Cognitive impairment increases in older people living with HIV: a systematic review of cohort studies

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Abstract

The progressive increase in HIV infection among older adults requires constant research and monitoring, given that geriatric syndromes associated with HIV comorbidities have become an important public health problem. We reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and it has a central question: Is the incidence of cognitive impairment higher in older patients living with HIV than in their seronegative peers? The following databases were searched for this review: MEDLINE/PubMed, EMBASE, LILACS, Web of Science, and Scopus. The inclusion criteria were studies whose samples were ≥ 50% patients aged ≥ 50 years, with and without HIV, and a main outcome related to the incidence of cognitive impairment. Only cohort studies with follow-up lasting ≥ 24 months were considered. Three reviewers independently screened the documents for eligibility criteria, extracted the data, assessed the risk of bias (Newcastle-Ottawa Scale), and evaluated the quality of evidence. A narrative synthesis was prepared. In total, 10 798 trials were screened, 8884 were excluded, 14 were analyzed, and 5 were included in this review. Only 1 applied cognitive assessment tests; the rest used secondary data from the medical records. Most found that the incidence of cognitive disorders was higher among older people living with HIV, which highlights the need for public policies aimed at primary and secondary prevention strategies. Further research from other countries is still required. PROSPERO register (CRD42022321914).

Keywords: Aged; Health Services for the Aged; HIV; Geriatrics; Infectious Disease Medicine; Public Health.
INTRODUCTION

Due to the introduction of highly active antiretroviral therapy for people living with HIV, the clinical course of HIV is different than in previous decades. The life expectancy and quality of life of this population is now similar to their non-infected peers.2,2

Thus, a higher number of older adults are living with HIV, while diseases that previously affected older populations are now increasingly occurring in younger populations. The Joint United Nations Programme on HIV/AIDS declared that 21% of those living with HIV in 2019 were older adults and, in the USA, more than 50% were ≥ 50 years of age.3 New concerns have emerged about the effects of aging and HIV, as well as how health care for patients in this age group can be improved. Specifically, neurological pathologies seem to be a central problem; around 52% of middle-aged people living with HIV have neurocognitive disorders.4 Similar studies have shown that 30-50% are affected multiple manifestations of dementia. In addition, it is unclear how HIV affects the central nervous system; these percentages are consistent with those from before the development of highly active antiretroviral therapy.4,5

It is well documented that antiretroviral therapy is associated with reduced HIV transmission risk (i.e., undetectable equals non-transmissible) and, thus, it has increased the patients’ life expectancy, contribution to society, and quality of life. The benefits of treatment adherence surpass the adverse effects.6-8

Neurocognitive disorders, conditions that lead to reduced cognitive function (memory, attention, evocation, language, orientation, behavior, etc.), can be classified as mild or major cognitive disorder and dementia (e.g. Alzheimer’s disease, Lewy body dementia, etc.).9 There are also cognitive disorders specific to people living with HIV: HIV-associated neurocognitive disorder, which is diagnosed through neuropsychological testing and functional status assessment, ranges from asymptomatic neurocognitive impairment to mild neurocognitive disorder to HIV-associated dementia.10 It is vital to screen for cognitive impairment among older adults because they still have active social, sex, and work lives that have a significant impact on society and families. Neurocognitive disorder affects these patients’ daily activities, whereas only 16-19% of seronegative individuals have a neurocognitive disease.11

This study gathered data on the incidence of cognitive impairment in older patients living with HIV compared to their seronegative peers.

METHODS

This systematic review was conducted according to the preferred reporting items for systematic review and meta-analysis protocols12 and is registered in PROSPERO (CRD42022321914).

In addition to information about cognitive impairment in older adults, the following variables were assessed: demographic variables (country, alcohol use, smoking, age ≥ 80 years), race; immunological stage (mean CD4+) or clinical stage of HIV (World Health Organization/U.S. Centers for Disease Control criteria); morbidity (other chronic pathologies); antiretroviral therapy and other drug therapies (i.e. drug classes and time of use); and dietary factors (including sedentary lifestyle, vegetarianism, and other diets).

The inclusion criteria were:

a) participants: studies with a sample aged ≥ 50 years and a mixed seropositive-seronegative population (≥ 50% of the sample aged ≥ 50 years to assess these patterns in older adults);
b) exposure: older adults with HIV;
c) control: older adults without HIV as an unexposed group;
d) main outcome: incidence of cognitive impairment (disorder evidenced by cognitive testing or medical diagnosis in the medical records);
e) study design: cohort studies
f) studies lasting ≥ 24 months.

The following were excluded: experimental, in vitro, and animal studies, guidelines and protocols, review studies, letters and editorials, qualitative studies, case reports, case-control studies, and preprints or studies that were not peer-reviewed. After the final selection, articles with high risk of bias scores (due to poor quality) and low quality of evidence (C) were also excluded.

In August 2022, the following electronic databases were searched: MEDLINE/PubMed, EMBASE, LILACS, Web of Science, and Scopus. The MEDLINE/PubMed search strategy was adapted for use in other electronic databases (see Appendix I). The search strategy was: original articles (cohort studies), published between 2012 and 2022 in any language. The strategy combined terms and controlled vocabulary regarding “cognitive impairment”, “HIV” and “aged.”

Mendeley and Excel software were used to import and deduplicate records, screen titles, abstracts, and full texts, and extract data. Three previously trained reviewers (ICM, ERL and YLR) independently screened the articles according to the eligibility criteria and, in included studies, extracted data, assessed the risk of bias, and evaluated the overall quality of evidence. A fourth senior author (PRPH, RHS) was consulted.
to resolve any problems. In the first stage, the titles and abstracts were classified according to the selection criteria as eligible, potentially eligible, or ineligible. The results of the research and the selection process (studies found, excluded duplicates, and excluded and included studies) are presented in the flowchart below.

The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale\(^\text{13}\) by 3 independent, previously trained, qualified reviewers. Because only observational studies were included, the authors assessed the strength of evidence according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.\(^\text{14-16}\) Following Mendes et al.,\(^\text{17}\) each of the 22 criteria was scored as 0 or 1, i.e., the study “did not meet” or “met” the criterion, respectively. As recommended by STROBE and Mataratzi et al.,\(^\text{18}\) the strength of the evidence in each study was classified as A (> 80% of the requested criteria), B (50-80%) or C (< 50%).

A detailed description of this review’s methodology was published in “Cognitive impairment among older adults with HIV: a systematic review protocol of cohort studies”\(^\text{19}\).

### RESULTS

Figure 1 is a flowchart of the search and study selection procedures. The initial search resulted in 10 798 studies. A total of 1900 duplicates were removed, leaving 8898 articles for analysis. After applying inclusion and exclusion criteria, 8848 studies were excluded, leaving 14 for analysis. Nine of these 14 were excluded due to the following reasons: 3 had different goals, 3 had insufficient follow-up, 1 had insufficient data, 1 had no control group, and the sample of 1 was too young. Thus, 5 studies were included in this review.

Table 1 shows the Newcastle-Ottawa Scale\(^\text{13}\) and STROBE\(^\text{14-16}\) classification results. All included studies presented good methodological quality and A-level strength of evidence.

Table 2 describes the main data and the most important conclusions of the included studies. Table 3 reports the characterization of the study population regarding race, substance use, CD4 level, and comorbidities. The included studies were conducted in the USA (4) and China (1). One study was retrospective and the others were prospective cohort studies. Only 1 study applied cognitive assessment tests; the others used secondary data from the medical records.\(^\text{20-24}\)

### DISCUSSION

This systematic review summarized the results of studies investigating the risk of cognitive impairment, including dementia, in older people living with HIV. Although limited in number, 4 out of the 5 studies indicated an increased risk in this population. However, only 1 of the articles used cognitive assessment instruments; the others assessed secondary data (medical records), the completeness of which depends on institutional data recording protocols and the medical professional who assessed the patient. Furthermore, 80% of the studies were from the USA, so the conclusions cannot be applied to developing countries.

<table>
<thead>
<tr>
<th>Study</th>
<th>NOS*</th>
<th>STROBE(^\text{1}) n (%)(^\text{4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al.(^\text{20})</td>
<td>Good</td>
<td>18 (81.85)</td>
</tr>
<tr>
<td>Yang et al.(^\text{21})</td>
<td>Good</td>
<td>21 (95.43)</td>
</tr>
<tr>
<td>Bobrow et al.(^\text{22})</td>
<td>Good</td>
<td>21 (95.43)</td>
</tr>
<tr>
<td>Lam et al.(^\text{23})</td>
<td>Good</td>
<td>21.3 (96.93)</td>
</tr>
<tr>
<td>Lam et al.(^\text{24})</td>
<td>Good</td>
<td>20.6 (93.95)</td>
</tr>
</tbody>
</table>

*Newcastle-Ottawa scale; \(^\text{1}\)Strengthening the Reporting of Observational Studies in Epidemiology; \(^\text{4}\)value corresponds to the average of the authors’ evaluation.
## TABLE 2. Summary of the most important characteristics of the included studies.

<table>
<thead>
<tr>
<th>Authors/country</th>
<th>Sample size: N* =</th>
<th>E† =</th>
<th>C‡ =</th>
<th>Median age: E† =</th>
<th>C‡ =</th>
<th>Sex: E† =</th>
<th>C‡ =</th>
<th>Participants</th>
<th>Methods</th>
<th>Dropouts</th>
<th>Outcomes</th>
<th>Additional descriptive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al.</td>
<td>1611</td>
<td>669</td>
<td>942</td>
<td>50.9</td>
<td>52.2</td>
<td></td>
<td></td>
<td></td>
<td>Prospective cohort</td>
<td>Follow-up: 12 years</td>
<td>Symbol Digit Modalities Test and Trail Making Test.</td>
<td>The authors restricted the sample to Multicenter AIDS Cohort Study participants with at least 5 follow-up visits in which depressive symptoms and executive function were measured.</td>
</tr>
<tr>
<td>China</td>
<td>N* = 5044</td>
<td>E† = 1261</td>
<td>C‡ = 3783</td>
<td>_median age: E† = 59.37</td>
<td>C‡ = 59.78</td>
<td>Sex: E† = 86.28% men</td>
<td>Retrospective cohort</td>
<td>Follow-up: 15 years</td>
<td>Not applicable</td>
<td>Dementia incidence during follow-up was 25 in the HIV group and 227 in the control group (656.25 vs. 913.15 per 100 000 person-years). The adjusted hazard ratio of the HIV cohort for dementia was 0.852 (95%CI 0.189–2.886, p = 0.415). HIV was not associated with an increased risk of either types of dementia, such as Alzheimer’s dementia (p = 0.365), vascular dementia (p = 0.964), or other dementia (p = 0.409) compared to the control group.</td>
<td>Patients with depression (p = 0.001), alcohol use disorders (p = 0.006), and higher CCI scores (p &lt; 0.001) were associated with a higher risk of dementia.</td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td>N* = 2228</td>
<td>E† = 1114</td>
<td>C‡ = 1114</td>
<td>Median age: E† = 62.59</td>
<td>C‡ = 62.41</td>
<td>Sex: E† = 98% men</td>
<td>Prospective cohort</td>
<td>Follow-up: 15 years</td>
<td>Not applicable</td>
<td>Dementia incidence during follow-up was 7 cases (5.1%) in PLWH vs 33 cases (3%) in the control group, p = 0.01. Considering the competing risk of death and adjusting for age, sex, race, substance use, education, and income, veterans with HIV were still 50% more likely to be diagnosed with dementia (hazard ratio 1.50, 95%CI 0.96–2.35).</td>
<td>A total of 467 (21%) veterans died during the follow-up period. Those in the HIV+ group were more likely to die during follow-up (unadjusted relative risk 1.67, 95%CI 1.41–1.97) than those in the HIV- group.</td>
<td></td>
</tr>
<tr>
<td>Bobrow et al.</td>
<td>N* = 124 403</td>
<td>E† = 5381</td>
<td>C‡ = 119 022</td>
<td>Median age: E† = 57</td>
<td>C‡ = 58</td>
<td>Sex: 91% men</td>
<td>Prospective cohort</td>
<td>Follow-up: 6 years</td>
<td>Not applicable</td>
<td>During follow-up, 117 (2.2%) HIV+ and 2427 (2.0%) HIV- participants were diagnosed with dementia. The cumulative proportion of individuals diagnosed with dementia by age 80 was 25.8% (95%CI 19.9–33.0) in the HIV+ group and 13.8% (95%CI 13.0–14.7) in the HIV- group (p &lt; 0.001). In Cox models, dementia risk was greater in the HIV+ group than the HIV- group (unadjusted hazard ratio = 1.98, 95%CI 1.64–2.39).</td>
<td>PLWH were less likely to be obese, have diabetes, or report unhealthy alcohol use, and were more likely to be current smokers or have a history of depression, hepatitis C virus infection, or substance use disorder. Of the total sample, 29 (0.5%) were PLWH and 4015 (3.4%) were aged ≥ 80.</td>
<td></td>
</tr>
<tr>
<td>Lam et al.</td>
<td>N* = 168 650</td>
<td>E† = 13296</td>
<td>C‡ = 155 354</td>
<td>Median age: E† = 53.9</td>
<td>C‡ = 53.5</td>
<td>Sex: 89% men</td>
<td>Prospective cohort</td>
<td>Follow-up: 16 years</td>
<td>Not applicable</td>
<td>During follow-up, 326 (2.5%) HIV+ and 2006 (1.3%) HIV- participants were diagnosed with dementia. The overall incidence of dementia was higher in the HIV+ group after adjusting for sociodemographics, substance use, cardiovascular disease, and other clinical factors (adjusted incidence rate ratio = 1.8 [1.6–2.0]). The higher dementia incidence in the HIV+ group was similar for each sex (p = 0.84) and race/ethnicity (p = 0.36).</td>
<td>PLWH were more likely than controls to have a history of substance use, cardiovascular disease, dyslipidemia, or depression, and were less likely to have hypertension, diabetes or be obese.</td>
<td></td>
</tr>
</tbody>
</table>

*N: total sample size; †E: exposed group (HIV+); ‡C: control group (HIV-). PLWH: people living with HIV.
TABLE 3. Characterization of the study population regarding race, substance use, CD4 level, and comorbidities.

<table>
<thead>
<tr>
<th>Trial Group</th>
<th>White %</th>
<th>Current smoking %</th>
<th>Alcohol use %</th>
<th>Illegal drug use %</th>
<th>Low CD4* %</th>
<th>Diabetes %</th>
<th>Hypertension %</th>
<th>Dyslipidemia %</th>
<th>Obesity %</th>
<th>Depression† %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al.,20 HIV +</td>
<td>70.9</td>
<td>N/A†</td>
<td>22.0</td>
<td>54.8</td>
<td>7.9</td>
<td>6.7</td>
<td>66.2</td>
<td>80.0</td>
<td>N/A†</td>
<td>21.7</td>
</tr>
<tr>
<td>HIV -</td>
<td>84.5</td>
<td>N/A†</td>
<td>23.4</td>
<td>42.4</td>
<td>-</td>
<td>3.2</td>
<td>58.6</td>
<td>65.1</td>
<td>N/A†</td>
<td>20.4</td>
</tr>
<tr>
<td>Yang et al.,21 HIV +</td>
<td>N/A†</td>
<td>N/A†</td>
<td>0.48</td>
<td>2.54</td>
<td>N/A†</td>
<td>10.86</td>
<td>11.42</td>
<td>1.98</td>
<td>1.90</td>
<td></td>
</tr>
<tr>
<td>HIV -</td>
<td>N/A†</td>
<td>N/A†</td>
<td>0.24</td>
<td>0.08</td>
<td>-</td>
<td>14.86</td>
<td>15.38</td>
<td>3.70</td>
<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Bobrow et al.,22 HIV +</td>
<td>50.1</td>
<td>23.5</td>
<td>19.0§</td>
<td>N/A†</td>
<td>17.6</td>
<td>39.8</td>
<td>N/A§</td>
<td>N/A§</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>HIV -</td>
<td>54.7</td>
<td>22.3</td>
<td>16.6§</td>
<td>-</td>
<td>16.8</td>
<td>34.1</td>
<td>N/A§</td>
<td>N/A§</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>Lam et al.,23 HIV +</td>
<td>79.0</td>
<td>17.1</td>
<td>7.8</td>
<td>38.5</td>
<td>3.7</td>
<td>14.2</td>
<td>N/A§</td>
<td>N/A§</td>
<td>18.8</td>
<td>40.4</td>
</tr>
<tr>
<td>HIV -</td>
<td>77.9</td>
<td>12.9</td>
<td>12.2</td>
<td>24.9</td>
<td>-</td>
<td>15.6</td>
<td>N/A§</td>
<td>N/A§</td>
<td>39.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Lam et al.,24 HIV +</td>
<td>70.1</td>
<td>51.9///</td>
<td>8.4</td>
<td>10.8</td>
<td>10.6</td>
<td>10.9</td>
<td>29.4</td>
<td>46.8</td>
<td>21.4</td>
<td>29.7</td>
</tr>
<tr>
<td>HIV -</td>
<td>67.5</td>
<td>41.8///</td>
<td>6.1</td>
<td>3.6</td>
<td>-</td>
<td>12.2</td>
<td>30.9</td>
<td>40.0</td>
<td>41.4</td>
<td>12.7</td>
</tr>
</tbody>
</table>

*Low CD4: < 200 cells/μL; †Depression: with medical diagnosis or antidepressant use; ‡N/A: not available; §the authors consolidated drug and alcohol use; //the authors consolidated former and current smokers.

Only 2 studies assessed dementia subtypes based on the International Classification of Diseases 11th revision;25 they found similar incidences of non-HIV related dementia in the exposed and unexposed groups,22 which may be associated with greater self-care, healthy aging, and minimizing preventable morbidities.26,27 Otherwise, dementia diagnosis in the exposed group occurred approximately 10 years earlier than in the unexposed group, and in up to 50% of the cases, the dementia subtypes remained unspecified.21

Factors such as healthy lifestyle (e.g., abstention from alcohol, tobacco, and drugs), longer time on antiretroviral therapy and, hence, greater CD4 count, were protective factors against dementia in people living with HIV.21,22,24,27 Depressive patterns were related to a greater odds ratio of mental illness.21,27,28 However, even after the introduction of antiretroviral therapy, older persons with HIV had higher mortality than their seronegative peers.22,24

Nevertheless, comorbidities, such as cardiovascular disease, dyslipidemia, depression, and substance abuse, were more frequent among those living with HIV. These results are in line with recent studies27,29 and, as mentioned above, patients have had better quality of life after the development of highly active antiretroviral therapy. However, it should be noted that comorbidities appeared up to 9.5 years earlier in the HIV population, despite active antiretroviral therapy and high CD4 counts. Furthermore, some factors are independent risk factors for dementia and, thus, increase the overall risk of HIV-associated neurocognitive disorder.27,29,30

We found little research into mild HIV-associated neurocognitive disorder. Further research in this field will be important for future public health. Early diagnosis can help prevent worsening mental health and its resultant restrictions on autonomy and quality of life.15

CONCLUSIONS

Although the lack of evidence compromised the analysis, what we found suggests a relationship between the risk of cognitive impairment and HIV infection in older adults. One article found no association, but the others demonstrated that the incidence of cognitive disorders was higher in the HIV group, which highlights the need for public policies aimed at primary and secondary prevention strategies.

Cognitive dysfunction can cause significant dependence, decreasing normal life expectancy in older people being treated for HIV. Further research is still needed in populations from other regions and regarding other sociocultural variables, especially social stigma and health habits, which play an important role in this problem. Moreover, the mechanisms of this disease have not been completely explained.

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Cognition and HIV: a systematic review

Additional supporting information may be found in the online version of this article at http://dx.doi.org/10.17632/dkmt4trkgx.1 (APPENDIX I)

Supporting information
Additional supporting information online may be found in this article, e.g., files available at a web site. You may copy and paste the following URL into your browser:

http://dx.doi.org/10.17632/dkmt4trkgx.1

REFERENCES


