Morbidity and Mortality in the Antiretroviral Era in Sub-saharan Africa: A Systematic Review Protocol

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Abstract

Background: Worldwide, Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS) remains a public health concern. The prevalence of HIV in Sub-Saharan Africa is one of the uppermost in the world. This study aims to identify the determinants of morbidity and specific causes of mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.

Method/design: Observational studies will be systematically reviewed reporting on morbidity and mortality in the antiretroviral therapy (ART) era in Sub-Saharan Africa. We will search for relevant studies from Google Scholar, PubMed, and CINAHL databases. Two review authors will independently screen titles, abstracts and full-text articles in duplicate, extract data and assess the bias. Discrepancies will be resolved by discussion or arbitration of a third review author. The study will use the Preferred Reporting Item of Systematic Review (PRISMA 2015) guideline. We will use R software to analyze and synthesize the data, the information will be captured into a spreadsheet regarding the most causes of hospitalization and death related to HIV in the antiretroviral treatment, Graphic displays will be used to visually compare the prevalence of comorbidities across the study region. This will also enable to provide any form of patterns in the comorbidities.

Discussion: This review will summarize the determinants of morbidity and causes of mortality in the antiretroviral era in Sub-Saharan Africa. The findings of this study will help to improve opportunistic infection's prevention and clinical outcomes in the ART era.

Systematic review registration: PROSPERO CDR42019141933

Background

Worldwide Human Immunodeficiency Virus (HIV) / Acquired Immunodeficiency Syndrome (AIDS) is one of the major causes of death with an estimation of 3.1 million of death each year [1]. Approximately 36.9 million persons in the world are living with HIV, and 1.8 million persons were newly infected in 2017 [2]. Moreover, it has been reported that 940,000 persons worldwide died from AIDS-related illnesses in 2017 [2].

Sub-Saharan Africa is the region most affected by HIV and AIDS in the World. The Southern African Development Community (SADC) countries are generally most affected by HIV and AIDS [3]. According to some authors, different factors that make African population more susceptible to HIV and AIDS in the world. Among them, concurrent or simultaneous sexual intercourse practices by African men is argued as a major role player in the vast spread of HIV in Sub-Saharan African countries as opposed to high-income countries where there are serial monogamy practices [4]. Other authors argued that political instability, underdevelopment, widespread poverty and poor infrastructure are the major reasons for the rapid spread of HIV in African countries [5]. Sub-Saharan Africa has the biggest share of the 40 million people currently living with HIV and AIDS in the world [6]. In 2014 studies reported that 25.8 (24.0-28.7) million people were estimated to be living with HIV, the region accounted for nearly 70% of new infections worldwide [6].

According to UNAIDS (2018), 300,000 men and 270,000 women died of AIDS-related illnesses in Sub-Saharan Africa in 2017 [7]. Antiretroviral therapy (ART) has decreased morbidity and mortality among people living with HIV [8]. However, despite the availability of antiretroviral therapy (ART), a substantial portion of HIV infected patients have continued to be hospitalised and die from both AIDS-related and non- AIDS-related causes [9]. This review is therefore aimed at identifying the determinant of morbidity and specific causes of mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa and suggest novel ideas for future research.

Methods/design

We are going to follow the Preferred Reporting Items for the Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 guideline (additional file1) [10]. We will systematically review observational studies reporting on morbidity and mortality in the ART era in Sub-Saharan Africa.

Research question

Main research question

What are the determinants of morbidity and specific causes of mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa?

Specific research questions

1. What are the research gaps on morbidity and mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa?

2. What are the reasons for hospitalizations in the antiretroviral treatment (ART) era in Sub-Saharan Africa?

3. What are the causes of death in the antiretroviral treatment (ART) era in Sub-Saharan Africa?

Eligibility of research questions

The Population, Intervention, Comparison and Outcomes (PICO) for the research questions will be used to break down the clinical questions into searchable keywords

Population

Participants included in eligible studies will be adult patients, 18 years or older infected with HIV during the antiretroviral therapy.

Interventions

The antiretroviral therapy (ART) used to treat people with HIV infection in Sub-Saharan Africa from 2008 to 2018.

Comparison

Not planned

Outcomes

The reasons for hospitalization and the causes of mortality among people with HIV infection, dying in the antiretroviral era will be described and that will help clinicians and patients living with HIV to have comprehensive information and find strategies to improve treatment outcomes.

Aims And Objectives Of The Study

Main aim

To identify the determinants of morbidity and specific causes of mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.

Objectives

1. To identify available literature or the research gaps on the morbidity and mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.
2. To reveal the reasons for hospitalizations in the antiretroviral treatment (ART) era in Sub-Saharan Africa.
3. To determine the causes of mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.

Eligibility criteria

Inclusion criteria

- Studies reporting on morbidity and mortality in the antiretroviral era in Sub-Saharan Africa.
- Studies conducted between 2008 and 2018.
- Studies reporting on adult males or females aged 18 years or older.
- Peer-reviewed English language publications
- Observational studies on Sub-Saharan Africa.

Exclusion Criteria

- Studies reporting on morbidity or mortality in HIV-uninfected patients.
- Studies reporting on adult males or females under the age of 18 years.

Search Strategy for identifying relevant studies

The first step is an initial limited search of the electronic databases. To identify relevant studies, we will search in the following database: Google Scholar, Pub Med, and CINAHL. Studies published in English from January 2008 to December 2018 in Sub-Saharan Africa. This initial search will be monitored, exported on EndNote X9 reference manager for abstract and full article screening. The duplicated article will be deleted. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. For abstracts and full article screening, the EndNote library will be shared with a second reviewer. Any discrepancies in the results of the abstract screening will be resolved through a discussion until consensus is reached. A third screener will help to resolve discrepancies in full article screening results.

Below is the main search strategy conducted in PubMed.

Table 1
Search strategy in PubMed

Search	Search terms
#1	(Morbidity OR Opportunistic infection related HIV) [MeSH Terms]
#2	(Mortality OR Death) [MeSH Terms]
#3	(ART OR Antiretroviral therapy) [MeSH Terms]
#4	(Sub-Saharan Africa) [Title/Abstract]
#5	#1 AND #2 AND #3 AND #4

We will adapt this search strategy for a possible extension to other databases and it will be adapted as we progress through the review. We will also contact experts in the field to identify additional eligible studies and we will manually search reference lists from relevant studies.

Publications duplicated in the research results will be treated as a single study for the review. To maintain transparency in the review selection process, a PRISMA Flow Diagram will be followed in each stage of the selection process[11]. In addition, a list of the studies excluded during the full-text review will be documented as an Additional file 2, with brief reasons for their exclusion.

Data collection and analysis

Two reviewers will follow the inclusion criteria for selecting studies, articles will be identified and screened by their titles and abstracts eligibility. The full texts of articles will be retrieved. The process of literature selection and reasons for exclusion and inclusion will be documented by a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram (Fig. 1) [11].

Data extraction and management

Data will be extracted in accordance with the methods outlined in the Cochrane Handbook for systematic reviews of interventions. The data extraction form will be designed, and it will be collected in the following order:

1. First author-name
2. Years of publication,
3. Geographical location
4. Sample size
5. Participants (age, sex)
6. Study design
7. Intervention
8. Outcome
9. Conclusion

If there are disagreements between the two review authors, it will be resolved through discussion and by consulting a third author. For managing missing data, we will contact the corresponding author of the respective studies to obtain the required details.

Data analysis and synthesis.

We will systematically review observational studies that examined morbidity and mortality in antiretroviral therapy in Sub-Saharan Africa. Statistical heterogeneity among the included studies will be assessed by the X^2 test on Cochrane's Q statistic. Significant heterogeneity will be indicated if *P*-value is less than 0.1. Heterogeneity will be quantified by using the I-squared values. Values of 25, 50, and 75% for I-squared will be represented low, medium, and high heterogeneity, respectively [12]. If substantial heterogeneity is detected, a subgroup will be performed to investigate the possible sources of heterogeneity using the following grouping variables: gender (male, female). R software will be used to analyze and synthesis the data. We will capture information into a spreadsheet about the most causes of hospitalization and death related to HIV in the antiretroviral treatment. Graphic displays such as Bar chart or multiple bar chart component will be used to visually compare the prevalence of comorbidities across the study region. This will also enable to provide any form of patterns in the comorbidities.

Subgroup analysis

A subgroup analysis will be conducted following Gender (male vs female). The heterogeneity between subgroups will be detected by using the X^2 test on Cochrane's Q statistic.

Risk Of Bias Assessment And Quality Of Evidence

Two reviewers (MRG and GAM) will independently perform each quality assessment. Differences in ratings will be resolved through discussions. We are going to use Cochrane risk of bias tool to assess publication bias, addressing assessments for random sequence generation, concealment of allocation, blinding and the outcome measurements, and completeness of outcome reporting [13]. The value of the low, high or unclear risk of bias will be used for the included study. To assess the statistical significance of publication bias across studies we will use Visual assessment of the funnel plot and the Egger's statistic [14].

The Mixed Methods Appraisal Tool (MMAT) version 2018 will be used to assess the quality of evidence for each outcome [15]. This tool will allow us to assess the appropriateness and the quality of research. Studies will be scored following the specific criterion. The tool permits to appraise the methodological quality of five categories of studies which are qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed methods studies.

Discussion

Antiretroviral treatment (ART) is known for improving the quality of life of infected individuals, reducing opportunistic infections and AIDS-related mortality [16]. It was anticipated initially that the dramatic scale-up of ART would result in clinics and services becoming over-stretched and have a negative quality of care, however, after one-year, studies have shown that there was no significant effect on patients results related to the increase in antiretroviral therapy provision, either in terms of either morbidity or mortality [17]. This study will systematically review articles reported in Sub-Saharan Africa on the morbidity and mortality in the antiretroviral therapy from 2008 to 2018, following the inclusion and exclusion criteria.

Abbreviations

ART
Antiretroviral therapy
HIV/AIDS
Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
PICO
Population, Intervention, Comparator and Outcome
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SADC
Southern African Development Community
UKZN
University of KwaZulu-Natal
GRADE
Grading of Recommendations Assessment, Development, and Evaluation

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated from this study will be included in the published systematic review article and will also be available on request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

MRG conceptualised the study and prepared the manuscript under the guidance and supervision of NM. AGAM revised the draft for its intellectual content. All authors contributed to the development and design of the study. MRG and BN contributed to the methodology and reviewing of the manuscript. All authors contributed to the final version. All authors read and approved the final manuscript.

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Figures

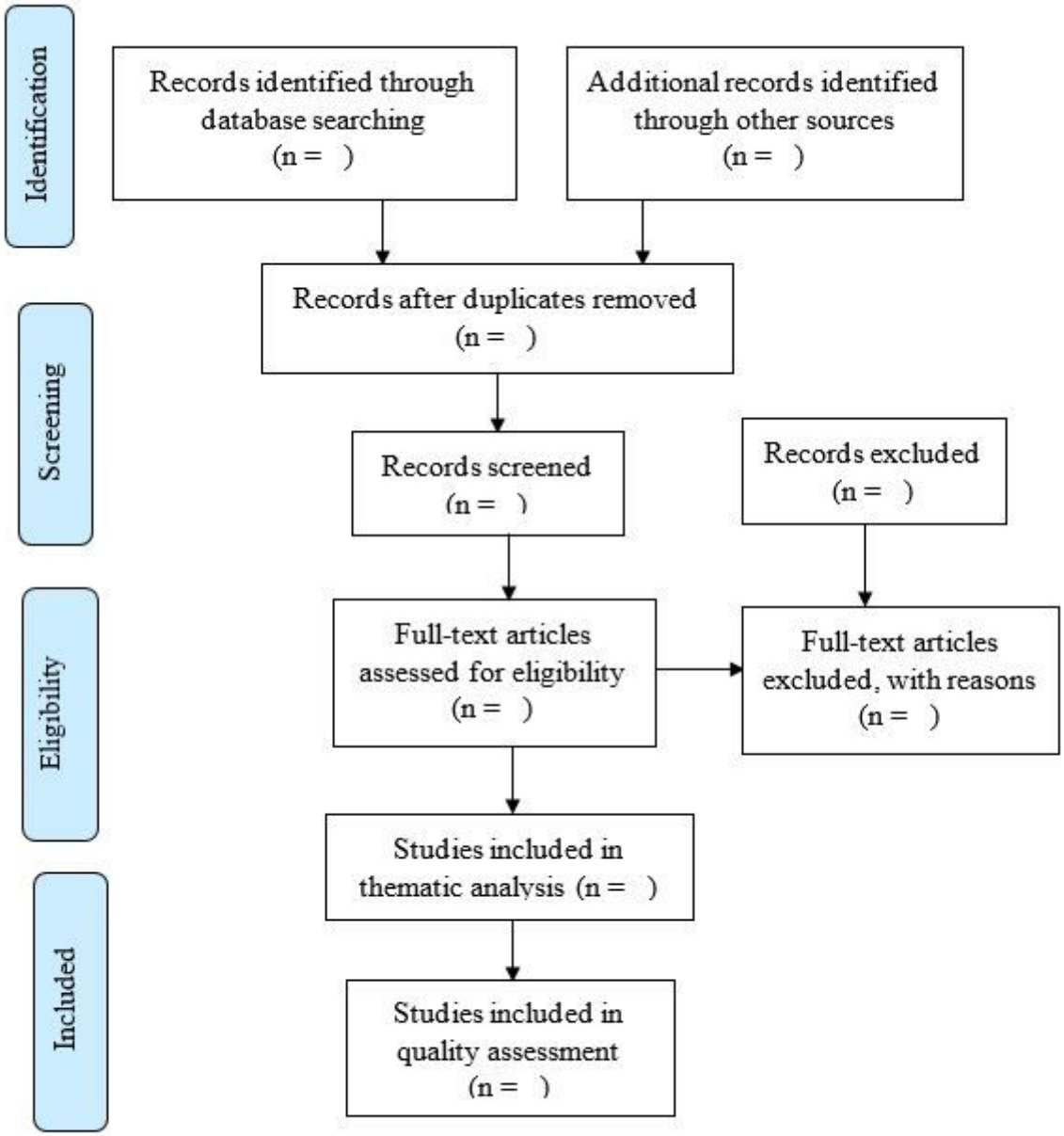

Figure 1

The PRISMA Flow Diagram for the systematic review screening process

Supplementary Files

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- PRISMAPCHECKLISTPROTOCOL.docx