Egyptian Journal of Community Medicine

Esophageal Cancer and HIV Infection in the East African Corridor: Protocol for Comprehensive Meta-Analysis of the Impact of CD4 Count and ARV Treatment Adherence in Disease Etiology

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Submission Date: 2024-06-18

Revision Date: 2024-09-09

Acceptance Date: 2024-10-05

Key Words: Esophageal cancer, HIV, CD4 count, ARV adherence, East African corridor.

A B S T R A C T

Background: The East African corridor is uniquely home to the highest concentrations of both esophageal cancer cases and HIV infections in the world. **Objective**: To investigate the relationship between HIV infection parameters such as CD4 count and ARV compliance and the development of esophageal cancer in this highly endemic area. **Methods:** Based on the PRISMA-P 2015 guidelines, this protocol has been written. We will systematically search Web of Science, African Journals Online, Embase, Scopus, Cochrane Library, and Medline/PubMed for relevant literature. Studies with esophageal cancer as an outcome, and HIV status as an exposure, will be considered eligible. Standards tools will be used in the quality assessment process. Egger's statistical test and funnel plots visualization will be used to assess for potential publication bias. Separate reviewers will choose the studies, gather data, and assess each included study's risk of bias. GRADE method will be used to assess the degree of certainty in the evidence, and RevMan 5.4 and Stata 17.0 will be used for the meta-analysis. Although the East African corridor has the highest number of people living with both HIV and esophageal cancer in the world, the level of association between these two diseases remains unknown. **Ethics and dissemination:** This study will comprehensively evaluate the available data on the subject to establish the possible links that exist between EC and HIV infection, to inform clinical practice on the need to strengthen disease surveillance and future research. **Review registration:** PROSPERO CRD42023473775.

INTRODUCTION

Esophageal cancer (EC) is a highly prevalent cancer worldwide and a major cause of death.[1] It kills over 544,076 people every year, most of whom live in two distinct geographical bands in Central Asia and along the East African corridor stretching from South Africa to Ethiopia.[2] In these high-risk regions, almost all cases are esophageal squamous cell carcinomas.[3] In the early stage of esophageal cancer, it usually doesn't show any symptoms. Dysphagia, with or without weight loss, becomes evident as the disease advances.[1] Most patients present with advanced disease, and survival is generally poor (3-6 months). Affected patients are easily identifiable on surgical and medical wards, deeply emaciated and holding spittoons to manage their secretions.[4] As coincidentally happens, this same corridor is also the main site of HIV infections in Africa and worldwide. According to a study carried out by UNAIDS in 2022, of the approximately 39 million people living with HIV (PLHIV) worldwide in 2022, more than 25.7 million live in Africa.[5] On the African continent, 20.3 million People living with HIV/AIDS (PLWHA) are found in the sub-regions of East and Southern Africa (East Africa Corridor), while the sub-regions of

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North, West and Central Africa have 5.4 million PLWHA.[6]

This geographical cohabitation of these two diseases, which have no real treatment, raises concerns about a potential crisis in this corridor. Above all, HIV infection is clearly recognized as a risk factor for several cancers, including liver, stomach and anal cancers, as well as Kaposi's sarcoma.[7,8] So far, the relationship between HIV infection and EC has been established in the USA as significant,[9] while a global meta-analysis of studies published before October 2020,[10] showed no relationship between HIV infection and EC risk. This difference could be explained by epidemiological, genetic, and clinical variations, as well as differences in healthcare access and regional environmental factors specific to each geographic area.[11] Additionally, medical practices, viral subtypes, and demographic characteristics may also play a significant role in this disparity.[12] Moreover, due to the limited number of studies (10), the systematic review by Geng et al.[10] did not consider the geographical location of the studies. At the time of writing, only two studies from the African continent were available. This oversight makes it difficult to assess the extent of the association between these two diseases in their main stronghold, Africa. Until today, no research has looked the link between CD4 count and ARV treatment adherence and EC in Africa, especially as several independent studies published on both sides of the corridor are available and present multiple controversies. This systematic review, covering studies published up to May 2024, aims to answer these two crucial questions: What is the scope of the correlation between HIV disease and esophageal cancer risk in highly endemic areas of Africa? What is the impact of falling CD4 levels and non-adherence to ARV treatment on the risk of EC in Africa? The seeks of this work is to provide an in-depth analysis of the involvement of HIV disease in the development of EC in the East African corridor. In addition, our research will elucidate the impact of CD4 count, disease duration, and adherence to ARV treatment on the risk of developing EC, using a wide range of analytical methods to fill any potential evidence gaps.

METHODS

***Protocol registration*:** This work protocol was created using the PRISMA-P guidelines that assess interventions in the field of medicine.[13,14] CRD42023473775 is the registration number of this study on PROSPERO website.

Eligibility Criteria: **Study types:** Original observational research (Cross-sectional, Cohort studies (prospective and retrospective), and Case-control studies) published before May 2024 will be included. There won't be any limitations put on trial design, year of publication, publication status, language, setting. **Types of participants:** Participants living in Africa for at least 10 years and with esophageal cancer (regardless of type) will be included in this study. Participants will be included if they are over 18 years old, regardless of gender or co-morbidities.

Types of outcome measures: The following Primary outcomes will be extracted: HIV status, Level of CD4, Duration of HIV infection, Adherence to ARV treatment. The following secondary outcomes will be extracted: Sex, Age, Study design, Geographical repartition of study by countries. Based on the results reported in the selected study, this preliminary list of outcomes will be expanded.

Search strategy and data sources

Electronic searches: Research released through October 2024 in the Web of Science, African Journals Online, Embase, Scopus, Cochrane Library, and PubMed/Medline databases will be searched. To increase the number of articles that may be relevant, a combination of free index and text terms will be used in these searches (see Table 1 for initial search strategy in PubMed/Medline). The keywords proposed by the researchers are as follows: “HIV Infection” OR “Level of CD4” OR “Adherence to ARV treatment” OR “HIV serology” OR “HIV status” OR “Risk factor” AND “Esophageal carcinoma” OR “Esophageal Adenocarcinoma” OR “Esophageal Neoplasm” OR “Esophageal Cancer” OR “Esophageal squamous cell carcinoma”. To adequately reduce selection risk and detection bias, no publication date and language constraint will be taken into consideration during searches process.[15]

Searching other resources: The International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), in ClinicalTrials.gov (www.clinicaltrials.gov), in Google Scholar (https://scholar.google.dk/), and in references list of including studies will then undergo manual cross-searches.

Selection of studies: To streamline the process of review and selection, initially, search findings will be automatically exported to Endnote for duplication removal before being transferred to the Rayyan

software.[16] The authors (EJN, GTK) will independently screen the abstracts and titles. After that, another independent selection will be made by looking through the complete texts of the articles that were kept after the first review. Any disagreement will be settled by conversation or, if required, by seeking the advice of an impartial third party. By using this process, bias can be reduced when choosing which studies to include or reject.[15] An adapted flow diagram will display trial selection in compliance with the PRISMA statement.

Data extraction: Authors will methodically gather an extensive set of data for every study that satisfies our eligibility requirements in order to guarantee a thorough analysis. Study's publication date, country, HIV status, first author, sample size, HIV diagnosis techniques, relative risk or odds ratio, and 95% confidence interval (CI), length of data collection, study population characteristics (sex, age), data collection techniques, and participant recruitment strategies will be gathered from included study. Specifically, data related to HIV status, Level of CD4, Number of years of HIV sick, and Adherence to ARV treatment will be a central focus. When comparable data could not be found in the study, they were computed using the relevant software. We will email the corresponding authors to request any additional data that might not have been reported in the publication, either inadequately or not at all. Research done in several different nations will be categorized by nation, with the initials of the nation coming after the author's name.

Quality assessment: An essential part of this research methodology is the evaluation of study quality. It will be independently assessed by the authors for each study to ensure impartial evaluation. Two well-known instruments that are suited to the study design will be used: the Agency for Healthcare Research and Quality (ARHQ) tool for cross-sectional studies[17] and the Newcastle-Ottawa Scale (NOS) for cohort studies and case-control.[18] The subsequent meta-analysis will only include studies that these assessment tools have categorized as being of moderate to good quality. This strict requirement guarantees that our analysis is supported by solid and trustworthy data.

Data synthesis and Statistical analysis: In order to obtain deeper insights, the data analysis and synthesis process will be conducted methodically, starting with a general overview of the studies and then classifying them. As recommended by Kufe et al.[16], we will perform both meta-regression analyses and meta-analysis for similar covariates found in the identified studies when a sufficient number of studies or data are available.[19] Effective summarization of the features of the included studies will be achieved by generating a detailed summary table and a forest diagram as a visual aid. RevMan 5.4 software will be used to carry out the statistical analyses. Using the approach proposed by Higgins et al.[20], we will compute the I^2 statistic to assess the relative heterogeneity among the included studies. I^2 equal to 25%, 50%, and between 75% to 100% are considered as low, medium, and high heterogeneity respectively. We will use "one study removed" strategy to find possible outliers and evaluate their impact on the overall estimates. Studies that fall outside the 95% CI for the mean effect size will be classified as outliers. Furthermore, a variety of categories, including study type, HIV status, Level of CD4, Number of years of HIV illness, Adherence to ARV treatment, age, sex, and geographic distribution of studies, will be explored through subgroup analyses and meta-regressions. Egger's regression test will be used to determine the strength and stability of associations, and the funnel plot will be utilized to evaluate publication bias.[21,22] The identification of publication bias occurs when the p-value is less than 0.10.

If there is little variation amongst the research work, a meta-analysis will be done to get a pooled estimate. Reversely, we will present each study's findings in a descriptive manner if substantial heterogeneity prevents data from being pooled. The main metric used to express the connection between HIV infection and EC will be the odds ratio. We will use the adjustment and filling methods described by Taylor and Tweedie[23] to evaluate the findings' resilience. If conducting a meta-analysis is not possible, a critical synthesis will be conducted in accordance with Popay et al.[24] guidelines. Lastly, in compliance with PRISMA guidelines, the findings will be painstakingly documented and submitted for publication.[13] Our research findings will be reliable, transparent, and rigorous thanks to this thorough approach.

Meta-bias(es): By closely examining the funnel plot, potential publication bias will be evaluated. Then, any asymmetry found in the funnel plot will be statistically evaluated using the Egger regression test.[21] An easier way to evaluate the bias in included studies is with this visual tool. The stability and strength of associations will be assessed using Trim and Fill test, Egger's regression test, and contoured

funnel plot to confirm that the potential asymmetry of the funnel plot is not linked to the publication bias of the studies.[21,22] Metabias will be acknowledged when P-value falls below 0.10.[25] STATA version 17.0 (StataCorp LP, Texas) will be used to assess the risk of bias. After each author completes their assessment, the authors will get together for a debriefing to discuss any discrepancies or uncertainties that may have arisen. The validity and reliability of our research findings are improved by this cooperative approach, which guarantees a cohesive and thorough evaluation process.

Summary of findings: The GRADE system, as proposed by Tipp et al.[26], will be employed by the authors to assess the quality of evidence. Criteria for upgrading confidence in effect estimates and for downgrading it will be used to evaluate the quality of the evidence.[27] Using each of the major outcomes (HIV status, level of CD4, number of years of HIV sick, and adherence to ARV treatment), a table summarizing the results will be created. The different evidence bodies will be handled in accordance with the Cuello-Garcia et al.[28] scale.

CURRENT STATUS OF KNOWLEDGE

This protocol aims to methodically compile the available data regarding the correlation between HIV infection and the risk of EC in regions of Africa that are endemic for the virus. The implications of our research will encompass a wider comprehension of the ways in which the etiology of EC in Africa is influenced by factors such as CD4 count, duration of the disease, and adherence to ARV therapy. Crucially, the goal of our work is to refute the disputes that have surfaced from independent research published across Africa. Once this knowledge is clarified, it will assist governments and organizations in crafting legislation to better control these two diseases in the East African corridor. Collectively, these measures will aid in decreasing the incidence and impact of these two diseases, which frequently result in tragic results for patients.

CONCLUSIONS

We hypothesize that there is no significant relationship between HIV/AIDS and susceptibility to esophageal cancer (EC) in the East African corridor, despite the increasing global incidence of EC and its notable impact on the region. Our goal is to provide accurate and data-driven insights regarding the precise contribution of patients' CD4 levels, ARV adherence, and HIV infection to the risk of EC. Equipped with this understanding, we can formulate efficacious policies and interventions with the objective of mitigating the spread of these two catastrophic illnesses that have established themselves in this area. By placing a strong emphasis on evidence-based practices, we hope to significantly lessen the incidence of esophageal cancer and HIV/AIDS in this area.

***Trial registration*:** PROSPERO CRD42023473775.
Fundings: This research is co-funded by the National Research Foundation (NRF) and the SA Medical Research Council (MRC).
Conflicts of interests: There is no conflict of interest.
Authors' Contributions: This work was designed, produced, validated, and edited by the authors (EJN and GTK). However, the funding was obtained by E.J.N. Additionally, they reviewed and gave their approval to the manuscript's published version.
Acknowledgments: We express our gratitude to Walter Sisulu University for providing complimentary network access; and to the librarian for assisting us in formulating the search strategies that we employed to look up studies in the databases.

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Cite this article as Eugene Jamot Ndebia, Gabriel Tchuente Kamsu. Esophageal Cancer and HIV Infection in the East African Corridor: Protocol for Comprehensive Meta-Analysis of the Impact of CD4 Count and ARV Treatment Adherence in Disease Etiology. *Egyptian Journal of Community Medicine*, 2025;43(2):92-98.
DOI: 10.21608/ejcm.2024.298036.1304

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	31
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-7
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	239-241
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	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	247-250
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	247-250
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	247-250
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	34-61
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	62-69
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	77-103
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	104-126
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	☒	☐	111-120
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	128-129

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	127-130 201-204 155-156
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	140-153
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	(106-107)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	(91-103)
Risk of bias in individual studies	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	☒	☐	154-161
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	163-181
	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 (e.g., I^2, Kendall's tau)	☒	☐	176-178
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	164-167
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	187-190
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	192-204
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	205-214

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015 Jan 2;349(jan02 1): g7647.