abstract

Introduction:

The increasing highly active antiretroviral therapy (HAART) coverage in sub-Saharan Africa has been associated with increasing cardiovascular disease (CVD) incidence. However, the epidemiology of the association between highly active antiretroviral therapy and cardiovascular disease risk factors in sub-Saharan Africa (SSA) is sparse. We aim to assess the extent to highly active antiretroviral therapy is associated to selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia) in sub-Saharan Africa.

Methods and Analysis:

This will be a systematic review and meta-analysis of published studies on the association between HAART and CVD risk factors retrieved from Medline, Embase, Popline, Africa-Wide Information, African Index Medicus and the Cochrane library databases. Studies will be screened for eligibility and inclusion according to the selection criteria by two independent reviewers. Eligible studies will be assessed for the quality of their evidence and risk of bias using the STROBE checklist and the GRADE assessment with respect to the measured outcomes (hypertension, diabetes and dyslipidemia). A data abstraction will be produced on Epi info version 7 and data analysis done on STATA version 14 statistical software. Summary estimates of measures of effects for the association between HAART use and hypertension, diabetes and dyslipidemia respectively will be derived. Random-effects and fixed effects meta-analyses will be performed and compared as appropriate and I^2 statistic used to assess for heterogeneity between studies with respect to measured parameters. Qualitative synthesis will be used where data is insufficient to produce quantitative synthesis.

Ethics and Dissemination:

The protocol has been reviewed by the Research Governance & Integrity Office of the Research Ethics Committee of the London School of Hygiene and Tropical Medicine and confirmed as not requiring ethical approval. The findings of this study will be made widely available especially to national HIV/AIDS committees formulating HIV/AIDS guidelines for their respective settings.

Prospero registration number:

CRD42016042306

Strengths and limitations of this study

Strengths

- This review will provide a summary of published studies on the extent to which antiretroviral therapy is associated to cardiovascular disease risk factors (hypertension, diabetes and dyslipidemia).
- This findings of this review will be very important to authorities involved in health policy formulation in the HIV/AIDS domain especially as several African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS with massive HAART scale-up.

Limitations

- This study will be limited to sub-Saharan Africa, however, this is the region in the world with the greatest HIV/AIDS burden.

Introduction

The past decade has seen the rapid increase in highly active antiretroviral therapy (HAART) coverage worldwide with about 15 million HIV/AIDS patients having access to treatment in 2014, and more than 90% of them being from low and middle income countries most affected by HIV/AIDS [1]. In 2014, HAART coverage stood at 41% in Africa, however, HAART has been increasingly associated with cardiovascular disease (CVD) [2–7]. Several mechanisms have been proposed to explain this association among which prolonged HAART use predisposing to atherosclerosis and major cardiovascular risk factors such as diabetes and hypertension [5,6,8–11] which consequently result in CVD. Even though, earlier studies already suggested a probable association between HAART and CVD, Bloomfield et al [2] in a systematic review of literature found that CVD appeared to be more frequent in HIV-infected populations in Low and Middle Income countries. This is particular important since the greatest increase in HAART coverage has been in these countries [1]. In sub-Saharan Africa (SSA), this association between HAART and CVD has been confounded by the marked epidemiological transition characterized by the increased prevalence and incidence of non-communicable diseases due to changes in lifestyle patterns. On the other hand, there have been contrary reports of no association between exposure to HAART and cardiovascular disease risk factors [12–15]. Understanding the overall effect of HAART on CVD risk is therefore of public health importance since the continuous HAART scale-up has to be accompanied by appropriate guidelines and measures to ensure the morbidity and long-term mortality of these patients is not negatively affected, especially in low and middle income countries with health systems inadequately equipped to manage these chronic conditions. In a recent systematic review by Dillon et al [16] on the association between HIV, HAART and cardio-metabolic traits in the sub-Saharan African population, there was a difference in these traits between HIV-infected patients and uninfected individuals and between HAART-treated and HAART-naive patients, suggesting a probable effect of HAART. However, this review compared the standardized mean differences in blood pressure, blood glucose and lipid profile parameters between the groups and not actually on hypertension, diabetes or dyslipidemia respectively. Moreover, more recent studies have been published since then comparing prevalence and incidence of these risks factors in HAART-treated and HAART-naïve patients. We therefore aim to systematically review, and where appropriate perform a meta-analysis of the published studies up to May 2016, on the extent to which exposure to HAART is associated to these cardiovascular disease risk factors in sub-Saharan Africa, together with potential determinants of any possible association.

Research Questions:

1. Is there an association between highly active antiretroviral therapy and selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia) in HIV/AIDS patients in sub-Saharan Africa?
2. What factors could affect the association between HAART and the selected CVD risk factors?

Research Objectives:

1. To estimate overall measures of effect for the association between HAART and hypertension in HIV/AIDS patients in SSA.

2. To estimate overall measures of effect for the association between HAART and diabetes in these patients.

3. To estimate overall measures of effect for the association between HAART and dyslipidemia in these patients

4. To assess factors associated to hypertension, diabetes and dyslipidemia in these patients

Methods

Study design and eligibility criteria

This will be a systematic review and meta-analysis of published studies.

We will include:

- Cross-sectional, cohort, case-control and randomized controlled trials with data on the prevalence and/or incidence of hypertension, diabetes or lipid profile in HIV/AIDS patients.
- Studies with comparable HAART-treated and HAART-naïve populations.
- Studies published in English up to May 2016 in the selected databases.
- Studies involving participants aged 18 and above, living in one of the countries in SSA.

We will exclude:

- Unpublished manuscripts and conference abstracts.

For the meta-analysis, we will include studies with a documented measure of effect on the selected cardiovascular risk factors comparing the HAART-treated and HAART-naïve groups. For studies without reported measures of effect, we will compute those if the data provided enables us to do so.

Search Strategy and Identification of Studies

The review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 (Table II).

The following databases will be searched for eligible studies: Medline, Embase, Popline, Africa Wide Information, African Index Medicus and the Cochrane library. We will use both medical subject headings and free text searches on both on Medline and Embase to identify studies conducted both in countries and regions of SSA up to May 2016 (Table I). Articles returned by the search will be saved to the Zotero version 4.0.29.10 software which will be used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates will be assessed for eligibility according to the inclusion and exclusion criteria. We will use the studies with the largest sample size for those with several publications of their findings over time.

The full text of all potentially eligible studies will then be reviewed by two independent reviewers (CAD and HB) and any disagreement between reviewers with respect to eligible studies for inclusion in the analysis will be settled by a third reviewer. The reference lists of eligible studies and reviews will also be assessed for more eligible studies. A list of all articles from the searches will be produced and all excluded studies together with the reasons for exclusion will be mentioned. A PRISMA flow chart detailing the number of articles identified, screened, included and excluded will be produced.

Data abstraction, data analysis and quality assessment

A data abstraction form will be produced on Epi info version 7 statistical software and pretested by the principal investigator. The following data will be extracted from the selected studies: first author, publication year, study design and setting, duration of study, summary information of the socio-demographic and clinical details of the participants such as mean or median age, sex distribution, duration of HIV infection and of antiretroviral therapy, the measures of disease frequency and effect for the selected cardiovascular risk factors in the HAART and HAART-naïve groups. The appropriate measures of effect will be derived in studies that provide sufficient data to do so.

Data will be analyzed using STATA version 14 statistical software. Due to the possibility of heterogeneity, we are going to use random-effects meta-analysis and compare our random-effect estimates with fixed-effects estimates and the I^2 statistic used to assess heterogeneity between studies with respect to the measured parameters.

For objectives 1, 2 and 3 we will calculate and summarize relative risks (for incidence studies) and odds ratios (for prevalence studies) comparing the HAART+ and HAART- groups. The exposure variable will be HAART use and the outcome variable will be the respective cardiovascular risk factors hypertension, diabetes and dyslipidemia. Pooled estimates of

measures of effect will be derived using random effects and fixed effects as appropriate after performing I^2 test statistics for heterogeneity of studies and forests plots produced. Stratified analyses will be done according to study characteristics such as study design and study quality in cases of substantial heterogeneity among included studies. Qualitative synthesis will be used in cases where data extracted is insufficient to perform quantitative synthesis. For objective 4, reported significant risk factors of hypertension, diabetes, and dyslipidemia respectively in HIV/AIDS patients will be described through qualitative synthesis. Publication bias will be assessed using funnel plots.

Eligible studies will be assessed for the quality of their evidence and risk of bias by two independent reviewers (CAD and HB) with respect to: flaws in study design, comparability of the HAART+ and HAART- groups, inadequately measured or managed confounders, inaccuracies in the measurements of the key parameters such as hypertension, diabetes and lipid profile or inappropriate diagnostic cut-off values. We will complement these checks with the STROBE checklist for observational studies. The GRADE assessment will be used to assess for quality of evidence of the included studies with respect to the measured outcomes (hypertension, diabetes and dyslipidemia) by the two reviewers (CAD and HB) taking into account the study limitations, inconsistencies, indirectness, imprecision and publication bias. Overall quality of evidence following assessment will be graded as high, moderate, low or very low.

Reporting and Amendments to protocol

The PRISMA-P guidelines for the reporting of the systematic reviews and meta-analysis protocols have been used for this systematic review protocol as illustrated on Table II. The completed report will be reported in accordance with the PRISMA guidelines using the PRISMA checklist. Amendments will be made to the study if and only if necessary and will be clearly documented and justified.

Conclusion

There still remains contradictory evidence on this association between HAART and CVD. As such this review will present a summary of what is documented in sub-Saharan Africa as far as cardiovascular disease epidemiology and HIV/AIDs is concerned. This is of utmost importance since many sub-Saharan African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS. This massive HAART scale-up could be faced with rather increasing morbidity and mortality from cardiovascular diseases in HIV/AIDS patients, if these

underlying mechanisms are not well understood and measures such as concurrent scale-up of CVD screening and treatment services envisaged.

Ethical considerations and dissemination

The Research Governance & Integrity Office of the Research Ethics Committee of the London School of Hygiene and Tropical Medicine reviewed the study and affirmed no ethical approval is required. The findings of this study will be made widely available to the appropriate authorities involved in health policy formulation especially with respect to HIV/AIDS treatment guidelines and also to the scientific community for subsequent updating as more recent studies become available.

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Authors' contribution:

CAD and HB conceived and designed the experiments. CAD produced the manuscript. HB reviewed the manuscript. Both authors approved the final copy of the manuscript

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Competing Interests:

The authors declare no competing interests exists

Table I: Search strategy for the Medline, Embase and Africa-Wide Information for the review on the association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa

#	Search words
1	Africa [MeSH terms] OR Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Canary Islands OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Ivory Coast OR Cote dIvoire OR Jamahiriya OR Jamahiryia OR Kenya OR Lesotho OR Liberia OR Libya OR Libia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Mocambique 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 St Helena OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Western Sahara OR Zaire 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 North Africa OR North African OR Northern Africa OR Northern African OR South African OR Southern Africa OR Southern African OR subSaharan Africa OR subSaharan African OR sub-Saharan Africa OR sub-Saharan African
2	Antiretroviral therapy, Highly Active [MeSH terms] OR highly active antiretroviral therapy OR antiretroviral therapy OR antiretroviral OR HAART OR ART OR anti-retroviral OR Nucleotide reverse transcriptase inhibitor OR NRTI OR Non-nucleoside reverse transcriptase inhibitor OR NNRTI OR Protease inhibitor OR PI OR PIs OR lopinavir OR ritonavir OR lamivudine OR zidovudine OR stavudine OR nevirapine OR efavirenz OR tenofovir OR emtricitabine OR atazanavir OR darunavir
3	Cardiovascular diseases [MeSH terms] OR hypertension OR high blood pressure OR systolic blood pressure OR diastolic blood pressure OR SBP OR DBP OR diabetes mellitus OR diabetes OR type 2 diabetes OR type 2 diabetes mellitus OR diabetic OR type 2 diabetic OR dysglycemia OR dysglycaemia OR hyperglycemia OR hyperglycaemia OR glucose OR insulin resistance OR insulin OR hyperinsulinemia OR hyperinsulinaemia OR dyslipidemias OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR hypertriglyceridemia OR cholesterol OR triglyceride OR triglycerides OR HDL OR LDL OR VLDL OR hyperlipoproteinemia OR lipoprotein OR hyperlipidaemia OR hypercholesterolaemia OR hypertriglyceridaemia
4	#1 AND #2 AND #3

Table II: PRISMA-P 2015 checklist for the study protocol of the systematic review on the association between highly active anti-retroviral therapy and selected cardiovascular risk factors in sub-Saharan Africa.

Section and Topic	Item No	Checklist Item	Page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NAP
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the 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	6
Support			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	NAP
Role of sponsor	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4&5
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
Study records			
Data management	11a	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4&5
Selection criteria			
Data collection	11b	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4&5
	11c	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Data items	12		
Outcome and prioritisation	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5&6
Risk of bias in individual subjects	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	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	5&6
	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 (such as I2, Kendall's τ)	5&6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5&6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5&6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5&6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

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Abstract

Introduction:

The increasing highly active antiretroviral therapy (HAART) coverage in sub-Saharan Africa has been associated with increasing cardiovascular disease (CVD) incidence. However, the epidemiology of the association between highly active antiretroviral therapy and cardiovascular disease risk factors in sub-Saharan Africa (SSA) is sparse. We aim to assess the extent to which HAART is associated to selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia and metabolic syndrome) in SSA.

Methods and Analysis:

This will be a systematic review and meta-analysis of published studies on the association between HAART and CVD risk factors retrieved from Medline, Embase, Popline, Africa-Wide Information, African Index Medicus and the Cochrane library databases. Studies will be screened for eligibility according to the selection criteria by two independent reviewers. Eligible studies will be assessed for the quality of their evidence and risk of bias using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute and the GRADE approach with respect to the measured outcomes (hypertension, diabetes, dyslipidemia and metabolic syndrome). A data abstraction form will be produced on Epi info version 7 and data analysis done on STATA version 14 statistical software. Summary estimates of measures of effects for the association between HAART use and the outcomes will be derived. Random-effects meta-analyses will be performed and I^2 statistic used to assess for heterogeneity between studies with respect to measured parameters. Qualitative synthesis will be used where data is insufficient to produce quantitative synthesis.

Ethics and Dissemination:

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Prospero registration number: CRD42016042306

Strengths and limitations of this study

Strengths

- This review will provide a summary of published studies on the extent to which antiretroviral therapy is associated to cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia and metabolic syndrome).
- The findings of this review will be very important to authorities involved in health policy formulation in the HIV/AIDS domain especially as several African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS with massive HAART scale-up.

Limitations

- This study will be limited to sub-Saharan Africa, however, this is the region in the world with the greatest HIV/AIDS burden.

Introduction

The past decade has seen the rapid increase in highly active antiretroviral therapy (HAART) coverage worldwide with about 15 million HIV/AIDS patients having access to treatment in 2014, and more than 90% of them being from low and middle income countries most affected by HIV/AIDS [1]. In 2014, HAART coverage stood at 41% in Africa, however, HAART has been increasingly associated with cardiovascular disease (CVD) [2–7]. Several mechanisms have been proposed to explain this association among which prolonged HAART use predisposing to atherosclerosis and major cardiovascular risk factors such as diabetes and hypertension [5,6,8–11] which consequently result in CVD. Even though, earlier studies already suggested a probable association between HAART and CVD, Bloomfield et al [2] in a systematic review of literature found that CVD appeared to be more frequent in HIV-infected populations in Low and Middle Income countries. This is particularly important since the greatest increase in HAART coverage has been in these countries [1]. In sub-Saharan Africa (SSA), this association between HAART and CVD has been confounded by the epidemiological transition characterized by the increased prevalence and incidence of non-communicable diseases due to changes in lifestyle patterns. On the other hand, there have been contrary reports of no association between exposure to HAART and cardiovascular disease risk factors [12–15]. Understanding the overall effect of HAART on CVD risk is therefore of public health importance since the continuous HAART scale-up has to be accompanied by appropriate guidelines and measures to ensure the morbidity and long-term mortality of these patients is not negatively affected, especially in low and middle income countries with health systems inadequately equipped to manage these chronic conditions. In a recent systematic review by Dillon *et al* [16] on the association between HIV, HAART and cardio-metabolic traits in the sub-Saharan African population, there was a difference in these traits between HIV-infected patients and uninfected individuals and between HAART-treated and HAART-naive patients, suggesting a probable effect of HAART. However, this review compared the standardized mean differences in blood pressure, blood glucose and lipid profile parameters between the groups and not actually on hypertension, diabetes or dyslipidemia respectively. Moreover, more recent studies have been published since then comparing prevalence and incidence of these risks factors in HAART-treated and HAART-naïve patients. We therefore aim to systematically review, and where appropriate perform a meta-analysis of the published studies on the extent to which exposure to HAART is associated to these cardiovascular disease risk factors in sub-Saharan Africa (Figure 1).

Research Question:

1. Is there an association between highly active antiretroviral therapy and selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia, metabolic syndrome) in HIV/AIDS patients in sub-Saharan Africa?

Research Objectives:

1. To estimate overall measures of effect for the association between HAART and hypertension in HIV/AIDS patients in SSA.

2. To estimate overall measures of effect for the association between HAART and diabetes in these patients.

3. To estimate overall measures of effect for the association between HAART and dyslipidemia in these patients

4. To estimate overall measures of effect for the association between HAART and metabolic syndrome in these patients.

Methods

Study design and eligibility criteria

This will be a systematic review and meta-analysis of published studies.

We will include:

- Cross-sectional, cohort, case-control and randomized controlled trials with data on the prevalence and/or incidence of hypertension, diabetes, lipid profile or metabolic syndrome in HIV/AIDS patients.
- Studies with comparable HAART-treated and HAART-naïve populations.
- Studies published in English and between January 1, 2003 and July 1, 2016 in the selected databases.
- Studies involving participants aged 18 and above, living in one of the countries in SSA.

We will exclude:

- Unpublished manuscripts and conference abstracts.
- Studies comparing the mean blood pressure, glucose and lipid levels in the HAART-treated and HAART-naïve groups rather than the actual prevalence or incidence of hypertension, DM, dyslipidemia and metabolic syndrome respectively.

- Studies with diagnostic criteria and cut-off values for hypertension, DM, abnormal lipid profiles and metabolic syndrome different from those internationally recognized.
- Studies whose data will not be sufficient to calculate appropriate measures of effect
- Same studies published in different journals with the same or a different title.

For studies with several publications of their findings over time, the most recent of the studies will be chosen. For the meta-analysis, we will include studies with a documented measure of effect on the selected cardiovascular risk factors comparing the HAART-treated and HAART-naïve groups. For studies without reported measures of effect, we will compute those if the data provided enables us to do so.

Search Strategy and Identification of Studies

The following databases will be searched for eligible studies: Medline, Embase, Popline, Africa Wide Information, African Index Medicus and the Cochrane library. We will use both medical subject headings and free text searches on both on Medline and Embase databases (Table I). Articles returned by the search will be saved to the Zotero version 4.0.29.10 software which will be used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates will be assessed for eligibility according to the inclusion and exclusion criteria. Based on the year of introduction of HAART in sub-Saharan African we will focus on articles published between 2003 and 2016.

The full text of all potentially eligible studies will then be reviewed by two independent reviewers (CAD and HB) and any disagreement between reviewers with respect to eligible studies for inclusion in the analysis will be settled by a third reviewer. The reference lists of eligible studies and reviews will also be assessed for more eligible studies. A list of the potentially eligible studies excluded from the final analysis will be produced with the reasons for exclusion mentioned. A PRISMA flow chart detailing the number of articles identified, screened, included and excluded will be produced.

Data abstraction, data analysis and quality assessment

A data abstraction form will be produced on Epi info version 7 statistical software and pretested by the principal investigator. The following data will be extracted from the selected studies: first author, publication year, study design and setting, duration of study, summary information of the socio-demographic and clinical details of the participants such as mean or median age, sex distribution, duration of HIV infection and of antiretroviral therapy, the measures of disease frequency and effect for the selected cardiovascular risk factors in the HAART and HAART-naïve groups, statin use among participants, distinction between garden-variety hyperlipidemia

and that resulting from probable HAART use, and any other information considered relevant. The appropriate measures of effect will be derived in studies that provide sufficient data to do so.

Data will be analyzed using STATA version 14 statistical software. Due to the possibility of heterogeneity among the studies, random-effects meta-analysis models will be preferentially reported over fixed-effects models.

For objectives 1, 2, 3 and 4, odds ratios comparing the HAART+ and HAART- groups will be calculated and summarized. The exposure variable will be HAART use and the outcome variable will be the respective cardiovascular risk factors hypertension, diabetes, dyslipidemia and metabolic syndrome. These outcomes will be defined according to the standard International criteria (Table II). Pooled estimates of measures of effect will be derived using random effects models, the Cochran's Q test used to assess for evidence of between-study heterogeneity and the I^2 test statistics used to assess the degree of heterogeneity among the studies. Corresponding forests plots will also be produced. The Harbord's test and the Peter's test [17] will be used to statistically assess for funnel plot asymmetry and small-study effects with low P values indicating evidence of plot asymmetry, small-study effect and possibly publication bias. Meta-regressions and subgroup stratified analyses will be done according to the important study characteristics such as; study quality, study location, sample size, adjusting of confounders or not, antiretroviral therapy agents and regimens, statin use, and any other relevant parameters identified during the abstraction, to explore if these study characteristics could be potential sources of heterogeneity among the studies. Qualitative synthesis will be used in cases where data extracted is insufficient to perform quantitative synthesis.

Eligible studies will be assessed for the quality of their evidence and risk of bias by two independent reviewers (CAD and HB) with respect to: flaws in study design, comparability of the HAART+ and HAART- groups, inadequately measured or managed confounders, determination of associations at univariate or multivariate levels of analysis, inaccuracies in the measurements of the key parameters such as hypertension, diabetes, lipid profile and metabolic syndrome or inappropriate diagnostic cut-off values. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Table III) which takes into account all these parameters will be used to grade the overall quality of each individual study as good, fair or poor.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess for quality of evidence provided by the included studies with respect to the measured outcomes (hypertension, diabetes, dyslipidemia and metabolic

syndrome), by the two reviewers (CAD and HB) taking into account the study limitations, inconsistencies, indirectness, imprecision and publication bias. Overall quality of evidence following assessment will be graded as high, moderate, low or very low.

Reporting and Amendments to protocol

The PRISMA-P guidelines for the reporting of systematic reviews and meta-analysis protocols have been used for this systematic review protocol as illustrated on Table IV. The completed report will be reported in accordance with the PRISMA guidelines using the PRISMA checklist. Amendments will be made to the study if and only if necessary and will be clearly documented and justified.

Conclusion

There still remains contradictory evidence on this association between HAART and CVD in SSA. As such this review will present a summary of what is documented in sub-Saharan Africa as far as cardiovascular disease epidemiology and HIV/AIDS is concerned. This is of utmost importance since many sub-Saharan African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS. This massive HAART scale-up could be faced with rather increasing morbidity and mortality from cardiovascular diseases in HIV/AIDS patients, if these underlying mechanisms are not well understood and measures such as concurrent scale-up of CVD screening and treatment services envisaged.

Ethical considerations and dissemination

The Research Governance & Integrity Office of the Research Ethics Committee of the London School of Hygiene and Tropical Medicine reviewed the study and affirmed no ethical approval is required. The findings of this study will be made widely available to the appropriate authorities involved in health policy formulation especially with respect to HIV/AIDS treatment guidelines and also to the scientific community for subsequent updating as more recent studies become available.

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Authors' contribution:

CAD and HB conceived and designed the experiments. CAD produced the manuscript. HB reviewed the manuscript. Both authors approved the final copy of the manuscript

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Competing Interests:

The authors declare no competing interests exists

Table I: Search strategy for the Medline, Embase and Africa-Wide Information for the review on the association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa

#	Search words
1	Africa [MeSH terms] OR Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Canary Islands OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Ivory Coast OR Cote dIvoire OR Jamahiriya OR Jamahiryia OR Kenya OR Lesotho OR Liberia OR Libya OR Libia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Mocambique 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 St Helena OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Western Sahara OR Zaire 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 North Africa OR North African OR Northern Africa OR Northern African OR South African OR Southern Africa OR Southern African OR subSaharan Africa OR subSaharan African OR sub-Saharan Africa OR sub-Saharan African
2	Antiretroviral therapy, Highly Active [MeSH terms] OR highly active antiretroviral therapy OR antiretroviral therapy OR antiretroviral OR HAART OR ART OR anti-retroviral OR Nucleotide reverse transcriptase inhibitor OR NRTI OR Non-nucleoside reverse transcriptase inhibitor OR NNRTI OR Protease inhibitor OR PI OR PIs OR lopinavir OR ritonavir OR lamivudine OR zidovudine OR stavudine OR nevirapine OR efavirenz OR tenofovir OR emtricitabine OR atazanavir OR darunavir
3	Cardiovascular diseases [MeSH terms] OR hypertension OR high blood pressure OR systolic blood pressure OR diastolic blood pressure OR SBP OR DBP OR diabetes mellitus OR diabetes OR type 2 diabetes OR type 2 diabetes mellitus OR diabetic OR type 2 diabetic OR dysglycemia OR dysglycaemia OR hyperglycemia OR hyperglycaemia OR glucose OR insulin resistance OR insulin OR hyperinsulinemia OR hyperinsulinaemia OR dyslipidemias OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR hypertriglyceridemia OR cholesterol OR triglyceride OR triglycerides OR HDL OR LDL OR VLDL OR hyperlipoproteinemia OR lipoprotein OR hyperlipidaemia OR hypercholesterolaemia OR hypertriglyceridaemia OR metabolic syndrome
4	#1 AND #2 AND #3

Table II: Definition of outcomes per included studies

Outcome	Criteria	Organization
Hypertension	SBP ≥ 140 and/or DBP ≥ 90 mmHg	WHO/JNC 7
Diabetes	FBG ≥ 126 mg/dL (7.0 mmol/L) OR RBG ≥ 200 mg/dL (11.1 mmol/L)	WHO/ADA
High TC	Serum TC ≥ 200 mg/dL (5.17 mmol/L)	NCEP/ATP III
High TG	Serum TG ≥ 200 mg/dL (2.23 mmol/L) Serum TG ≥ 150 mg/dL (1.70 mmol/L)	NCEP/ATP II NCEP/ATP III
Low HDL	Men: Serum HDL < 40 mg/dL (1.03 mmol/L) Women: Serum HDL < 50 mg/dL (1.29 mmol/L)	NCEP/ATP III
High LDL	Serum LDL ≥ 130 mg/dL (3.36 mmol/L) Serum LDL ≥ 100 mg/dL (2.59 mmol/L)	NCEP/ATP III NCEP/ATP III
Metabolic Syndrome (≥3 parameters)	WC - Men >102 cm, WC - Women >88 cm Triglycerides ≥150 mg/dL HDL - Men <40 mg/dL, HDL - Women <50 mg/dL Blood pressure ≥130/85 mmHg Fasting glucose ≥110 mg/dL	NCEP/ATP III

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, FBG – Fasting blood glucose, RBG – Random blood glucose, WC – Waist Circumference, WHO – World Health Organization
JNC 7 - 7th report of the Joint National Committee on the prevention, detection, evaluation and treatment of high blood pressure, ADA – American Diabetes Association.
NCEP/ATP III - National Cholesterol Education Program/Adult Treatment Panel guidelines III
NCEP/ATP II - National Cholesterol Education Program/Adult Treatment Panel guidelines II
TG – Triglycerides, TC – Total Cholesterol, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein

Table III: Quality Assessment Tool for Observational Cohort and Cross-Sectional-Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Table IV: PRISMA-P 2015 checklist for the study protocol of the systematic review on the association between highly active anti-retroviral therapy and selected cardiovascular risk factors in sub-Saharan Africa.

Section and Topic	Item No	Checklist Item	Page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NAP
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the 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	NAP
Support			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	NAP
Role of sponsor	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
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	11
Study records			
Data management	11a	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6&7
Selection criteria			
Data collection	11b	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6&7
	11c	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6&7
Data items	12		
Outcome and prioritisation	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6&7
Riskofbias in individual subjects	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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies,	7
	15c	including any planned exploration of consistency (such as I2, Kendall's ô) Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

Figure Legend

Figure 1: Conceptual framework showing the multiple CVD risk factors and the investigated association between HAART and the selected CVD risk factors.

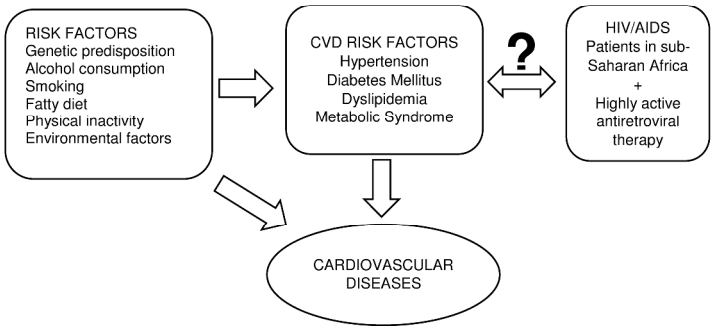

Figure 1: Conceptual framework showing the multiple CVD risk factors and the investigated association between HAART and the selected CVD risk factors.
The single headed arrows indicate causality and the double headed arrow indicates association.

251x324mm (600 x 600 DPI)

Table IV: PRISMA-P 2015 checklist for the study protocol of the systematic review on the association between highly active anti-retroviral therapy and selected cardiovascular risk factors in sub-Saharan Africa.

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Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the 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	NAP
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Sources	5a	Indicate sources of financial or other support for the review	10
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Role of sponsor	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
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BMJ Open

The association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa: A systematic review and meta-analysis protocol

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The association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa: A systematic review and meta-analysis protocol

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Running Title: The Association between antiretroviral therapy and cardiovascular disease risk factors in sub-Saharan Africa

Number of tables: 4

Number of figures: 1

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Abstract

Introduction:

The increasing highly active antiretroviral therapy (HAART) coverage in sub-Saharan Africa (SSA) has been associated with increasing cardiovascular disease (CVD) incidence. However, the epidemiology of the association between highly active antiretroviral therapy and cardiovascular disease risk factors in sub-Saharan Africa is sparse. We aim to assess the extent to which HAART is associated to selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia and metabolic syndrome) in SSA.

Methods and Analysis:

This will be a systematic review and meta-analysis of published studies on the association between HAART and CVD risk factors retrieved from Medline, Embase, Popline, Africa-Wide Information, African Index Medicus and the Cochrane library databases. Studies will be screened for eligibility according to the selection criteria by two independent reviewers. Eligible studies will be assessed for the quality of their evidence and risk of bias using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute and the GRADE approach, with respect to the measured outcomes (hypertension, diabetes, dyslipidemia and metabolic syndrome). A data abstraction form will be produced on Epi info version 7 and data analysis done on STATA version 14 statistical software. Summary estimates of measures of effects for the association between HAART use and the outcomes will be derived. Random-effects meta-analyses will be performed and I^2 statistic used to assess for heterogeneity between studies with respect to measured parameters. Qualitative synthesis will be used where data is insufficient to produce quantitative synthesis.

Ethics and Dissemination:

The protocol has been reviewed by the Research Governance & Integrity Office of the Research Ethics Committee of the London School of Hygiene and Tropical Medicine and confirmed as not requiring ethical approval. The findings of this study will be made widely available especially to national HIV/AIDS committees formulating HIV/AIDS guidelines for their respective settings.

Prospero registration number: CRD42016042306

Strengths and limitations of this study

Strengths

- This review will provide a summary of published studies on the extent to which antiretroviral therapy is associated to cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia and metabolic syndrome).
- The findings of this review will be very important to authorities involved in health policy formulation in the HIV/AIDS domain especially as several African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS with massive HAART scale-up.

Limitations

- This study will be limited to sub-Saharan Africa, however, this is the region in the world with the greatest HIV/AIDS burden.

Introduction

The past decade has seen the rapid increase in highly active antiretroviral therapy (HAART) coverage worldwide with about 15 million HIV/AIDS patients having access to treatment in 2014, and more than 90% of them being from low and middle income countries most affected by HIV/AIDS [1]. In 2014, HAART coverage stood at 41% in Africa, however, HAART has been increasingly associated with cardiovascular disease (CVD) [2–7]. Several mechanisms have been proposed to explain this association among which prolonged HAART use predisposing to atherosclerosis and major cardiovascular risk factors such as diabetes and hypertension [5,6,8–11] which consequently result in CVD. Even though, earlier studies already suggested a probable association between HAART and CVD, Bloomfield *et al* [2] in a systematic review of literature found that CVD appeared to be more frequent in HIV-infected populations in Low and Middle Income countries. This is particularly important since the greatest increase in HAART coverage has been in these countries [1]. In sub-Saharan Africa (SSA), this association between HAART and CVD has been confounded by the epidemiological transition characterized by the increased prevalence and incidence of non-communicable diseases due to changes in lifestyle patterns. On the other hand, there have been contrary reports of no association between exposure to HAART and cardiovascular disease risk factors [12–15]. Understanding the overall effect of HAART on CVD risk is therefore of public health importance since the continuous HAART scale-up has to be accompanied by appropriate guidelines and measures to ensure the long-term morbidity and mortality of these patients is not negatively affected, especially in low and middle income countries with health systems inadequately equipped to manage these chronic conditions. In a recent systematic review by Dillon *et al* [16] on the association between HIV, HAART and cardio-metabolic traits in the sub-Saharan African population, there was a difference in these traits between HIV-infected patients and uninfected individuals and between HAART-treated and HAART-naive patients, suggesting a probable effect of HAART. However, this review compared the standardized mean differences in blood pressure, blood glucose and lipid profile parameters between the groups and not actually on hypertension, diabetes or dyslipidemia respectively. Moreover, more recent studies have been published since then comparing prevalence and incidence of these risks factors in HAART-treated and HAART-naïve patients. We therefore aim to systematically review, and where appropriate perform a meta-analysis of the published studies on the extent to which exposure to HAART is associated to these cardiovascular disease risk factors in sub-Saharan Africa (Figure 1).

Research Question:

1. Is there an association between highly active antiretroviral therapy and selected cardiovascular risk factors (hypertension, diabetes, dyslipidemia, metabolic syndrome) in HIV/AIDS patients in sub-Saharan Africa?

Research Objectives:

1. To estimate overall measures of effect for the association between HAART and hypertension in HIV/AIDS patients in SSA.

2. To estimate overall measures of effect for the association between HAART and diabetes in these patients.

3. To estimate overall measures of effect for the association between HAART and dyslipidemia in these patients

4. To estimate overall measures of effect for the association between HAART and metabolic syndrome in these patients.

Methods

Study design and eligibility criteria

This will be a systematic review and meta-analysis of published studies.

We will include:

- Cross-sectional, cohort, case-control and randomized controlled trials with data on the prevalence and/or incidence of hypertension, diabetes, lipid profile or metabolic syndrome in HIV/AIDS patients.
- Studies with comparable HAART-treated and HAART-naïve populations.
- Studies published in English and between January 1, 2003 and July 1, 2016 in the selected databases.
- Studies involving participants aged 18 and above, living in one of the countries in SSA.

We will exclude:

- Unpublished manuscripts and conference abstracts.
- Studies comparing the mean blood pressure, glucose and lipid levels in the HAART-treated and HAART-naïve groups rather than the actual prevalence or incidence of hypertension, DM, dyslipidemia and metabolic syndrome respectively.

- Studies with diagnostic criteria and cut-off values for hypertension, DM, abnormal lipid profiles and metabolic syndrome different from those internationally recognized.
- Studies whose data will not be sufficient to calculate appropriate measures of effect
- Same studies published in different journals with the same or a different title.

For studies with several publications of their findings over time, the most recent of the studies will be chosen. For the meta-analysis, studies with a documented measure of effect on the selected cardiovascular risk factors comparing the HAART-treated and HAART-naïve groups will be included. For studies without reported measures of effect, these will be computed if the provided data is adequate.

Search Strategy and Identification of Studies

The following databases will be searched for eligible studies: Medline, Embase, Popline, Africa Wide Information, African Index Medicus and the Cochrane library. Both medical subject headings and free text searches will be used on both on Medline and Embase databases (Table I). Articles returned by the search will be saved to the Zotero version 4.0.29.10 software which will be used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates will be assessed for eligibility according to the inclusion and exclusion criteria. Based on the year of introduction of HAART in sub-Saharan African the review will be focused on articles published between 2003 and 2016.

The full text of all potentially eligible studies will then be reviewed by two independent reviewers (CAD and HB) and any disagreement between reviewers with respect to eligible studies for inclusion in the analysis will be settled by a third reviewer. The reference lists of eligible studies and reviews will also be assessed for more eligible studies. A list of the potentially eligible studies excluded from the final analysis will be produced with the reasons for exclusion mentioned. A PRISMA flow chart detailing the number of articles identified, screened, included and excluded will be produced.

Data abstraction, data analysis and quality assessment

A data abstraction form will be produced on Epi info version 7 statistical software and pretested by the principal investigator. The following data will be extracted from the selected studies: first author, publication year, study design and setting, duration of study, summary information of the socio-demographic and clinical details of the participants such as mean or median age, sex distribution, duration of HIV infection and of antiretroviral therapy, the measures of central tendency, disease frequency and effect for the selected cardiovascular risk factors in the HAART and HAART-naïve groups, statin use among participants, distinction between garden-

variety hyperlipidemia and that resulting from probable HAART use, and any other information considered relevant. The appropriate measures of effect will be derived in studies that provide sufficient data to do so.

Data will be analyzed using STATA version 14 statistical software. Due to the possibility of heterogeneity among the studies, random-effects meta-analysis models will be preferentially reported over fixed-effects models.

For objectives 1, 2, 3 and 4, odds ratios comparing the HAART+ and HAART- groups will be calculated and summarized. The exposure variable will be HAART use and the outcome variable will be the respective cardiovascular risk factors; hypertension, diabetes, dyslipidemia and metabolic syndrome. These outcomes will be defined according to the standard International criteria (Table II). Pooled estimates of measures of effect will be derived using random effects models, the Cochran's Q test will be used to assess for evidence of between-study heterogeneity and the I^2 test statistics will be used to assess the degree of heterogeneity among the studies. Corresponding forests plots will also be produced. The Harbord's test and the Peter's test [17] will be used to statistically assess for funnel plot asymmetry and small-study effects with low P values indicating evidence of plot asymmetry, small-study effect and possibly publication bias. Meta-regressions and subgroup stratified analyses will be done according to important study characteristics such as; study quality, study location, sample size, adjusting of confounders or not, antiretroviral therapy agents and regimens, statin use, and any other relevant parameters identified during the abstraction, to explore if these study characteristics could be potential sources of heterogeneity among the studies. A minimum of 2 studies per subgroup will be considered adequate for the stratified analyses. Qualitative synthesis will be used in cases where data extracted is insufficient to perform quantitative synthesis.

Eligible studies will be assessed for the quality of their evidence and risk of bias by two independent reviewers (CAD and HB) with respect to: flaws in study design, comparability of the HAART+ and HAART- groups, inadequately measured or managed confounders, determination of associations at univariate or multivariate levels of analysis, inaccuracies in the measurements of the key parameters such as hypertension, diabetes, lipid profile and metabolic syndrome or inappropriate diagnostic cut-off values. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Table III) which takes into account all these parameters will be used to grade the overall quality of each individual study as good, fair or poor.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess for quality of evidence provided by the included studies with

respect to the measured outcomes (hypertension, diabetes, dyslipidemia and metabolic syndrome), by the two reviewers (CAD and HB) taking into account the study limitations, inconsistencies, indirectness, imprecision and publication bias. Overall quality of evidence following assessment will be graded as high, moderate, low or very low.

Reporting and Amendments to protocol

The PRISMA-P guidelines for the reporting of systematic reviews and meta-analysis protocols have been used for this systematic review protocol as illustrated on Table IV. The completed report will be reported in accordance with the PRISMA guidelines using the PRISMA checklist. Amendments will be made to the study if and only if necessary and will be clearly documented and justified.

Conclusion

There still remains contradictory evidence on this association between HAART and CVD in SSA. As such this review will present a summary of what is documented in sub-Saharan Africa as far as cardiovascular disease epidemiology and HIV/AIDS is concerned. This is of utmost importance since many sub-Saharan African countries are currently aligning to the WHO recommendations of test and treat for HIV/AIDS. This massive HAART scale-up could be faced with rather increasing morbidity and mortality from cardiovascular diseases in HIV/AIDS patients, if these underlying mechanisms are not well understood and measures such as concurrent scale-up of CVD screening and treatment services envisaged.

Ethical considerations and dissemination

The Research Governance & Integrity Office of the Research Ethics Committee of the London School of Hygiene and Tropical Medicine reviewed the study and affirmed no ethical approval is required. The findings of this study will be made widely available to the appropriate authorities involved in health policy formulation especially with respect to HIV/AIDS treatment guidelines and also to the scientific community for subsequent updating as more recent studies become available.

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List of Abbreviations

CVD	Cardiovascular Disease
HAART	Highly Active Antiretroviral Therapy
HIV/AIDS	Human Immuno-Deficiency Virus/Acquired Immuno-Deficiency syndrome
SSA	Sub-Saharan Africa

Authors' contribution:

CAD and HB conceived and designed the experiments. CAD produced the manuscript. HB reviewed the manuscript. Both authors approved the final copy of the manuscript

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Competing Interests:

The authors declare no competing interests exists

Table I: Search strategy for the Medline, Embase and Africa-Wide Information for the review on the association between highly active antiretroviral therapy and selected cardiovascular disease risk factors in sub-Saharan Africa

#	Search words
1	Africa [MeSH terms] OR Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Canary Islands OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Ivory Coast OR Cote dIvoire OR Jamahiriya OR Jamahiryia OR Kenya OR Lesotho OR Liberia OR Libya OR Libia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Mocambique 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 St Helena OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Western Sahara OR Zaire 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 North Africa OR North African OR Northern Africa OR Northern African OR South African OR Southern Africa OR Southern African OR subSaharan Africa OR subSaharan African OR sub-Saharan Africa OR sub-Saharan African
2	Antiretroviral therapy, Highly Active [MeSH terms] OR highly active antiretroviral therapy OR antiretroviral therapy OR antiretroviral OR HAART OR ART OR anti-retroviral OR Nucleotide reverse transcriptase inhibitor OR NRTI OR Non-nucleoside reverse transcriptase inhibitor OR NNRTI OR Protease inhibitor OR PI OR PIs OR lopinavir OR ritonavir OR lamivudine OR zidovudine OR stavudine OR nevirapine OR efavirenz OR tenofovir OR emtricitabine OR atazanavir OR darunavir
3	Cardiovascular diseases [MeSH terms] OR hypertension OR high blood pressure OR systolic blood pressure OR diastolic blood pressure OR SBP OR DBP OR diabetes mellitus OR diabetes OR type 2 diabetes OR type 2 diabetes mellitus OR diabetic OR type 2 diabetic OR dysglycemia OR dysglycaemia OR hyperglycemia OR hyperglycaemia OR glucose OR insulin resistance OR insulin OR hyperinsulinemia OR hyperinsulinaemia OR dyslipidemias OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR hypertriglyceridemia OR cholesterol OR triglyceride OR triglycerides OR HDL OR LDL OR VLDL OR hyperlipoproteinemia OR lipoprotein OR hyperlipidaemia OR hypercholesterolaemia OR hypertriglyceridaemia OR metabolic syndrome
4	#1 AND #2 AND #3

Table II: Definition of outcomes per included studies

Outcome	Criteria	Organization
Hypertension	SBP ≥ 140 and/or DBP ≥ 90 mmHg	WHO/JNC 7
Diabetes	FBG ≥ 126 mg/dL (7.0 mmol/L) OR RBG ≥ 200 mg/dL (11.1 mmol/L)	WHO/ADA
High TC	Serum TC ≥ 200 mg/dL (5.17 mmol/L)	NCEP/ATP III
High TG	Serum TG ≥ 200 mg/dL (2.23 mmol/L) Serum TG ≥ 150 mg/dL (1.70 mmol/L)	NCEP/ATP II NCEP/ATP III
Low HDL	Men: Serum HDL < 40 mg/dL (1.03 mmol/L) Women: Serum HDL < 50 mg/dL (1.29 mmol/L)	NCEP/ATP III
High LDL	Serum LDL ≥ 130 mg/dL (3.36 mmol/L) Serum LDL ≥ 100 mg/dL (2.59 mmol/L)	NCEP/ATP III NCEP/ATP III
Metabolic Syndrome (≥3 parameters)	WC - Men >102 cm, WC - Women >88 cm Triglycerides ≥150 mg/dL HDL - Men <40 mg/dL, HDL - Women <50 mg/dL Blood pressure ≥130/85 mmHg Fasting glucose ≥110 mg/dL	NCEP/ATP III

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, FBG – Fasting blood glucose, RBG – Random blood glucose, WC – Waist Circumference, WHO – World Health Organization
JNC 7 - 7th report of the Joint National Committee on the prevention, detection, evaluation and treatment of high blood pressure, ADA – American Diabetes Association.
NCEP/ATP III - National Cholesterol Education Program/Adult Treatment Panel guidelines III
NCEP/ATP II - National Cholesterol Education Program/Adult Treatment Panel guidelines II
TG – Triglycerides, TC – Total Cholesterol, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein

Table III: Quality Assessment Tool for Observational Cohort and Cross-Sectional-Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Table IV: PRISMA-P 2015 checklist for the study protocol of the systematic review on the association between highly active anti-retroviral therapy and selected cardiovascular risk factors in sub-Saharan Africa.

Section and Topic	Item No	Checklist Item	Page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NAP
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the 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	NAP
Support			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	NAP
Role of sponsor	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
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	11
Study records			
Data management	11a	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6&7
Selection criteria			
Data collection	11b	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6&7
	11c	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6&7
Data items	12		
Outcome and prioritisation	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6&7
Riskofbias in individual subjects	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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies,	7
	15c	including any planned exploration of consistency (such as I2, Kendall's ô) Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

Figure Legend

Figure 1: Conceptual framework showing the multiple CVD risk factors and the investigated association between HAART and the selected CVD risk factors.

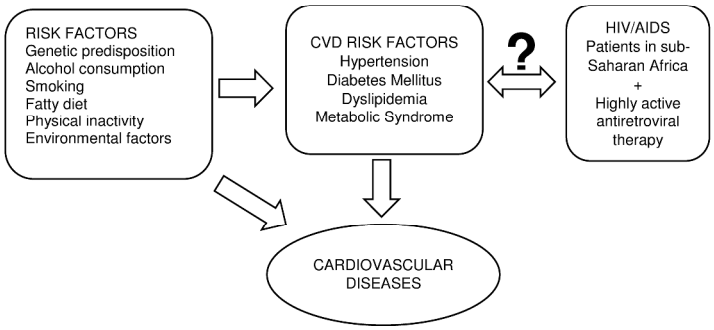

Figure 1: Conceptual framework showing the multiple CVD risk factors and the investigated association between HAART and the selected CVD risk factors.
The single headed arrows indicate causality and the double headed arrow indicates association.

251x324mm (600 x 600 DPI)

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