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Cognitive impairment among older adults with HIV: a systematic review protocol of cohort studies

Transtornos cognitivos em idosos vivendo com HIV: protocolo de revisão sistemática com estudos de coorte

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Abstract

Objectives: This review will determine whether the incidence of cognitive impairment in HIV patients aged ≥ 50 years is greater than that of their HIV-negative peers. **Methods:** The MEDLINE, EMBASE, LILACS, Web of Science, and Scopus databases will be searched for studies with a sample of individuals aged ≥ 50 years or a mixed population with ≥ 50% aged ≥ 50 years). It will include studies that evaluate seropositive patients compared to and an unexposed control group. **Study design:** Cohort studies with follow-up ≥ 24 months will be included. Three reviewers will independently screen for eligibility criteria, extract data, and assess the risk of bias in the included studies, as well as evaluate the overall quality of evidence. A narrative synthesis will be prepared according to synthesis without meta-analysis guidelines. **Expected results:** We expect to find correlations between older age, HIV, and cognitive impairment. **Relevance:** The association of geriatric syndromes and HIV is becoming an important field of study. Increased life expectancy accompanied by an active sex life is contributing to this public health problem. This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and is registered in PROSPERO (CRD42022321914). This study was financed in part by the CAPES foundation (financial code: 001).
Keywords: aged, health, hiv, geriatrics, communicable diseases.

Resumo

Objetivos: Esta revisão abordará o questionamento: a incidência de comprometimento cognitivo é maior em pacientes com 50 anos ou mais com o vírus da imunodeficiência humana do que em idosos soronegativos? **Metodologia:** As bases de dados Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Web of Science e Scopus serão pesquisadas. A estratégia de busca considerará estudos com amostra de 50 anos ou mais e população mista (pelo menos 50% com 50 anos ou mais). Incluirá estudos que avaliam pacientes soropositivos, e o controle considerará pesquisas que abordem pessoas não expostas. **Desenho do estudo:** Serão incluídos estudos de coorte com seguimento de pelo menos 24 meses. Três revisores, de forma independente, farão a triagem dos artigos quanto aos critérios de elegibilidade, extrairão dados, avaliarão o risco de viés dos trabalhos e avaliarão a qualidade geral das evidências. Uma síntese narrativa será preparada de acordo com a diretriz SWiM. **Resultados esperados:** Esperamos encontrar maior incidência de comprometimento cognitivo em idosos que vivem com o vírus da imunodeficiência humana. **Relevância:** As síndromes geriátricas associadas ao HIV tornam-se um importante escopo de estudo, uma vez que, o aumento da expectativa de vida acompanhado de uma vida sexual ativa sustenta o ciclo de contaminação desse problema de saúde pública. Este protocolo é relatado de acordo com os Itens Preferenciais de Relatórios para Protocolos de Revisão Sistemática e Metanálise e está registrado no International Prospective Register of Systematic Reviews — PROSPERO (CRD42022321914). Este estudo foi parcialmente financiado pela Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil – Código de financiamento: 001.
Palavras-chave: idoso, saúde, hiv, geriatria, doenças infecciosas.

INTRODUCTION

Since its discovery in the 1980s, HIV has affected millions of people around the world. The United Nations reports that approximately 38 million people are living with HIV worldwide. The development of effective antiretroviral therapy has increased the life expectancy of people with HIV.[1,2] The progressive spread of HIV among older adults requires constant reassessment and research. However, limited investment in primary and secondary prevention in this age group in low- and middle-income countries, in conjunction with increased life expectancy and an active sex life, are contributing to this public health problem.[3] Older adults with HIV are more likely to develop brain pathologies, cognitive impairment, and other neurocognitive disorders earlier than their HIV-negative counterparts, due both to viral damage and the harmful effects of aging. In comparison, among HIV-positive people aged 50 years, life expectancy is lower than among those who become infected at more advanced ages.[4-7]

The central nervous system is particularly susceptible to the effects of HIV due to the virus' high affinity for this tissue type. This is why approximately 50% of people with HIV will suffer from some type of neurocognitive disorder at some point in their lives.[7] This has negative consequences not only for patients but for their families and society, since it affects all aspects of memory, attention, and autonomy, increasing the risk of isolation, dependency, and lower treatment adherence.[7]

Therefore, this study aims to gather information on the incidence of cognitive impairment among older adults with HIV compared to their HIV-negative peers. The expected outcome is to find out higher cognitive impairment in the exposed group. We also will describe the following additional variables: demographic data (country, alcohol use, smoking, advanced age (≥ 80 years), race, immunological stage (mean CD4+) or clinical stage of HIV (according to WHO/CDC criteria), morbidity (other chronic pathologies), antiretroviral therapy and other medications (drug classes and time of use), and dietary factors (sedentary lifestyle, vegetarianism, other diet types).

METHODS

This protocol is reported according to the preferred reporting items for systematic review and meta-analysis protocols[8] and is registered in PROSPERO (CRD42022321914).

The search was performed in August 2022 in the following electronic databases: MEDLINE/PubMed, EMBASE, LILACS, Web of Science, and Scopus.

The reference lists of studies selected for critical appraisal will be screened for other potentially eligible studies. A gray literature search will be performed in Google Scholar.

The MEDLINE/PubMed search strategy, which will be adapted for use in other electronic databases (see Appendix I – supplementary material), will consist of original articles (cohort studies) published between 2012 and 2022, with no language limitations.

Controlled vocabulary will be used whenever possible (ie, MeSH terms for MEDLINE/PubMed, LILACS, WoS, and Scopus and EMTREE terms for EMBASE). The search strategy will combine terms and controlled vocabulary regarding "Cognitive Impairment", "HIV", and "Aged."

The inclusion criteria were determined using the PECO strategy, the most appropriated tool for cohort studies:

- Population: sample aged ≥ 50 years or a mixed population with ≥ 50% of the sample consisting of people aged ≥ 50 years).
- Exposure: this review will consider studies that evaluate patients infected with HIV.
- Comparator/control: This review will consider studies that included older people without HIV infection as an unexposed group.
- Main outcome: studies that report the incidence of cognitive impairment will be included.

Study design: cohort studies, either prospective or retrospective, will be included. Timing and setting: studies lasting ≥ 24 months will be included.

Experimental, in vitro, and animal studies; guidelines and protocols; review studies; letters and editorials; qualitative studies, case reports, and case-control studies will all be eligible for inclusion. Preprints or studies that have not been peer-reviewed will be excluded. After final selection, articles with high risk of bias scores (according the Newcastle-Ottawa Scale) or low quality of evidence scores (C, according the STROBE) will be excluded. Further classification details will be presented in the "methodological quality" and "strength of evidence" sections.

Data management: Rayyan and Excel will be used for importing and deduplicating records, title/abstract screening, full-text screening, and data extraction. Three reviewers (ICM, ERL and, YLR) will independently screen publications regarding the eligibility criteria, extract the data, and assess the risk of bias and overall quality of evidence in the included studies. When consensus cannot be reached, a fourth author (RHS or PRPB) will be consulted.

Selection process: the initial screening will be performed independently, assessing the titles and abstracts according to

the selection criteria and classifying them as eligible, potentially eligible, and ineligible. The results of the search and selection process (total studies found, duplicates, and excluded and included studies) will be recorded, reported in the final review article, and presented in a flow chart.

Data collection process: data will be extracted using a standard form to minimize the risk of error. The extracted data will include specific details about the study characteristics (title, authors, country, year of publication, and aims), the participants (sample size, mean age, proportion of participants ≥ 50 years of age, and sex), methods (study design and follow-up duration), dropouts (all groups), outcomes related to the objective (incidence of cognitive impairment in both groups), additional outcomes (demographic variables, immunological stage [mean CD4+] or clinical stage of HIV [according to WHO/CDC criteria], morbidity, antiretroviral therapy, other medications, and dietary factors) and the results (mean, SD or percentage in both groups and measures of association).

The data extraction form will be tested on 3 articles. If necessary, the authors of included publications will be contacted to request missing or additional data.

We will independently assess the risk of bias of included studies according to:

1. Study design;
2. Inclusion criteria;
3. Data availability;
4. Sample size; and
5. Journal impact.

Studies will be considered high-quality if they have a prospective design, use standardized definitions, and are multicenter studies with large sample sizes.

Three independent, previously trained, and qualified reviewers will assess methodological quality using the Newcastle-Ottawa Scale.[9] The score for cohort studies will be calculated according to 3 categories: group selection (0 – 4 points), quality of adjustment for confounding factors (0 – 2 points), and ascertainment of exposure and assessment of outcome (0 – 3 points).

The thresholds for converting the Newcastle-Ottawa scores to Agency for Healthcare Research and Quality categories will be:

- Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain;
- Fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain;
- Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in the outcome/exposure domain;

Disagreements between reviewers will be resolved by a fourth reviewer.

The data will be presented in a narrative according to synthesis without meta-analysis[10] and meta-analysis of observational studies in epidemiology[11] guidelines.

The authors will follow Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions,[12] using standardized tables to describe the data. The results will be will presented in a forest plot in which articles will be grouped according to risk of bias to focus attention on the most reliable evidence, describing the available association measures (odds ratio, relative risk, or hazard ratio) and 95%CI.

This review will analyze the strength of evidence according to STROBE criteria[13-15] since it will exclusively include observational studies. Assessment will follow Mendes et al.[16] with each of the 22 criteria receiving a score of 0 or 1 (ie, "does not meet" or "meets" the criterion, respectively). As recommended by STROBE and Mataratzis et al.[17] the studies will be classified into 3 categories: A (meeting ≥ 80% of the criteria), B (meeting 50% to 80% of the criteria) and C (meeting < 50%) of the criteria.

Publication bias will be evaluated using funnel plots if ≥10 studies investigated the outcome of interest.[18] The asymmetry of the funnel plots will be assessed using statistical tests, such as the Egger and Begg test.[18] $p < 0.05$ will be considered statistically significant.

EXPECTED RESULTS

The authors expect to find articles that show a higher incidence of cognitive impairment in older people with HIV than their HIV-negative peers, especially in cases of polypharmacy and among those who have been diagnosed with HIV for the longest time.

RELEVANCE AND DISSEMINATION

The increasing incidence and prevalence of HIV infection among older adults associated with increased life expectancy has led to a new public health problem. Considering the physiological changes involved in the aging process and the systemic changes that result from HIV infection and treatment, research in this area is becoming increasingly important.

If we find associations between health conditions or behavior with cognitive impairment in HIV-positive individuals,

dissemination of this evidence could ultimately lead to better quality of life and greater social acceptance for them. The results will be disseminated through peer-reviewed journals, scientific meetings, and direct presentations to the general population.

Conflict of interest

The authors declare no conflicts of interest.

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Author contributions

ICM: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft and review & editing. ERL: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, writing – original draft and review & editing. YRL: data curation, formal analysis, investigation, methodology, resources, software, writing – original draft and review & editing. PRPB: formal analysis, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing. RHS: formal analysis, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing.

Supplementary material

Supplementary material is available at: http://dx.doi.org/10.17632/dkmt4trkgx.1.

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