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A REVIEW OF THE LITERATURE ON HIV AND NEUROPSYCHOLOGICAL FUNCTIONING IN OLDER ADULTS: IS MORE RESEARCH NEEDED?

Panagiota Tragantzopoulou
University of Westminster, United Kingdom
E-mail: G.Tragantzopoulou@westminster.ac.uk

Vaitsa Giannouli
University of Western Macedonia, Greece
E-mail: giannouliv@hotmail.com

Abstract

The increase in the number of ageing people living with HIV and the documented neurocognitive impairments have highlighted the need to illuminate the existing findings and evaluate the impact that HIV has on older individuals.

A review of the evidence for neuropsychological declines in memory, executive functions, attention and language in people aged 60 years or more was conducted. The databases MEDLINE, PsychINFO and Pubmed were searched for eligible studies based on keywords.

Eight studies of low to high quality that looked at HIV+ older adults (≥ 60) were identified. The majority of older HIV+ adults experienced severe declines in all the cognitive domains under study. There were mixed results regarding the association among advancing age, functioning decline and HIV. Comparisons between HIV-infected and HIV-uninfected older adults showed that HIV+ subjects demonstrate higher scores of cognitive decline in memory, attention, language and executive functions. Further, comparisons among HIV+ adults, demographically matched individuals with mild cognitive impairment of the Alzheimer's type and healthy controls demonstrated that both disease groups perform worse, but the Alzheimer's type group reports a greater decline in memory and language.

Neuropsychological functioning in HIV+ adults presents great decline but studies on this population are limited. As individuals with HIV are increasingly living longer, studies should pay attention to these individuals and examine predictors of neuropsychological decline in the face of well-controlled interventions and treatments.

Keywords: *HIV, memory, neuropsychological function, executive functions, older adults*

Introduction

Ageing with Human Immunodeficiency Virus (HIV) is a growing global concern, as the population of older individuals with HIV is steadily increasing. Between 2011 and 2016, there was a significant 57% increase in HIV prevalence among individuals aged 65 and older, while

in 2015, 47% of those affected were over 50 (Centers for Disease Control and Prevention, 2018). Older HIV-infected individuals, especially those over 40, are estimated to have twice the risk of HIV-associated cognitive impairments (CI) and an 18% increase in the likelihood of developing cognitive deficiencies every ten years (Coban et al., 2017).

Neurocognitive impairment stands out as a prevalent syndrome among older individuals living with HIV, significantly impacting their quality of life. Studies from the USA have revealed an alarming 58% increased risk of dementia in this population, despite them receiving antiretroviral therapy (ART). What's concerning is that these individuals are diagnosed with dementia around the age of 67, a significantly younger age compared to those without HIV, typically diagnosed at 78 years old(Heaton et al., 2010).Remarkably, even with undetectable viral loads at the time of dementia diagnosis, a staggering 91% of individuals with HIV had progressed to this cognitive impairment(Lam et al., 2021). Another study, the AIDS Clinical Trials Group Longitudinal Linked Randomised Trials study, found that around 26% of participants showed cognitive impairment during their initial neuro-screening(Robertson et al., 2007). It's evident that neurocognitive impairment in individuals with HIV is a widely prevalent yet often overlooked issue.

HIV-associated Neurocognitive Disorder (HAND) stands out as a prevalent source of cognitive impairment in individuals living with HIV(Saylor et al., 2016). It's diagnosed by excluding pre-existing neurobehavioral conditions or strong confounding factors that might influence those with HIV(Chan & Wong, 2013). This disorder progresses through three stages of cognitive impairment: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia(Antinori et al., 2007). Understanding the root cause of HAND remains challenging due to its diagnostic intricacies and the varied ways it manifests(Olivier et al., 2018). However, it's believed that HIV infiltrates the central nervous system (CNS) during the infection phase, where it persists, replicates within resident immune and supporting cells, and triggers the host's immune response, leading to inflammation and cellular damage(Olivier et al., 2018). Despite effective peripheral viral suppression through combination antiretroviral therapy (cART), chronic inflammation and viral activity within the CNS can disrupt the endothelial barrier and neural pathways, contributing to milder forms of HAND(de Almeida et al., 2018). Moreover, individuals' genetic makeup differences may influence how effectively their immune system responds, affecting their susceptibility to HAND. This complexity in the interplay of viral activity, immune response, and genetic factors contributes to the vulnerability of individuals to HIV-associated neurocognitive disorders.

Several contributing factors, beyond just HIV infection, play a role in this impairment, challenging the conventional screening criteria used in the general population. Healthcare providers attending to older individuals with HIV often lack training in assessing and managing the specific needs associated with this geriatric syndrome(Siapera et al., 2018). Conversely, geriatricians might not be well-versed in the unique care requirements of older individuals with HIV. This impairment often likened to a pervasive fog affecting every aspect of life, presents with associated behavioural and psychological symptoms that severely hinder self-care and the management of daily activities(Alford et al., 2022). Consequently, it exerts a detrimental impact on both physical and mental health, undermining self-awareness, self-control, and ultimately reducing social connections. This ripple effect extends to employment stability, chronic medical condition management, and adherence to medications, posing significant challenges for individuals living with HIV(Ng et al., 2023). The absence of comprehensive care tailored to their specific needs exacerbates the issue, resulting in substandard care and poorer health outcomes.

Despite the introduction of cART, the incidence of HIV-associated neuropsychological abnormalities remains common. Verbal memory declines in older HIV+ individuals have been associated with age and HIV (Seider et al., 2014). Additionally, older HIV+ individuals exhibit higher scores of cognitive declines in memory, attention, language, and executive functions compared to their younger HIV+ counterparts. For every 1-year increase in age, there are 1.11-fold higher odds of a memory deficit(Tan et al., 2013). However, some studies have raised questions about whether HIV-related cognitive declines are solely an outcome of older age (Seider et al., 2015; Valcour et

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al., 2010). Yet, it is not firmly established to what extent ageing accelerates HIV-associated neuropsychological functioning.

This systematic review aimed to collect and compare current scientific findings in the literature regarding four key areas of neuropsychological functioning (memory, executive functions, attention, and language) in HIV-infected older individuals. Understanding the neuropsychological effects of HIV is a critical research priority, especially in older people, where age increases the risk of both neurocognitive impairment and age-associated neurodegenerative diseases. Therefore, a comprehensive synthesis of existing evidence on neuropsychological functioning in older adults with HIV is essential to inform the clinical and research community.

Research Methodology

Search Strategy and Inclusion Criteria

Literature searches were conducted in three major databases (MEDLINE, PsycINFO, and PubMed) up to August 2021 using keywords such as 'older adults,' 'HIV in older adults,' 'memory,' 'language,' 'executive functions,' 'attention,' and 'neuropsychological functioning.' After completing the literature search, duplicate entries were removed.

In terms of inclusion criteria, studies that addressed the neuropsychological effects of HIV were included in our sample if they met the following criteria: (i) the sample included individuals aged ≥60 years, as this is the commonly used age cut-off in research; (ii) the studies were written in English; and (iii) they were published within the last 10 years to ensure the most recent recommendations were considered. Research papers were included, while reviews, commentaries, editorials, and case studies were excluded. Studies without full-text availability were also excluded. Additionally, relevant studies were identified by screening the reference lists of the papers obtained from the databases.

Study Selection and Data Extraction

A two-step strategy was employed to assess the relevance of the search results. Initially, one reviewer independently evaluated the references based on their titles and abstracts, applying the inclusion criteria. The reference lists of the included articles were also manually searched. Subsequently, after excluding non-relevant records, the full texts were analysed to determine the eligibility of the remaining records, and key findings were highlighted by the same reviewer. Demographic details of the sample, including the year of publication, type of neurocognitive function measured, number of participants, patient demographics, reported outcomes, and methodological strengths and limitations, were recorded in a data extraction Excel form. Any questions or disagreements regarding relevant references were discussed and resolved with the consultation of a second reviewer.

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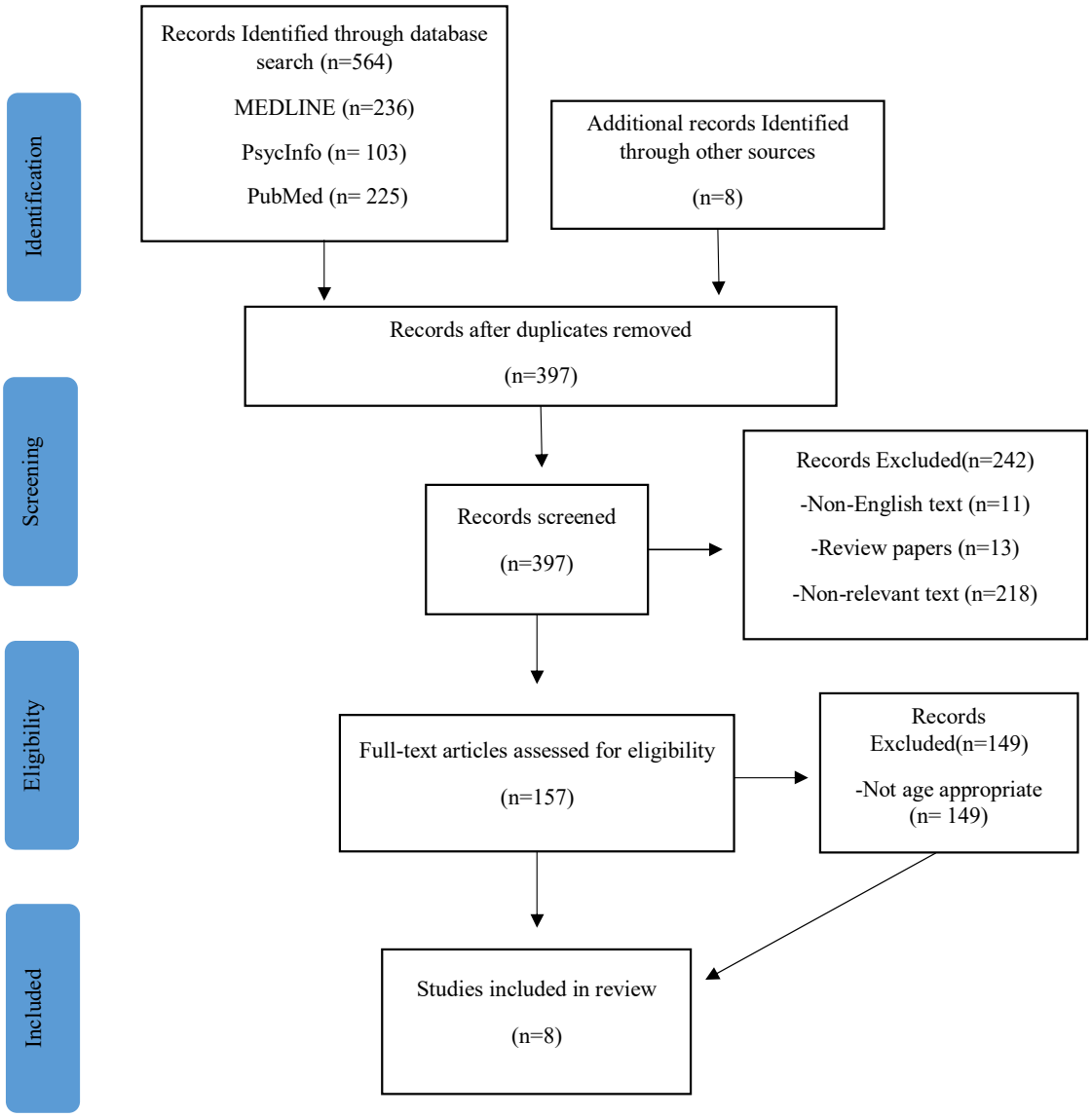
Figure 1

Identification Strategy and Included Articles



Assessment of Quality

The validated Standard Quality Assessment criteria guidelines were used to evaluate the quantitative papers (Ciccarelli et al., 2017). Fourteen items are scored depending on the degree to which the specific criteria are met (yes = 2, partial = 1, no = 0). Items not applicable to a certain study were marked 'n/a' and excluded from the total calculation. The total is expressed as an overall percentage.

Research Results

The initial analysis search yielded 564 articles. After excluding duplicates and studies on younger samples, fifty full texts were reviewed of which forty-two were excluded as they did not meet the eligibility criteria for the age. Thus, eight full-text studies which assessed 812 HIV+ older individuals (≥ 60) were included.

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Table 1

Summary of Key Characteristics of Included Studies

Study	HIV+ Participants	Mean Age
Milanini et al. 2019	61	64
Watson et al. 2017	65	63
Xiao et al. 2019	250	66
Milanini et al. 2016	60	66
E Silva et al. 2011	8	71
Ciccarelli et al. 2017	22	70
Hellmuth et al. 2018	1	79
Ding et al. 2017	345	66

Memory

Cognitive changes in memory domains were extensively documented in seven studies. Milanini et al. (2019) conducted a cross-sectional study comparing 61 virally suppressed older adults with HAND, 53 demographically matched individuals with mild cognitive impairment of the Alzheimer's type (MCI-AD), and 89 healthy controls over a 20-month period. The results showed that both disease groups performed worse on memory tasks compared to controls. Notably, MCI-AD participants exhibited more significant memory deficits than HAND individuals (p=.002). In 2017, researchers investigated memory decline among various groups, including 22 HIV+ adults (aged ≥60), 31 younger HIV+ individuals (aged <60), 18 participants with Alzheimer's Disease (AD), 23 subjects with Parkinson's Disease (PD), and 28 healthy subjects (Ciccarelli et al., 2017). The study found that the HIV+ group aged 60 and above had a memory profile similar to that of PD participants but performed worse compared to younger HIV+ individuals. However, the study did not confirm a significant interaction between age and HIV.

An additional study confirmed declines in episodic and working memory in HIV+ adults over the age of 60 (Milanini et al., 2016). Furthermore, Watson et al. (2017) aimed to illustrate the difference in memory between HIV+ adults and HIV-uninfected individuals. They recruited 65 HIV+ participants over the age of 60 and 29 demographically matched HIV-uninfected individuals. After completing the UCSF Memory and Aging Center Bedside Screen, the HIV+ group displayed a more significant decline in memory (difference = -.942, p< .001) (Watson et al., 2017). Supporting these findings, a study in China confirmed that HIV-infected patients were more likely to exhibit memory impairments compared to HIV-uninfected individuals (Ding et al., 2017). In a smaller sample of seven individuals over the age of 70, researchers identified mild dementia with psychiatric alterations, including cognitive symptoms like impaired working memory and compromised immediate and delayed memory. However, recognition memory remained intact (e Silva et al., 2011). Similarly, when Hellmuth et al. (2018) reported the case study of a 79-year-old man with a diagnosis of HIV-associated dementia (HAD), they documented significant difficulties in verbal and visual episodic memory. Despite the initiation of ART treatment, his cognitive abilities progressively declined, and marked dysfunction in memory domains was observed.

Executive Functions

Six studies reported on executive functions among older HIV+ adults (e Silva et al., 2011; Hellmuth et al., 2018; Milanini et al., 2016, 2019; Watson et al., 2017; Xiao et al., 2020). Two of the studies, which employed the Mini-Mental State Exam (MMSE) in their sample of HIV+ adults aged over 70, reported substantial difficulties in executive functions (e Silva et al., 2011; Hellmuth et al., 2018). An additional study observed a higher proportion of pathological performances (27%, n=16) in executive functions when using the Multiple Features Target Cancellation (MFTC) (Milanini et al., 2016). Furthermore, in a Chinese sample where cognitive function was assessed using the Bei-

jing version of the Montreal Cognitive Assessment (MoCA), executive functions showed a decline. However, men and those with higher education scored better (Xiao et al., 2020). In a comparison of HIV adults over 60 with demographically matched HIV-uninfected controls, the HIV+ group performed worse on executive functioning (difference = -.665, $p < .001$) (Watson et al., 2017). Lastly, when HIV+ adults were compared with demographically matched individuals with mild cognitive impairment of the Alzheimer's type, both groups scored lower compared to controls. Surprisingly, they performed similarly on executive functions (p=.265) (Milanini et al., 2019).

Attention

Attention was also measured in most of the included studies, with findings documented in seven papers. Comparisons between HIV+ older adults and individuals with MCI-AD indicated that both groups performed similarly on attention (p=.084) (Milanini et al., 2019). Similarly, HIV+ older adults performed worse on attention compared to HIV-uninfected individuals (Ding et al., 2017; Watson et al., 2017). Moreover, e Silva and colleagues (2011) found that all of their cases displayed poor attention performance, with a mean z-score of less than -2. Additionally, attention deficits became more prominent with advancing age (Xiao et al., 2020). In line with these findings, Hellmuth and colleagues (2018) after following a 79-year-old man for almost four years and completing neuropsychological reports, found attention impairments throughout the years. In contrast, Milanini et al. (2016) found that in their sample of 60 older HIV+ adults, attention scores were within the normal cognitive range.

Language

Five out of the eight studies explored language deficits. Hellmuth et al. (2018) recounted a case study involving a 79-year-old man with untreated HIV and cognitive impairments. The patient initiated antiretroviral therapy (ART), leading to mild improvements in language. However, over time, impairments worsened, and progressive deficits in language continued for four years until his passing. In a Chinese sample living with HIV on ART, deficits in language were evident in all adults aged above 60, with those in the 80 or older group showing significant differences (p=.001) in language capacity (Xiao et al., 2020). Additionally, in another sample, the clinical presentation of HIV included a pattern of cortical and subcortical symptoms. Specifically, except for dyscalculia, visuo-spatial alterations, and praxia, 57.14% of cases exhibited language deficits (e Silva et al., 2011). In a comparison of older HIV-infected patients and demographically matched individuals with mild cognitive impairment of the Alzheimer's type, the latter group performed significantly worse on language (p=.017), with a statistically significant decline observed after a longitudinal examination (Milanini et al., 2019). In contrast, Milanini et al. (2016) found low scores of language decline, suggesting that cognitive reserve (CR) can represent a resilience factor against cognitive decline.

Discussion

This review aimed to understand the neuropsychological functioning in older adults with HIV and critically discuss the existing findings. Neuropsychological functioning in older adults with HIV appears to be on a decline, with memory, attention, executive functioning, and language showing the most significant declines. The review revealed that older adults with HIV perform worse in episodic and working memory tasks compared to younger HIV+ individuals (aged <60) and demographically matched HIV-uninfected individuals. However, their memory profile seems to be better than that of individuals with AD. The differences in memory changes were attributed to the widespread atrophy observed in most brain regions in individuals with AD, while HIV+ subjects demonstrated focal atrophy in frontal gray matter and the cerebellum (Milanini et al., 2019). Furthermore, language deficits are evident in HIV+ individuals, with research showing a positive correlation between language decline and advancing age (Hellmuth et al., 2018; Xiao et al., 2020). Although the rates of cognitive change were similar between HIV+ individuals and MCI-AD adults, language was the only domain in which the MCI-AD group performed worse (Milanini

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et al., 2019). Progressive cognitive decay is typically observed in both HIV+ and AD individuals, but comparative studies provide insights into the different trajectories in memory and language observed in these specific populations.

Although HIV+ older adults have been found to perform worse on memory tasks compared to HIV+ younger adults, Ciccarelli and colleagues (2017) concluded that there is no interaction between age and HIV. However, this conclusion contradicts previous findings that indicated larger declines in verbal memory observed only in HIV+ older adults and associated with age (Seider et al., 2014). The discrepancies in these findings may be a result of methodological differences. For instance, the former study was cross-sectional and had a higher chronological cut-off for older HIV+ adults, while the latter was a longitudinal study that included seropositive and seronegative individuals aged 40-74 years. Furthermore, Ciccarelli et al.(2017) recruited only White, well-educated, and neuroasymptomatic individuals, limiting the generalizability of their findings, while Seider et al. (2014)included a more diverse sample. Finally, different tests were used to assess memory, potentially leading to different results.

Research in HIV+ adults has demonstrated that executive functions are of significant concern, as a substantial decrease with advancing age has been documented (e Silva et al., 2011; Hellmuth et al., 2018; Milanini et al., 2016). Previous studies have supported the idea that declines in executive functions and HAND are more prevalent in ageing patients due to advanced age and several other clinical factors, as well as comorbid health conditions, such as malignancies and vascular diseases(Fogel et al., 2014; Vance & Cody, 2015). It is important to mention, however, that men and highly educated individuals were found to perform better on executive function (Xiao et al., 2020). This finding aligns with previous research indicating that gender can impact global cognitive function in HIV+ older adults (Fogel et al., 2014). Future studies should strive for a more balanced representation of both sexes so that the effects of gender and education on HIV+ older adults can be better determined.

Attention was another neuropsychological function found to be significantly impaired in HIV+ older adults, supporting the hypothesis that HIV infection and older age can synergistically affect specific cognitive domains. Watson and colleagues (2017) discovered that the worse performance in attention compared to HIV-uninfected older individuals is related to white matter changes, with the greatest white matter hyperintensity volumes located in the frontal lobes. These findings align with previous research that reported associations between frontostriatal white matter abnormalities and associated frontal-executive cognitive deficits in HIV+ individuals (Ipser et al., 2015; Pfefferbaum et al., 2009; Plessis et al., 2014). However, Milanini and colleagues (2016), found in their sample that HIV+ older adults demonstrated normal attention, suggesting that higher CR may protect against the negative effects of ageing- and HIV-related impairments. Nonetheless, uncontrolled biases may have occurred in this cross-sectional survey. Therefore, future longitudinal studies are needed to confirm the findings and better clarify the impact of CR on cognitive functioning in elders with HIV.

Although this review has identified key findings regarding the neuropsychological functioning in older adults with HIV, certain limitations must be acknowledged. Despite an extensive search, a limited number of studies met our inclusion criteria, assessing only 812 HIV+ older individuals (aged ≥ 60), most of whom were males. Research has focused more on younger HIV+ individuals and males, while investigations into cognitive decline in HIV+ older individuals over the age of 60 and females are scarce. Furthermore, our study was limited to research published in English, which means that we may have potentially missed other relevant studies. Given the continued prevalence of neurocognitive decline in ageing people living with HIV, additional follow-up studies are warranted. These studies should not only observe the trajectories of cognitive changes among HIV-infected individuals but also document the differences between genders.

Conclusions

Given the widely available access to therapy and extended life expectancy, ageing with HIV reflects a novel phenomenon. However, the impacts on the ageing brain structure and cognitive functioning are not yet fully understood. The current review has demonstrated severe impairments in neuropsychological functions, namely memory, executive functions, language, and attention,

in HIV+ older adults (aged ≥ 60). In clinical settings, these results could aid in implementing prevention and rehabilitation strategies against impairments in cognitive performance in HIV+ populations. As the HIV+ population gets older, neuropsychological assessments are mandatory to both prevent and understand cognitive declines over time. Longitudinal studies should also be employed to more accurately examine the neuropsychological and everyday functional trajectories of this population. Most research has focused on younger individuals or has set the cut-off point at 60 years of age. Therefore, research on older HIV+ adults over 60 must be conducted. Living with HIV and getting older brings a unique set of clinical needs and diagnostic issues. Hence, further research is considered of great importance to illustrate the cognitive declines experienced and inform new ways of treatment.

Declaration of Interest

The authors declare no competing interest.

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Panagiota Tragantzopoulou MA, MSc, Visiting Lecturer, University of Westminster, United Kingdom.
E-mail: G.Tragantzopoulou@westminster.ac.uk
ORCID: https://orcid.org/0000-0002-9678-9928

Vaitsa Giannouli PhD, Adjunct Lecturer, University of Western Macedonia, Greece.
(Corresponding author) E-mail: giannouliv@hotmail.com
ORCID: https://orcid.org/0000-0003-2176-8986