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PROTOCOL

Immunological Parameters Associated With AIDS-Defining and Non-AIDS-Defining Conditions in People Living with HIV on Antiretroviral Therapy: A Scoping Review Protocol

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Abstract

Despite the effectiveness of antiretroviral therapy (ART), people living with HIV (PLWH) remain susceptible to a wide range of clinical complications, including AIDS-defining illnesses (ADIs) and non-AIDS-defining conditions (NADCs). While $CD4^+$ T cell count is the most widely used immunological marker in clinical settings, additional parameters such as $CD8^+$ T cell subsets, the CD4/CD8 ratio, markers of immune activation, and inflammatory cytokines have also been associated with disease outcomes in this population. However, evidence regarding these associations remains fragmented across different studies, populations, and methodologies. This scoping review aims to systematically map the immunological parameters that have been reported in relation to ADIs and NADCs in PLWH receiving ART. The review follows the Joanna Briggs Institute (JBI) methodological guidance and the PRISMA-ScR reporting framework. Searches will be conducted in Ovid MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and LILACS, with supplementary searches in Google Scholar and institutional repositories. Eligible studies will include original research involving adults living with HIV on ART reporting associations between immunological parameters and clinical outcomes. Two independent reviewers will conduct screening and data extraction using Rayyan, with blinded bibliographic fields during title and abstract screening. Discrepancies will be resolved by a third reviewer. Descriptive synthesis will be used to summarize findings; no critical appraisal or meta-analysis is planned. This protocol was registered on the Open Science Framework (OSF) on July 26, 2025 (DOI: https://doi.org/10.17605/OSF.IO/XJ4ZT). The results of this review are expected to inform future research and support the development of immunological monitoring strategies for ART-treated PLWH by identifying studied biomarkers, methodological trends, and knowledge gaps.

Keywords: HIV; AIDS-defining conditions; non-AIDS comorbidities; immunological parameters; ART; immune activation.

1. Introduction

The widespread use of ART has significantly reduced morbidity and mortality associated with HIV infection. Nevertheless, people living with HIV (PLWH) continue to experience both ADIs and NADCs, including cardiovascular disease, chronic kidney disease, metabolic disorders, and certain malignancies [1–3]. These comorbidities persist despite effective viral suppression and have become increasingly relevant as the HIV-positive population ages.

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Traditionally, immunological monitoring in PLWH has relied primarily on $CD4^+$ T cell counts and CD4/CD8 ratios to assess immune recovery and predict disease progression [2,4]. However, evidence suggests that these markers alone may not fully capture the complexity of immune dysregulation in the context of chronic HIV infection. Additional parameters, including $CD8^+$ T cell subsets, B cell phenotypes, natural killer (NK) cells, monocyte subsets, immune activation markers, and various cytokines, may play important roles in susceptibility to both opportunistic infections and chronic inflammatory conditions [5–7].

While individual studies have explored these associations, the evidence remains scattered across different conditions, populations, and methodologies. There is currently no comprehensive synthesis of the immunological parameters that have been evaluated in relation to ADIs and NADCs in PLWH receiving ART. A structured mapping of this literature could inform future research, clinical monitoring strategies, and biomarker development.

This scoping review aims to systematically identify and categorize immunological parameters that have been reported in association with ADIs and NADCs clinical outcomes in adult PLWH on ART. By charting the range of studied biomarkers, study contexts, and associated health conditions, this review will contribute to a broader understanding of immune function and its clinical relevance in treated HIV infection. In addition to characterizing the immunological parameters and their associated clinical outcomes, the review will look at the methodological aspects of the studies that were included, such as the type of design, the characteristics of the population, and the definitions of biomarkers and endpoints. This broader scope aims to give us a better understanding of how immune markers affect health outcomes in different situations and to find possible reasons for differences in the literature.

2. Methods

2.1. Aim and objectives

The aim of this scoping review is to map the immunological parameters investigated in association with ADIs and NADCs in PLWH receiving ART. The specific objectives are:

- To identify and categorize immunological parameters associated with clinical outcomes in adult PLWH on ART.
- To describe the methodological characteristics of the included studies, including study design, population, biomarker definitions, and clinical endpoints.
- To map the clinical conditions (ADIs and NADCs) for which these immunological parameters have been studied.
- To explore whether reported associations differ according to study setting, geographic region, or population characteristics.

2.2. Study design

The review follows the methodological guidance of the JBI and is reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. The protocol was preregistered in the Open Science Framework (OSF) on July 26, 2025 [8].

2.3. Search strategy

Searches will be developed using the JBI methodology [9] and structured through the PCC (Population–Concept–Context) frameworkand guided by the PCC (Population–Concept–Context) framework. Comprehensive searches will be conducted in MEDLINE (via Ovid), Embase (via Embase.com), Cochrane CENTRAL (via Ovid), Web of Science, and LILACS (via BVS), covering studies published up to January 2025. Search terms combined controlled vocabulary (*e.g.*, MeSH, Emtree) and free-text keywords related to HIV, immunological markers, ADIs, and NADCs. Strategies were adapted to each database using Boolean logic, truncation, and proximity operators. Full search strategies are detailed in Supplementary Material A–C.

To assess sensitivity, a predefined set of sentinel studies was used to confirm the inclusion of key references. No search updates are planned, as this is a time-delimited, non-living review. Although grey literature was not systematically targeted, reference lists of included studies and relevant reviews were screened, and opportunistic searches were conducted in Google Scholar and institutional repositories if information gaps were identified.

2.4. Eligibility Criteria

Inclusion criteria

- Peer-reviewed original studies involving adult PLWH ($\geq$ 18 years).
- Use of ART at the time of data collection.
- Reported associations between immunological parameters and clinical outcomes related to ADIs or NADCs.

Exclusion criteria

- Studies on pediatric or adolescent populations.
- Studies not reporting immunological parameters.
- Non-original publications (*e.g.*, narrative reviews, commentaries, editorials, protocols, or abstracts without full text).
- Animal or *in vitro* research.
- Articles published in languages other than English or Spanish.

2.5. Quality appraisal

Formal quality or risk of bias assessments will not be performed. This decision aligns with the objective of a scoping review, which is to map the range and nature of available evidence rather than evaluate study quality or strength of associations.

2.6. Data management

All search results will be imported into Rayyan [10] for deduplication and screening management. Title/abstract and full-text screening will be conducted independently by two reviewers using predefined eligibility criteria. To minimize bias, bibliographic fields—such as authorship, journal

name, and year of publication—will be blinded during the initial screening phase. Disagreements will be resolved through discussion or adjudicated by a third reviewer. All screening decisions and exclusion reasons will be documented and exported for auditability and transparency.

2.7. Data Extraction

Data will be extracted using a structured Microsoft Excel template. Variables will include study identifiers, population characteristics, immunological parameters assessed, clinical outcomes, study design, and reported statistical associations (*e.g.*, effect sizes, confidence intervals, p-values). A pilot extraction involving 10 studies will be conducted to calibrate procedures and ensure consistency across reviewers. Two reviewers will perform independent extractions, and any discrepancies will be resolved through consensus or adjudication by a third party. Version control and detailed annotations will be maintained throughout the process. Final data files will be uploaded to the OSF repository and made publicly available under a CC-BY 4.0 license.

2.8. Data analysis

Extracted data will be synthesized descriptively and presented in both tabular and narrative formats. Immunological parameters will be grouped by type (*e.g.*, T cells, B cells, cytokines) and mapped to their associated ADIs and NADCs. Study-level characteristics—such as design, setting, biomarker definitions, and geographic context—will also be summarized. No quantitative synthesis or meta-analysis will be conducted. Incomplete, heterogeneous, or non-comparable data will be described narratively, and no imputation will be performed for missing values.

3. Discussion

This scoping review will map the immunological parameters that have been studied in relation to ADIs and NADCs conditions in PLWH receiving ART. Despite sustained viral suppression achieved through ART, PLWH remain at risk of a wide range of clinical complications, including opportunistic infections, malignancies, and chronic non-infectious comorbidities. While $CD4^+$ T-cell count remains the most widely used immune marker in clinical practice, increasing evidence suggests that additional immunological parameters may contribute to the pathogenesis or clinical trajectory of these conditions [2–4].

By systematically identifying and classifying the types of immune-related variables investigated in the literature, this review will contribute to clarifying which biomarkers have been more frequently assessed, in what contexts, and with respect to which clinical endpoints. This review may also identify potential gaps in the literature, such as the underrepresentation of certain immunological compartments (*e.g.*, B-cell subsets or innate immune markers), the limited study of certain NADCs, or the geographic concentration of research in high-income countries. Identifying these gaps is critical for informing future research agendas and supporting the development of biomarker-guided monitoring strategies for PLWH.

Although no formal risk-of-bias assessment or evaluation of effect strength will be undertaken, the descriptive synthesis may help to generate hypotheses about immunological parameters with potential prognostic relevance. These hypotheses could be further explored in future longitudinal or interventional studies aimed at refining immune monitoring in the context of long-term treated HIV infection.

4. Acknowledgements

This review protocol is part of the research project titled "Implementación de estrategias adecuadas de monitorización inmunológica y caracterización clínica en pacientes VIH+ en diferentes fases de la enfermedad y en pacientes con linfomas asociados a SIDA – Bogotá," which received financial support from the Fondo de Ciencia, Tecnología e Innovación del Sistema General de Regalías of the Republic of Colombia, under Grant Code BPIN 2020000100358. The project is led by the Pontificia Universidad Javeriana, in collaboration with Hospital Universitario San Ignacio, Fundación Santa Fe de Bogotá, and Universidad Industrial de Santander, and is registered under internal project code ID 9081 at Pontificia Universidad Javeriana.

5. Conflict of interest

The authors declare that there are no conflicts of interest related to the development, execution, or reporting of this review.

6. Conclusion

As this is a protocol, no definitive conclusions can be drawn at this stage. The planned scoping review will systematically map the immunological parameters evaluated in relation to ADIs and NADCs in PLWH receiving ART. The findings are expected to inform future research priorities and contribute to the development of immunologically guided clinical strategies in the context of chronic HIV management.

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Parámetros Inmunológicos Asociados Con Enfermedades Definitorias Y No Definitorias De SIDA En Personas Que Viven Con VIH Y Reciben Terapia Antirretroviral: Un Protocolo De Revisión De Alcance.

Resumen: A pesar de la efectividad de la terapia antirretroviral (ART), las personas que viven con VIH (PLWH) siguen siendo susceptibles a una amplia gama de complicaciones clínicas, incluidas enfermedades definitorias de SIDA (ADIs) y condiciones no definitorias de SIDA (NADCs). Aunque el conteo de células T $CD4^+$ es el marcador inmunológico más utilizado en la práctica clínica, otros parámetros como subpoblaciones de células T $CD8^+$, la relación CD4/CD8, los marcadores de activación inmunitaria y las citocinas inflamatorias también se han asociado con desenlaces clínicos en esta población. Sin embargo, la evidencia sobre estas asociaciones permanece fragmentada entre diferentes estudios, poblaciones y metodologías. Esta revisión de alcance tiene como objetivo mapear sistemáticamente los parámetros inmunológicos que se han reportado en relación con las ADIs y las NADCs en PLWH que reciben ART. La revisión seguirá la guía metodológica del Instituto Joanna Briggs (JBI) y el marco de reporte PRISMA-ScR. Las búsquedas se realizarán en Ovid MEDLINE, Embase, Cochrane CENTRAL, Web of Science y LILACS, con búsquedas complementarias en Google Scholar y repositorios institucionales. Los estudios elegibles incluirán investigaciones originales que involucren adultos que viven con VIH y reciben ART y que reporten asociaciones entre parámetros inmunológicos y desenlaces clínicos. Dos revisores independientes llevarán a cabo la selección y la extracción de datos utilizando Rayyan, con campos bibliográficos cegados durante la etapa de cribado de títulos y resúmenes. Las discrepancias serán resueltas por un tercer revisor. Se utilizará una síntesis descriptiva para resumir los hallazgos; no se planea realizar una evaluación crítica ni un metanálisis. Este protocolo fue registrado en el Open Science Framework (OSF) el 26 de julio de 2025 (DOI: https://doi.org/10.17605/OSF.IO/XJ4ZT). Se espera que los resultados de esta revisión informen futuras investigaciones y respalden el desarrollo de estrategias de monitoreo inmunológico PLWH tratadas con ART, al identificar biomarcadores estudiados, tendencias metodológicas y vacíos de conocimiento.

Palabras Clave: Activación inmunitaria; Comorbilidades no definitorias de SIDA; Condiciones definitorias de SIDA; Parámetros inmunológicos; Terapia Antirretroviral; VIH.

Parâmetros imunológicos associados a doenças definidoras e não definidoras de AIDS em pessoas vivendo com HIV e recebendo terapia antirretroviral: um protocolo de revisão de escopo

Resumo: Apesar da efetividade da terapia antirretroviral (ART), pessoas vivendo com HIV (PLWH) continuam sendo suscetíveis a uma ampla gama de complicações clínicas, incluindo doenças definidoras de AIDS (ADIs) e condições não definidoras de AIDS (NADCs). Embora a contagem de células T $CD4^+$ seja o marcador imunológico mais utilizado na prática clínica, outros parâmetros, como subpopulações de células T $CD8^+$, a razão CD4/CD8, marcadores de ativação imunológica e citocinas inflamatórias, também têm sido associados a desfechos clínicos nessa população. No entanto, a evidência sobre essas associações permanece fragmentada entre diferentes estudos, populações e metodologias. Esta revisão de escopo tem como objetivo mapear sistematicamente os parâmetros imunológicos relatados em relação às ADIs e às NADCs em PLWH que recebem ART. A revisão seguirá a orientação metodológica do Joanna Briggs Institute (JBI) e o framework de relato PRISMA-ScR. As buscas serão realizadas em Ovid MEDLINE, Embase, Cochrane CENTRAL, Web of Science e LILACS, com buscas complementares no Google Scholar e em repositórios institucionais. Serão incluídos estudos originais envolvendo adultos vivendo com HIV tratados com ART que relatem associações entre parâmetros imunológicos e desfechos clínicos. Dois revisores independentes realizarão a triagem e a extração de dados utilizando Rayyan, com campos bibliográficos cegados durante a etapa de triagem de títulos e resumos. As discrepâncias serão resolvidas por um terceiro revisor. Será utilizada uma síntese descritiva para resumir os achados; não se planeja realizar avaliação crítica nem metanálise. Este protocolo foi registrado no Open Science Framework (OSF) em 26 de julho de 2025 (DOI: https://doi.org/10.17605/OSF.IO/XJ4ZT). Espera-se que os resultados desta revisão orientem pesquisas futuras e apoiem o desenvolvimento de estratégias de monitoramento imunológico para PLWH tratadas com ART, ao identificar biomarcadores estudados, tendências metodológicas e lacunas de conhecimento.

Palavras-chave: Ativação imunológica; Comorbidades não definidoras de AIDS; Doenças definidoras de AIDS; HIV; Parâmetros imunológicos; Terapia Antirretroviral.

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