STUDY PROTOCOL

REVISED Salivary biomarkers associated with the progression of disease in people living with HIV: A scoping review protocol [version 2; peer review: 2 approved, 1 approved with reservations, 1 not approved]

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Abstract

Background: Biomarkers are measurable indicators of normal biological processes, which provide an objective assessment of the physiologic state of living systems. Saliva contains several biomarkers that serve as a diagnostic tool in health and disease. Evaluation of a multitude of salivary components could potentially predict the clinical outcome. This is especially critical in a chronic, potentially life-threatening condition like human immunodeficiency virus (HIV) infection. Scrupulous evaluation of relevant biomarkers could facilitate the early detection of HIV, determine the stage of infection and monitor the disease progression. Currently, there is a paucity of validated biomarkers in saliva predicting the disease progression in people living with HIV. In this scoping review, we aim to provide an overview of the available evidence on salivary markers associated with the progression of disease in people living with HIV.
Methods: The authors shall develop a tailored search strategy for each database using relevant keywords. We will search for eligible studies indexed in the following databases: MEDLINE, EMBASE, and the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and gray literature. We will restrict the search to studies published in the English language. Following deduplication, all search results will be exported to the EPPI reviewer web, where two independent reviewers using a data extraction tool developed and

Open Peer Review

Approval Status ✓ ✗ ? ✓

	1	2	3	4
version 2 (revision) 17 Sep 2021				✓ view
version 1 19 Feb 2021	✓ view	✗ view	? view	

1. **Sudhir Prabhu**, Father Muller Medical College, Mangalore, India
2. **Pascale Ondoa**, African Society for Laboratory Medicine, Addis Ababa, Ethiopia
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Abidemi Okechukwu, University of Arizona,

pretested by the review authors will screen eligible studies. The result of this review will be reported using the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist and reporting guidelines.
Discussion: The proposed scoping review protocol will enable the identification and assessment of salivary biomarkers, which can predict disease progression in patients with HIV infection. The synthesis of evidence from this review will assist in improving our current understanding of biomarkers used to evaluate the progression of HIV infection.

Keywords
People living with HIV, PLWHA, HIV, AIDS, Biomarker, Saliva

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the Pathogens gateway.

This article is included in the Manipal Academy of Higher Education gateway.

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Author roles: Prasad P: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software; **D'Souza V**: Conceptualization, Data Curation, Formal Analysis, Investigation, Resources, Software; **Mithra P**: Conceptualization, Data Curation, Formal Analysis, Investigation, Software, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Radhakrishnan R**: Conceptualization, Methodology, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

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REVISED **Amendments from Version 1**

Changes made in the manuscript are in response to the third reviewer's comments who has approved the current version with reservation

1) The title change: As per "2017 Guidance for the Conduct of JBI Scoping Reviews", which states that protocols should also be identified with "protocol", we have included the term "protocol" in our title.

2) Two citations have been added to the manuscript. (In response to comments given by the third reviewer)

3) In specific sections of the version 1 manuscript, biomarkers were used by the authors to imply salivary biomarkers. This scoping review is limited to salivary biomarkers and changes have been made in the manuscript to make it clear to the reader in version 2.

4) In response to the third reviewer's comments, we have changed "HIV positive individuals" to "people living with HIV/AIDS"

Any further responses from the reviewers can be found at the end of the article

Introduction

The human immunodeficiency virus (HIV), belonging to the *Retroviridae* family, targets the body's immune system[1]. Since it has high affinity for the receptors present on the surface of CD4+ T-lymphocytes and macrophages, it makes a person vulnerable to infection[2]. Infection of the target cell by HIV results in the production of progeny virions depleting the CD4+ lymphocytes and ensuing immunosuppression of the host. The pathophysiology of HIV involves a dynamic host-virus interaction, resulting in acquired immunodeficiency syndrome (AIDS) in severe cases[3]. The incubation period for the virus is around 5–10 years in adults[4,5]. This broad interval between HIV infection and the development of symptoms can be attributed to several hosts and virus-related factors such as the development of new viral strains, the immune status of the host, as well as environmental cofactors[6].

HIV viral load, CD4+ T-cell count in peripheral blood and quantitative measurements of soluble markers present in plasma, like neopterin, tumor necrosis factor-alpha (TNFα), interleukins (ILs), beta 2-microglobulin (B2M), soluble CD8, etc have been used as surrogate markers to assess the progression of HIV infection in patients[7]. CD4+ T-cell count also evaluates the efficacy of the host's immune response to antiretroviral therapy (ART)[8–11]. The onset of AIDS, which implies a progression of HIV infection, could be predicted accurately by monitoring the percentage of CD4+ T lymphocytes in the peripheral blood[12]. However, in patients on ART, the CD4+ T-cell counts are not reliable markers to recognize virologic failure in the individual[13].

According to the National Institutes of Health (NIH), "a biomarker is an objectively measured and evaluated indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[14]. Essentially, a biomarker can represent any entity and can exist as antibodies, microbes, DNA, RNA, lipids, metabolites, or proteins[15]. These biomolecules provide crucial information that helps us understand the physiologic state of a biological system. Any alteration in their concentration, structure, function, or action within a biological system can be correlated with disease characteristics such as onset, progression, or even regression of the particular disease or a measure of the host response to foreign bodies[16]. According to a review by Kanekar *et al.* in 2010, the clinical utility of biomarkers to assess the disease progression for HIV infection is inconclusive[17].

Saliva is a complex biological fluid that can mirror the body's health[18]. It contains several biomolecules such as enzymes, hormones, antibodies, growth factors, antimicrobial constituents, etc. which can function as useful prognostic markers[19]. A good salivary biomarker to detect the progression of HIV (with high sensitivity and specificity) would help clinicians and oral pathologists to monitor the deterioration of clinical condition in people living with HIV/AIDS (PLWHA)[16,20].

The literature reveals the dearth of evidence on validated biomarkers associated with HIV[17]. Much of the information on the topic is largely experimental, which has to be systematically compiled and objectively assessed. As a first step in evidence synthesis, efforts will be made to locate & map the available evidence related to salivary biomarkers in PLHIV; thereby providing a bird eye view about the research question. Furthermore, since there is documentation in literature about CD4+ counts not being effective while on ART, the findings of this scoping review would throw further light on this. Therefore, this scoping review is aimed at synthesizing available evidence on salivary markers for disease progression in HIV infection.

Objectives

- To identify pertinent salivary biomarkers consistent with the progression of HIV infection in people living with HIV
- To systematically review the existing literature on salivary biomarkers in HIV to identify key concepts and gaps
- To assess the current, the quality of evidence and provide a synthesis of the currently available salivary biomarkers in HIV infection

Methods

Eligibility criteria

People diagnosed with HIV/AIDS as per WHO clinical case definition is "an individual with HIV infection irrespective of the clinical stage (including severe or stage 4 clinical disease, also known as AIDS) confirmed by laboratory criteria according to country definitions and requirements"[21]. We will include longitudinal studies that have measured outcomes of at least two different time points. Cross-sectional studies measuring clinical parameters at only one point will be excluded. Only studies that have reported an association between salivary biomarkers and change in the clinical measure

will be included in our scoping review. Due to lack of sufficient resources, studies will be excluded if English language texts are not available.

We will not limit our inclusion based on age, gender, duration of HIV infection, ART status, or demography. Only studies that have reported measurable and quantifiable biological parameters associated with salivary biomarkers will be included. These parameters include, but are not limited to the presence of specific biomolecules, their biologic concentrations, specific gene-phenotype distribution in a population.

Parameters by which a biomarker will be assessed

Its association with disease progression, its potential to be generalizable to PLWHA irrespective of their age, gender, sensitivity, specificity, reliability, ease of measurement, safety and acceptance to the patient. Additionally, it should reflect a true change in the clinical condition and remain unaffected by symptomatic treatment. We will exclude those studies that fail to meet the criterion of biomarker parameters mentioned. Studies that have not specified the type of surrogate marker used or include the objective measures of a particular biomarker or related only to specific opportunistic infections in HIV will be excluded.

Protocol design

The methodological framework proposed by Arksey and O'Malley[22] and the methodological enhancement developed by Levac *et al.*[23] were referred to for this scoping review. The six-stage methodical framework for conducting a scoping review include: "(1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing and reporting the results and (6) consulting with relevant stakeholders."

Stage 1: Identifying the research question

The research question developed by the research team in consultation with key stakeholders will address the role of salivary biomarkers in assessing the progression of disease in PLWHA. For this review, a quality indicator is 'an explicitly and measurable item which act as building blocks in the assessment of care'.

Stage 2: Identifying relevant studies

Search terms were finalized based on the feedback from the research team, subject experts, and extensive literature review. An experienced search scientist developed the search strategy and co-authors as per the Medline format and tailored to other databases and sources. The search strategy used in this scoping review included: (PLWHA OR PLHIV OR PLWH OR PLWA OR HIV OR (people living with HIV/AIDS) OR (people living with AIDS) OR (acquired AND (immunodeficiency OR immune-deficiency OR immuno-deficiency) AND syndrome) OR Immunocompromised OR immune-compromised OR Slim disease) AND ((HIV related oral lesions) OR (Periodontal disease) OR Periodontitis OR (periodontal infection) OR Xerostomia or (dry mouth) OR (salivary gland disease)) OR (Oral candidiasis) OR (hairy leukoplakia) OR (Kaposi sarcoma) OR (linear gingival erythema) OR (necrotizing ulcerative periodontitis) OR (aphthous ulcer) OR (wasting disease))) AND ((biological marker*) OR biomarker* OR saliva* OR biomolecule* OR (bacterial burden*) OR marker*).

The selected search terms will be searched in the title and/or abstract as well as subject headings keywords (eg, MeSH, EMTREE) as appropriate. We will include all articles from the beginning of the databases until October 2020. Only English language studies will be included. The search results from each database will be downloaded and imported onto Mendeley for the removal of duplicates. Following de-duplication, the remaining studies will be imported into the EPPI reviewer Web.

We will use the PICO (Population, Intervention, Control and Outcomes) strategy for formulating a foreground research question (Table 1). Primary studies indexed in the following

Table 1. PICO framework for the selection of studies.

Criteria	Inclusion criteria	Exclusion criteria
Population	People of all age groups and both genders diagnosed with HIV/AIDS belonging to any region without any restriction on duration of the disease and staging	------
Intervention/ Exposure	Any salivary biomarker, which is measurable and quantifiable	Studies reporting salivary biomarker, but not measured
Comparison	With or without any placebo or comparison of one biomarker with another	----
Outcome	Progression with respect to the staging of HIV or any other quantifiable outcome of the condition reported in the study including symptomatic improvements	------
Study design	Randomized control trials, non-randomized control trials, longitudinal studies with at least two time-point measurements, cohort studies, before and after comparison studies	Cross-sectional studies reporting the association between the salivary biomarker and clinical staging of HIV/AIDS at a single point in time
Time frame	Studies carried out till the search date irrespective of the duration of the study	-----

databases will be searched for inclusion in our review: MEDLINE, EMBASE, the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL). The reference lists of all included studies will be hand searched for potentially relevant studies.

To ensure that all information pertinent to the research question is adequately captured, our search will include several grey literature sources from relevant databases (e.g. Grey Literature Report, OpenGrey, Web of Science Conference Proceedings). We will further conduct a targeted search of grey literature in the websites of organizations working on HIV/AIDS research on the local, provincial, national, and international levels. Any studies, reports, and conference abstracts identified through these databases, which are of relevance to this review, will be included.

Stage 3: Study selection

We will undertake a two-step screening process to include all potentially relevant articles in this review: (1) title and abstract screening; (2) full-text screening. In the first stage of screening, two review authors (VD and PP) will independently screen the title and abstract of all retrieved citations for inclusion against a set of minimum inclusion criteria. These criteria will be determined by testing on a sample of abstracts before beginning the abstract review to ensure that they are robust enough to capture all studies pertinent to the primary objective. Articles will be included for full-text screening if either one or both of the review authors deem them relevant to the research question.

All the studies included in the T&A stage will be subject to full-text screening. In this step, both the investigators (VD and PP) will independently screen the full-text articles to assess if they meet the inclusion/exclusion criteria. We will calculate Cohen's κ statistics at both the T&A review stage and the full article review stage to determine inter-rater agreement. Studies will be reviewed another time if there is any discordance regarding the study eligibility. If there are further disagreements, it will be resolved through discussion with a third investigator (RR) until a consensus is reached. A flow diagram will be used to represent the inclusion and exclusion of retrieved studies.

Stage 4: Data collection

The research team will develop a data collection instrument to extract information from the included studies and to confirm study relevance. Study characteristics including publication year, publication type (e.g. original research), study design, country, study setting, a specific biomarker used, statistical analysis performed, the association between biomarker tested and disease progression, the effect of therapeutic agents on biomarker changes, economic aspects and acceptability of biomarker, etc will be extracted (see Table 2). The research team will review and pretest the form to make sure that the data extraction form captures all the required information from the included studies accurately.

Table 2. Data charting form.

Parameters
Author and Year
Title of the study
Country
Aim/ objective of the study
Study design
Population
Settings
Sample size
Age
Duration of infection (length of infection)
Biomarker used
Biomarker classification
Method of biomarker obtained
Main findings of the study
Association between biomarker tested and disease progression
Does the biomarker associated with increase mortality
Correlation
Effect of therapeutic agents on biomarker changes
The method used for statistical analysis
Acceptability of biomarker
Conclusion
Confounders adjusted
Most relevant findings
Comment

Data from the included studies will be extracted independently by the two review authors (VD and PP) using the EPPI reviewer[24]. To ensure a high degree of accuracy of the data extraction, we will compare the independently abstracted data of each reviewer. Both the review authors to ensure consistency in the extracted data will discuss any discrepancies identified in the collected data. The data will be compiled by the EPPI reviewer[24].

Methodological quality

The quality tool developed by McGhee *et al.* in 2014 to assess the quality of surrogate biomarkers will be used to assess the overall methodological quality of the studies[25].

Stage 5: Data summary and synthesis of results

We will synthesize the data narratively for each biomarker. All the outcomes stated in the studies will be reported. Additionally,

we will present a summary of the range of outcomes where feasible.

We will assess the relationship between HIV infection and salivary biomarkers. We will report the effects of this relationship by variables reported in the studies, which were accounted for in the analysis. This review will further include a table of research implications, which will be extracted from each paper by research priorities. Additionally, we will report implications for clinical practice, where relevant. We will report the scoping review according to the PRISMA statement on reporting scoping reviews[26].

Dissemination of information

The results of this scoping review will be disseminated through stakeholder meetings, conference presentations and peer-reviewed publications.

Study status

The search strategy and final plan for data extraction are complete. Formal screening of search results against eligibility criteria is ongoing.

Discussion

The proposed scoping review protocol will enable the identification and assessment of salivary biomarkers, which can predict disease progression in people living with HIV. Salivary components that mimic HIV infection progression can act as early predictors of the deteriorating clinical condition and serve as an alternative method to monitor the clinical condition. Moreover, its ease of extraction will correspond to greater compliance amongst patients when compared to other biofluids like blood.

The synthesis of evidence from this review will assist in improving our current understanding of biomarkers used to evaluate HIV disease progression. This paper will be the pilot in a series of studies aimed at identifying and validating a salivary biomarker for the potential development of a point of care device, which can assess HIV infection progression.

Data availability

Underlying data

No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ✘ ? ✔

Version 2

Reviewer Report 02 June 2023

https://doi.org/10.5256/f1000research.77491.r173565

✔ **Helen C. Steel**
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Prasad *et al.* propose identifying potential biomarkers present in saliva that can be associated with disease progression in PLWH. The Authors outline a scoping review protocol that will enable the identification and assessment of potential salivary biomarkers to be used to predict disease progression in these individuals.

At present, biomarkers that are used to predict disease progression in PLWH are largely systemic in origin. The Authors propose that reliable saliva biomarkers could exclude the need for drawing blood from PLWH improving patient compliance, an important consideration with these individuals. In addition, this may, potentially, lead to the development of a point of care device to assess disease progression.

Having said this, the Authors should be careful of dismissing the importance of VL, and CD4+ T-cell counts in assessing disease progression, and, importantly, treatment failure. These proposed biomarkers may not be an efficient, early marker of the latter. Biomarkers may also reflect other underlying conditions in these individuals. Please see Justice *et al.* (2018)[1] for clarity. Consider suggesting the use of these markers as an additional means of evaluating these aspects of the disease, possibly in the periods between VL and CD4+ T-cell counts.

The rationale for, and objectives of, the study are clearly described and the study design is appropriate for the research question. Sufficient details of the methods are provided to allow replication by others.

After reviewing the article I would like to give the status as "Approved" for this article as the comments or queries raised don't alter the quality of the review.

References

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Care in the Antiretroviral Therapy Era?. *J Infect Dis*. 2018; **217** (4): 521-528 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology, infectious diseases, HIV, biomarkers. proteomics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 23 August 2021

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?

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This review was conducted by Namoonga Mantina and Abidemi Okechukwu under the guidance of Purnima Madhivanan.

General Review
This scoping review protocol was reviewed using the PRISMA-SCR checklist and the JBI Manual for Evidence Synthesis.

General comments

- In general, the methodology section of this protocol addresses most of the items in the PRISMA-SCR checklist.

- This protocol as it is written, however it communicates conflicting statuses to the reader. In some sections, it reads as a protocol and in other instances, it reads like the final report of the scoping review. In the methodology section, the authors noted that the search terms were finalized, however, within the same section, the authors noted that they "will use the PICO…strategy for formulating a foreground research question".

Specific comments

Title:

- Authors did not specify in the article title that the paper was a scoping review **protocol**. Leaves the reader to figure it out at the very end of the manuscript.

Introduction:

- While the salivary biomarkers for disease progression in HIV infection appears to be an under researched area, the area of study aligns well with the authors' decision to conduct a scoping review. However, the introduction fails to explain why the questions and objectives of this study support a scoping review rather than a systematic review.

- Paragraph 2, first statement is missing a citation. Please include citations for the statement.

- Paragraph 5: The authors state that there is a "dearth of evidence of validated biomarkers". As a general statement (encompassing all conditions), this seems inaccurate. If the authors mean to specifically refer to HIV/the condition being evaluated, then this should be added for clarification.

- The objectives of the study did not specify key components of the scoping review, which should be population or participants, concepts, and context. The authors might want to consider revising the objectives to specify each element. The PRISMA_SCR checklist can provide additional details.

- In addition, Objective 2 is not specific to salivary biomarkers implying a much broader scope for review. This needs to be clarified along with clearly defining the limits of the scoping review. It seems this objective aims to explore all biomarkers related to HIV yet the stated premise of the review is to review salivary biomarkers. This objective seems beyond the scope of the review.

- The terminology to identify people living with HIV has be to used appropriately. We no longer use HIV positive individuals as a term to address people living with HIV.

- The case to evaluate saliva as a biomarker could be further explanation. From the information provided it seems that the only reason for choosing saliva is because CD4+ T-

cell count aren't reliable to detect virologic failure under ART. Has there been research to indicate that saliva would perform better under this condition and be worth investigating?

Methodology:

- Paragraph 1: Provide a reference for the clinical definition of PLWHA.
- Given the statement written by the authors that there is a dearth of studies on salivary biomarkers for monitoring HIV progression (paraphrased), limiting the search to studies published in English language may leave out important studies and limit the breadth of the scoping review. This is contrary to the very basis for conducting this review. Furthermore, the review, if limited to English language only, will bias the findings and the scope of the review will be further reduced.
- The third objective stated that "level of evidence" and "quality of evidence" will be assessed. How are the authors distinguishing these two? Furthermore, the methods section only details methodological quality. Furthermore, additional information on the tool being used would be helpful.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic Reviews and Meta-analysis, Infectious Diseases, HIV/AIDS, Diagnostics for developing world

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 17 Sep 2021

Raghu Radhakrishnan

Dear Reviewers,

The authors thank the reviewer for their kind comments. We are pleased to respond to the reviewer's comments.

Title:

- Authors did not specify in the article title that the paper was a scoping review protocol. Leaves the reader to figure it out at the very end of the manuscript. - **Changes have been made in the manuscript and re uploaded**

Introduction:

- While the salivary biomarkers for disease progression in HIV infection appears to be an under researched area, the area of study aligns well with the authors' decision to conduct a scoping review. However, the introduction fails to explain why the questions and objectives of this study support a scoping review rather than a systematic review. **– A sentence in this regard is now added at the end of Introduction.**

- Paragraph 2, first statement is missing a citation. Please include citations for the statement. **- Changes have been made in the manuscript and re uploaded.**
- Paragraph 5: The authors state that there is a "dearth of evidence of validated biomarkers". As a general statement (encompassing all conditions), this seems inaccurate. If the authors mean to specifically refer to HIV/the condition being evaluated, then this should be added for clarification. **- Changes have been made in the manuscript and re uploaded.**
- The objectives of the study did not specify key components of the scoping review, which should be population or participants, concepts, and context. The authors might want to consider revising the objectives to specify each element. The PRISMA_SCR checklist can provide additional details.

Objectives:

1. **To identify pertinent salivary biomarkers consistent with the progression of HIV infection in HIV positive individuals.**
2. **To systematically review the existing literature on biomarkers in HIV to identify key concepts and gaps.**
3. **To assess the current levels of evidence the quality of evidence and provide a synthesis of the currently available salivary biomarkers in HIV infection.**

- **P - HIV positive individuals**
- **E - Salivary biomarker**
- **O - progression of the disease**

- In addition, Objective 2 is not specific to salivary biomarkers implying a much broader scope for review. This needs to be clarified along with clearly defining the limits of the scoping review. It seems this objective aims to explore all biomarkers related to HIV yet the stated premise of the review is to review salivary biomarkers. This objective seems beyond the scope of the review. **- Changes have been made in the manuscript and re uploaded.**
- The terminology to identify people living with HIV has be to used appropriately. We no longer use HIV positive individuals as a term to address people living with HIV **– Changes have been made in the manuscript and re uploaded.**
- The case to evaluate saliva as a biomarker could be further explanation. From the information provided it seems that the only reason for choosing saliva is because CD4+ T-cell count aren't reliable to detect virologic failure under ART. Has there been research to indicate that saliva would perform better under this condition

and be worth investigating? **- We have added more explanation in the introduction section in this regard.**

Methodology:

- Paragraph 1: Provide a reference for the clinical definition of PLWHA. **- Changes have been made in the manuscript and re uploaded.**
- Given the statement written by the authors that there is a dearth of studies on salivary biomarkers for monitoring HIV progression (paraphrased), limiting the search to studies published in English language may leave out important studies and limit the breadth of the scoping review. This is contrary to the very basis for conducting this review. Furthermore, the review, if limited to English language only, will bias the findings and the scope of the review will be further reduced. **- This is beyond the scope of the current review**
- The third objective stated that "level of evidence" and "quality of evidence" will be assessed. How are the authors distinguishing these two? Furthermore, the methods section only details methodological quality. Furthermore, additional information on the tool being used would be helpful. **– Changes have been made in the manuscript and re uploaded.**

Competing Interests: none

Reviewer Report 21 June 2021

https://doi.org/10.5256/f1000research.53901.r87039

Pascale Ondoa
African Society for Laboratory Medicine, Addis Ababa, Ethiopia

30/06/2021 - Updated review (In response to the author's comments):
I acknowledged that I mistakenly reviewed the paper as a Systematic Review Study Protocol instead of a Scoping Review Study Protocol.

I still think that the paper has many gaps and should not be accepted as is. The authors should revise their piece and include the requested information. Looking at the JBI manual for scoping review https://wiki.jbi.global/display/MANUAL/11.2.7+Data+extraction, https://guides.library.unisa.edu.au/ScopingReviews/Protocol the minimum information one expects to see in a protocol are not provided.

21/06/2021 - Original review:
This paper intends to introduce a systematic review of available data on markers for HIV disease progression in saliva.

The introduction is brief and does not correctly bring the rationale for identifying markers of disease progression. Viral Load is considered a reliable and early indicator of virological failure in patients receiving ART and is recommended by the WHO. Alternative markers might be useful, but we need to understand why. The discussion on the lesser value of CD4 to swiftly identify disease progression is an old one. Maybe the authors would like to develop assays that do not require blood collection and molecular testing? Then it should be more clearly outlined.

In addition to the poor background information, a systematic review protocol is supposed to provide a detailed plan of the methodology and analysis beforehand. Should the research question not be defined at this stage? The following are missing in the paper:

- The search terms (key words) for the search.
- The time frame of coverage.
- The search strategy.
- The extraction of data.
- The outcome measures: how is a pertinent salivary marker defined?
- The strategy to handle biases

Is the rationale for, and objectives of, the study clearly described?

No

Is the study design appropriate for the research question?

No

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Laboratory science, HIV immunology and virology, Laboratory system strengthening, diagnostics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 29 Jun 2021

Raghu Radhakrishnan

Dear Reviewer
Thank you for your comments. As a corresponding author, I am pleased to respond to your comments. Please find my responses as follows.

Query - 1: This paper intends to introduce a systematic review of available data on markers for HIV disease progression in saliva. This paper intends to introduce a systematic review of available data on markers for HIV disease progression in saliva

Response - 1: This paper is a scoping review and not a systematic review. This paper aims to 'map the literature of available data on markers for HIV disease progression in saliva and to provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research' (Daudt *et al.*)

Query - 2: The introduction is brief and does not correctly bring the rationale for identifying markers of disease progression. Viral Load is considered a reliable and early indicator of virological failure in patients receiving ART and is recommended by the WHO. Alternative markers might be useful, but we need to understand why. The discussion on the lesser value of CD4 to swiftly identify disease progression is an old one. Maybe the authors would like to develop assays that do not require blood collection and molecular testing? Then it should be more clearly outlined.

Response - 2: We agree with the reviewer that "Viral Load is considered a reliable and early indicator of virological failure in patients receiving ART and is recommended by the WHO". However, they might not be readily available in resource-limited settings (Ford *et al*; Ferreyra *et al.*)

Query - 3: In addition to the poor background information, a systematic review protocol is supposed to provide a detailed methodology and analysis plan beforehand. Should the research question not be defined at this stage? The following are missing in the paper:

Response - 3: This is a protocol for a scoping review and not a systematic review and the following information are quoted from the manuscript. The search terms (keywords) for the search, The time frame of coverage. I wish to inform the reviewer that this paper intends to introduce a systematic review of available data on markers for HIV disease progression in saliva.

References:

Daudt HM, van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Medical Research Methodology. 2013;13:48. DOI: 10.1186/1471-2288-13-48.

Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, *et al.* The future role of CD4 cell count for monitoring antiretroviral therapy. Lancet Infect Dis. Elsevier Ltd; 2015;15(2):241–7.

Ferreyra C, Yun O, Eisenberg N, Alonso E, Khamadi AS, Mwau M, *et al.* Evaluation of Clinical and Immunological Markers for Predicting Virological Failure in an HIV/AIDS Treatment Cohort in Busia, Kenya. PLoS One. 2012;7(11)

Competing Interests: Authors do not have anything, in particular, to disclose that would influence the judgment of the peer review reports.

Author Response 01 Jul 2021

Raghu Radhakrishnan

Dear Reviewer
We acknowledge the reviewer's comments and thank F1000 for inviting Dr. Pascale Ondoa to review our manuscript. The authors would like to humbly respond to the information that the reviewer has sought. For ease of understanding, we would like to draw information from our manuscript for each JBI criteria and presented it below for your kind consideration.

(1) An introduction detailing:

- **Definitions**
  - Per our manuscript: "According to the National Institutes of Health (NIH), "a biomarker is an objectively measured and evaluated indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"13. Essentially, a biomarker can represent any entity and can exist as antibodies, microbes, DNA, RNA, lipids, metabolites, or proteins"
- **Overall review objective**
  - From the manuscript:
  - "Objectives -
    - To identify pertinent salivary biomarkers consistent with the progression of HIV infection in HIV positive individuals
    - To systematically review the existing literature on biomarkers in HIV to identify key concepts and gaps
    - To assess the current levels of evidence, the quality of evidence and provide a synthesis of the currently available salivary biomarkers in HIV infection"
- **Aim:**
  - Per our manuscript: "aimed at synthesizing available evidence on salivary markers for disease progression in HIV infection".
- **Details of any preliminary searches undertaken**
- **Explanation of the need for review**
  - Per our manuscript: "The literature reveals the dearth of evidence on validated biomarkers16. Much of the information on the topic is largely experimental, which has to be systematically compiled and objectively assessed."
- **Eligibility criteria (with contextualization and rationalisation)**
  - From the manuscript: "People diagnosed with HIV/AIDS (PLWHA) as per WHO clinical case definition is "an individual with HIV infection irrespective of the clinical stage (including severe or stage 4 clinical disease, also known as AIDS) confirmed by laboratory criteria according to country definitions and

requirements".

- We will include longitudinal studies that have measured outcomes of at least two different time points. Cross-sectional studies measuring clinical parameters at only one point will be excluded. Only studies that have reported an association between salivary biomarkers and change in the clinical measure will be included in our scoping review. Due to a lack of sufficient resources, studies will be excluded if English language texts are not available.

- We will not limit our inclusion based on age, gender, duration of HIV infection, ART status, or demography. Only studies that have reported measurable and quantifiable biological parameters associated with salivary biomarkers will be included. These parameters include, but are not limited to the presence of specific biomolecules, their biologic concentrations, specific gene-phenotype distribution in a population.

(2) Sample Search Strategy

- From the manuscript: "The search strategy used in this scoping review included: (PLWHA OR PLHIV OR PLWH OR PLWA OR HIV OR (people living with HIV/AIDS) OR (people living with AIDS) OR (acquired AND (immunodeficiency OR immune-deficiency OR immuno-deficiency) AND syndrome) OR Immunocompromised OR immune-compromised OR Slim disease) AND ((HIV related oral lesions) OR (Periodontal disease) OR Periodontitis OR (periodontal infection) OR Xerostomia or (dry mouth) OR (salivary gland disease)) OR (Oral candidiasis) OR (hairy leukoplakia) OR (Kaposi sarcoma) OR (linear gingival erythema) OR (necrotizing ulcerative periodontitis) OR (aphthous ulcer) OR (wasting disease))) AND ((biological marker*) OR biomarker* OR saliva* OR biomolecule* OR (bacterial burden*) OR marker*)"

3) Explanation of search approach, including:

- **Which black and grey literature will be searched?**
  - Per manuscript: "To ensure that all information pertinent to the research question is adequately captured, our search will include several grey literature sources from relevant databases (e.g. Grey Literature Report, OpenGrey, Web of Science Conference Proceedings). We will further conduct a targeted search of grey literature on the websites of organizations working on HIV/AIDS research on the local, provincial, national, and international levels. Any studies, reports, and conference abstracts identified through these databases, which are of relevance to this review, will be included."

- **Justification for choices**
  - From the manuscript: "To ensure that all information pertinent to the research question is adequately captured"

(4) Study selection process, including resolving disagreements between reviewers

- From the manuscript: "We will undertake a two-step screening process to include all potentially relevant articles in this review: (1) title and abstract screening; (2) full-text screening.

- In the first stage of screening, two review authors (VD and PP) will independently screen the title and abstract of all retrieved citations for inclusion against a set of

minimum inclusion criteria. These criteria will be determined by testing on a sample of abstracts before beginning the abstract review to ensure that they are robust enough to capture all studies pertinent to the primary objective. Articles will be included for full-text screening if either one or both of the review authors deem them relevant to the research question.

- All the studies included in the T&A stage will be subject to full-text screening. In this step, both the investigators (VD and PP) will independently screen the full-text articles to assess if they meet the inclusion/exclusion criteria. We will calculate Cohen's κ statistics at both the T&A review stage and the full article review stage to determine inter-rater agreement. Studies will be reviewed another time if there is any discordance regarding the study eligibility. If there are further disagreements, they will be resolved through discussion with a third investigator (RR) until a consensus is reached. A flow diagram will be used to represent the inclusion and exclusion of retrieved studies"

(5) A draft charting table/form for data extraction and accompanying explanation

- Data charting form: Table number 2.
  - From the manuscript: "The research team will develop a data collection instrument to extract information from the included studies and to confirm study relevance. Study characteristics including publication year, publication type (eg, original research), study design, country, study setting, a specific biomarker used, statistical analysis performed, the association between biomarker tested and disease progression, the effect of therapeutic agents on biomarker changes, economic aspects and acceptability of biomarker, etc will be extracted (see Table 2). The research team will review and pretest the form to make sure that the data extraction form captures all the required information from the included studies accurately."

(6) How results and data will be presented (e.g. draft chart, figure or table)

- From the manuscript:
  - "We will synthesize the data narratively for each biomarker. All the outcomes stated in the studies will be reported. Additionally, we will present a summary of the range of outcomes where feasible.
  - We will assess the relationship between HIV infection and salivary biomarkers.
  - We will report the effects of this relationship by variables reported in the studies, which were accounted for in the analysis.
  - This review will further include a table of research implications, which will be extracted from each paper by research priorities.
  - Additionally, we will report implications for clinical practice, where relevant.
  - We will report the scoping review according to the PRISMA statement on reporting scoping reviews24."

(7) Data Extraction:

- We have grouped the information and presented it across the JBI charting form for

your reference and ease in table 2

- Author(s): From the manuscript: “Author”.
- Year of publication: From the manuscript: “Year of publication”.
- Origin/country of origin (where the source was published or conducted): From the manuscript: “country”.
- Aims/purpose: From the manuscript: “Aim/ objective of the study”.
- Population and sample size within the source of evidence (if applicable): From the manuscript: “population, sample size”.
- Methodology/methods: From the manuscript: “Study design, settings, age, duration of infection”.
- Intervention type, comparator, and details of these (e.g. duration of the intervention) (if applicable). Duration of the intervention (if applicable): From the manuscript: “biomarker used, biomarker classification.
- Outcomes and details of these (e.g. how measured) (if applicable) (method of biomarker obtained): From the manuscript: “Main findings of the study, the association between biomarker tested and disease progression, does the biomarker associated with increase mortality, Correlation, Effect of therapeutic agents on biomarker changes, The method used for statistical analysis, Acceptability of biomarker.
- Key findings that relate to the scoping review question/s.: From the manuscript: “Conclusion, Confounders adjusted, most relevant findings”.

The authors once again wish to place on record our sincere gratitude and appreciation to the editorial board for providing us an opportunity to contribute to F1000.

Thanking you.

Kind regards
Raghu

Competing Interests: The authors do not have any conflicting interest

Reviewer Report 18 May 2021

https://doi.org/10.5256/f1000research.53901.r85113

Sudhir Prabhu
Department of Community Medicine, Father Muller Medical College, Mangalore, India

The review article planned is clinically relevant and scientifically sound without any major errors.

However the following minor technical issues might need to be addressed for the readers mainly for better clarity and understanding the purpose of the review:

1. Objective 2 mentions "to identify key concepts and gaps" it is not clear whether it is with respect to existing biomarkers or only salivary biomarkers or both. Are the authors trying to convey through this review that due to limitations of biomarkers (lab/clinical), salivary biomarkers could fill that knowledge gap in the natural history of HIV?

2. Outcome variables in HIV is normally assessed using Clinical, Immunological (CD4) and Virological (viral load) progression, when the authors mention outcomes in the PICO framework to be "quantifiable" does it mean only CD4 and viral load, both of them couldn't be seen in MeSH terms.

3. Also progression of HIV which is mentioned as clinical staging, can be better mentioned as WHO staging and could be cited. Were there any other staging used for monitoring?

After reviewing the article I would like to give the status as **"Approved"** for this article as the comments or queries raised don't alter the quality of the review. Even if the authors don't comply with the changes suggested here, the scientific and ethical validity of the systematic review planned by them will not change.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Community medicine, vaccines, non-communicable diseases, maternal and child health, HIV, infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 May 2021

Raghu Radhakrishnan

Dear Reviewer
The authors thank the reviewer for their kind comments. We are pleased to respond to the reviewer's comments.

Comment: Objective 2 mentions "to identify key concepts and gaps" it is not clear whether it is for existing biomarkers or only salivary biomarkers or both. Are the authors trying to convey through this review that due to limitations of biomarkers (lab/clinical), salivary biomarkers could fill that knowledge gap in the natural history of HIV?.

Response: We are systematically reviewing the existing literature only on salivary biomarkers in HIV.

Comment: Outcome variables in HIV are normally assessed using Clinical, Immunological (CD4) and Virological (viral load) progression, when the authors mention outcomes in the PICO framework to be "quantifiable" does it mean only CD4 and viral load, both of them couldn't be seen in MeSH terms.

Response: Often scientists do not include outcome measures in the search strategy, because many abstracts do not contain a description of these outcome measures. (Laboratory Animals 2012;46: 24–31. DOI: 10.1258/la.2011.01108)

Comment: The progression of HIV, which is mentioned as clinical staging, can be better mentioned as WHO staging and cited. Was there any other staging used for monitoring?

Response: Progression was with the immunological and clinical staging of HIV (https://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf).

Competing Interests: There is no competing interest that might be construed to influence the judgment of the article or peer review reports