

Invited Review

Living With Chronic HIV Disease in the Antiretroviral Era: The Impact of Neurocognitive Impairment on Everyday Life Functions

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Although there is extensive literature around the biologic correlations of neurocognitive function in HIV/AIDS, less is known about the impact in everyday living. We conducted a systematic review of the association of neurocognitive impairment with everyday life functions in people with HIV on antiretroviral therapy. We specifically focused on attention, executive function, processing speed, and the central executive component of the working memory. We considered 3 domains of everyday functions: (1) autonomy, (2) decision making and adherence to treatment, and (3) quality of life and psychological wellbeing. The relationship between neurocognitive impairment and mental health was examined, given its correlation with everyday life functions. Results indicate that people with HIV do experience problems with autonomy of daily living (especially if aged older than 50 years) and with decision making, and neurocognitive impairment plays a role in this regard. Psychological wellbeing is associated with executive function and processing speed. These patients may also have a reduced quality of life, but the relationship between quality of life and cognition is uncertain or could be mediated by other factors. Neurocognitive impairment correlates with depression and anxiety; however, the relationship of cognitive performance with apathy is still controversial.

Keywords: chronic HIV disease; AIDS; antiretroviral therapy; everyday life; neurocognitive impairment; depression; anxiety

Introduction

HIV infection can directly affect the central nervous system,¹ is associated with reduced brain volume,² and can impact the structure and function of grey matter^{3,4} and white matter circuits.⁵⁻⁷ Consequently, roughly 30% to 55% of patients with chronic HIV infection and taking antiretroviral therapy (ART)⁸ present with HIV-associated neurocognitive disorder (HAND).⁹ This heterogeneous condition may involve the central executive component of working memory,¹⁰⁻¹² attention,¹³ executive function,¹³ and processing speed.¹⁴⁻¹⁶ In this article, we specifically target the role of these functions.

Although other functions can be involved in HAND (eg, long-term memory,

motor function), this review is limited to those functions strongly implicated in the supervision and qualitative control or realization of everyday life activities. The central executive component of working memory provides high-level attention regulation and activates the executive processes for tasks that cannot be automatically controlled by routine and implicit attentive resources (ie, focusing, dividing, shifting attention).^{17,18} The central executive component of working memory is not a discrete function but is a manifestation of other functions,¹⁹ such as executive control,¹³ attention, and processing speed. These functions should be studied in conjunction with one another. Currently, there is no consensus regarding their impact on everyday life

outcomes²⁰ or on the relationships between neurocognitive impairment and sex,²¹ age and aging,²² falls,²³ frailty,²⁴ body composition,²⁵ sarcopenia,²⁶ immunosuppression, inflammation,²⁷ comorbidity²⁸ and disease severity,²⁹ timing of ART initiation or deintensification,³⁰ and polypharmacy. Although neurocognition may be associated with these variables, the timing, strength of correlation, mediating factors, and relationships with everyday life activities are still to be ascertained.

In this article, we aimed to systematically review the literature in this field of HIV/AIDS research. We evaluated the putative association of neurocognitive impairment, as operationalized above, with everyday life outcomes in people with chronic HIV. We also studied the relationship between neurocognitive impairment and mental health, given its relevance to everyday life functions.

Methods

Eligibility Criteria

For this review, only descriptive or observational studies (cross-sectional, cohort, case-control, and hybrid designs; prospective or retrospective) were considered. Eligible studies included (1) those with adults with HIV (older than 18 years of age) who had been prescribed ART; (2) those with recorded information in terms of a raw or standardized score derived from formal neuropsychologic testing on the central executive, attention, executive function, and processing speed; and (3) those that considered or discussed everyday life outcomes. Animal and

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pediatric studies were not included. The review was reported following the recommendations set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) working group.³¹

Information Sources and Search Strategy

We systematically searched the PubMed database for contributions published between January 1, 2000, and December 31, 2019. We also examined pertinent articles cited in the references of selected original research papers, book chapters, relevant reviews, and papers reporting the results of meta-analyses. Information retrieval used the same keywords in Google Scholar. Only original papers published in English were considered. A detailed description of the search strategy is provided in the protocol of this systematic review, which is available as Supplementary Information (together with the PRISMA checklist), and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO).³²

Outcomes

Given the multifaceted nature of the outcomes of this study, we considered a 3-dimension classification of everyday life function. The first dimension concerned independence and the possibility to conduct an autonomous life, as measured by autonomy in activities of daily living (ADL), instrumental activities of daily living (iADL), and employment status. ADL scores measure a person's ability to perform basic self-care tasks and iADL scores measure a person's ability to live independently. ADL and iADL are generally preserved in healthy aging; however, impairment has been described in people with HIV. The second dimension referred to a person's capacity to make decisions and adhere to treatment. For the third dimension, we examined quality of life and psychologic wellbeing in light of their theoretical relevance and practical importance.^{33,34} We considered mental health (which is highly correlated with

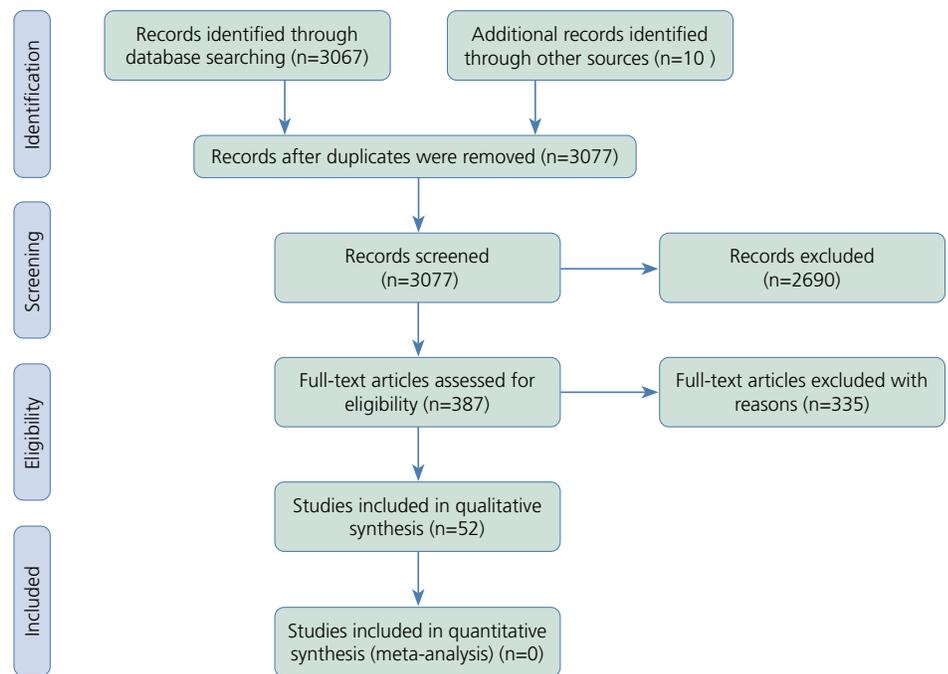


Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart of the studies included in the systematic review. From those screened, 377 items were initially retrieved from the PubMed database; 42 studies matched the inclusion criteria and were comprised in the present paper, and 10 studies were included by manual search for a total of 52 studies (see the Supplementary Tables). These 52 studies were published between 2000 and 2019, and had sample sizes ranging from 11 to 2863.

everyday function) as a secondary outcome in terms of depression, apathy, and anxiety. These conditions have been assessed in the HIV literature in terms of the presence of symptoms, not necessarily diagnosis of a major disorder.

Data Management and Analysis

After the first screening of records identified in PubMed, selected items (data and metadata) were stored in a database and queried through structured query language (SQL). Two blinded reviewers (ER and MC) searched for papers eligible for inclusion by screening titles and abstracts. Information regarding the general setting, study design, sample size, follow-up duration, demographic characteristics of participants, and neuropsychologic testing was extracted from each paper. Selected baseline covariates included age, sex, duration of HIV infection, nadir and current CD4+ cell count, CD8+ cell count, viral load, duration of ART,

presence of infections other than HIV (eg, hepatitis C virus [HCV]), and presence of other medical conditions. Results of the neuropsychologic evaluation (central executive, attention, executive function, and processing speed) presented as raw or standardized scores were extracted from each paper. Included studies were assessed for the possibility of selection bias and residual or unmeasured confounding. Given the high degree of heterogeneity and the methodologic differences observed across study designs and the potential bias that could be artificially created by meta-analyzing data under these conditions,³⁵ we only summarized data qualitatively.

Results

Descriptive Findings

After removing duplicates, 3067 items were identified in PubMed and preliminarily screened. Of these, 377 were

potentially eligible, and after exclusions, 42 studies were selected for the inclusion. Another 10 studies were added from a systematic search in books, book chapters, and bibliographies (Figure 1).

Clinical trials, letters, commentaries, and observational studies with no detailed assessment of neuropsychologic function or no consideration or discussion of everyday life outcomes were excluded, as was with testing of patients with acute HIV. In Supplemental Tables 1, 2, and 3, we show a summary of the main results obtained in each study.

The sample size of included studies ranged from 11 to 2863 (Supplemental Table 2). Most studies tested patients aged 30 to 49 years, except for 6 studies^{24,36-40} that selected patients aged 50 to 59. Outcomes were measured with different tools by different authors (Supplemental Table 3). Apathy was measured with a formal scale (the Apathy Evaluation Scale^{41,42}), through an adaptation of subscales from the Neuropsychiatric Inventory,⁴³ or by means of an ad hoc index.⁴⁴

Only 27 of 52 studies tested a sample of matched controls, and several studies were affected by residual or unmeasured confounding. In addition, important medical variables and conditions potentially related to cognition, such as diabetes, hypertension, circulatory function, thyroid function, and HCV coinfection, were not included in the statistic models or the results of the analyses were not discussed in detail. Although 45 of 52 studies collected information on current CD4+ cell count, the nadir CD4+ cell count was reported in only 25 studies; current or nadir CD4+ cell count could independently correlate with neurocognition.^{45,46}

The Autonomy in Everyday Life

Activities and Instrumental Activities of Daily Living

ADL or iADL were tested in 13 of 52 studies.^{24,38-40,44,47-53} Seven studies^{24,38-40,47,48,52} documented association of neurocognitive impairment with ADL. In one study, executive function pre-

dicted self-reported iADL decline and unemployment status in people with HIV.⁴⁷ Similar results were reported by Marquine and colleagues, who found that worse health conditions and presence of neurocognitive impairment are associated with ADL decline and unemployment.⁴⁸ According to Watson and colleagues, trauma, economic hardship, and stress are expected to be associated with worse neurocognitive performance and functional decline in people with HIV.⁵⁸ Two studies described correlation of neurocognitive impairment and iADL scores in middle- and older-aged participants.^{39,40} In Erlandson and colleagues' study, frailty and neurocognitive impairment were associated with greater risk of falls, disability, or death in people with HIV.²⁴

Generally, the role of neurocognitive impairment in the ADL or iADL performance of people with HIV is controversial in the reviewed literature. Although asymptomatic people with HIV underperformed in tasks involving central executive activation and showed reduced information processing speed compared with those in the control group(s), this was not predictive of their ADL performance.⁵⁰ A similar result was reported by Lawler and colleagues, who found that people with HIV were impaired in attention and central executive with no direct consequences in terms of ADL.⁵¹ In a study by Kamat and colleagues, no clear involvement of neurocognitive impairment in ADL was found, but people with HIV showed symptoms of the apathy spectrum that predicted poor ADL.⁴⁴ In another study from the same authors, apathy, not executive function, was a predictor of iADL performance.⁴⁹ Similar results were reported by Sadek and colleagues, who found that depressive symptoms were more sensitive in predicting a decline in instrumental iADL than neurocognitive impairment, including the central executive.⁵³ Few studies reviewed herein controlled for relevant medical variables such as hypertension, occurrence of coronary artery disease, or cerebrovascular events in the analyses, which may have led to residual confounding (Supplemental Table 2).

Employment Status

Employment status was considered in 11 of 52 studies.^{47,48,52-60} Correlation of neurocognitive performance with employment status was found in 8 of these 11 studies.^{47,48,52-54,56,59,60} One study in particular showed that neurocognitive function (including central executive performance) together with ART status and presence of HCV infection were associated with the employment indicator.⁵⁶ A specific contribution of the central executive in predicting employment status was also described.⁵⁹ Similar results were found by Rabkin and colleagues, who reported that the executive function was a significant predictor of employment status,⁶⁰ and by Heaton and colleagues, who found a correlation between employment status and neurocognitive performance, including testing of the central executive, attention, and executive function.⁵² Sadek and colleagues also reported that neurocognitive impairment was predictive of employment status, but the contributions of the central executive, attention, or executive control were not clear.⁵³ However, from the preliminary findings of a longitudinal study conducted in the Netherlands, the TREVI project,⁵⁵ a specific contribution of attention, central executive, or another neurocognitive function in predicting employment status in people with HIV did not emerge cross-sectionally. These patients aged 40 to 54 years had significantly lower employment rates than the general population in the Netherlands, and an association between employment status and depression did emerge. Similarly, Atkins and colleagues did not report an association between neurocognitive impairment and employment status.⁵⁷ Moreover, Chernoff and colleagues did not find correlations between the central executive or executive function performance and employment status.⁵⁸

Making Decisions and Adhering to Treatment

Decision Making

The ability to make decisions was discussed in 5 of 52 studies,⁶¹⁻⁶⁵ which all

documented an association with neurocognitive impairment. Gomez and colleagues tested people with HIV using a comprehensive neuropsychologic battery, including testing of the central executive. Participants were also assessed with a decision-making test (Game of Dice Task [GDT]). Neuropsychologic performance, presence of psychiatric comorbidities, and alcohol abuse were predictive of GDT performance.⁶¹ In a study by Fujiwara and colleagues, impairment in GDT performance was related to current immune status and was associated with executive function and processing speed.⁶² Thames and colleagues found that performance in a gambling task could be predicted by executive function and was partially mediated by presence of depression.⁶⁴ An effect of central executive impairment and failure in inhibitory processes on decision making was found by Hardy and colleagues.⁶³

Adherence to ART

Adherence to ART was considered in 6 of 52 studies.⁶⁶⁻⁷¹ Association between neurocognitive impairment, as operationalized in this article, and adherence to treatment was documented in 2 studies.^{67,69} Ettenhofer and colleagues found that central executive performance was predictive of medical treatment adherence; however, the reverse association was also significant.⁶⁷ Another study showed that the severity of neurocognitive impairment was associated with performance in everyday life function in terms of medication management.⁶⁹ Childers and colleagues found that, during temporary treatment interruption, mood state and neurocognitive function remained relatively stable, despite worsened viral load and CD4+ cell count. Nevertheless, improved viral suppression and immune restoration when reinitiating ART led to an improvement in neurocognitive performance.⁶⁶ By contrast, other authors did not describe a clear relationship between neurocognitive impairment and adherence to treatment. In a study by Fong and colleagues, partial drug

adherence was associated with forgetfulness and missing medical appointments; this may be linked to long-term memory performance and not with impairment of the central executive or supervisory control.⁶⁸ In another study, depression, not neurocognitive performance (which included a null effect of attention, executive function, and processing speed), emerged as a predictor of medication adherence, together with patients' satisfaction with their practitioners.⁷⁰

Quality of Life and Psychologic Wellbeing

Quality of Life

Quality of life was considered in 8 of 52 studies.^{37,54,72-77} Association of neurocognitive impairment with reduced quality of life was documented in 5 studies.^{54,72,74,76,77} Harrison and colleagues measured central executive performance with an *n*-back task in a sample of people with HIV, and found that the scores were negatively correlated with quality of life and depression.⁷² Similar results were reported when considering attention and processing speed performance.⁷² In a study by Osowiecki and colleagues, executive control and processing speed were associated with quality of life in women with HIV, independent of emotional distress.⁷⁴ Decreased neurocognitive performance, together with increased fatigue, determined a worse perceived quality of life in a sample of clade C-infected patients.⁷⁶ In a study by Catalan and colleagues, everyday memory difficulties (with uncertain involvement of the central executive), anxiety, and depression were associated with self-reported measures of quality of life.³⁷ Other authors did not describe association between neurocognitive performance and quality of life. In a study by Thein and colleagues, neither central executive nor attention performance correlated with quality of life.⁷³ Apathy, not neurocognitive impairment or depression, has been reported in association with a reduced quality of life.⁷⁵

Psychologic Wellbeing

Psychologic wellbeing was measured in 3 of 52 studies.⁷⁸⁻⁸⁰ Two studies reported association between this outcome and neurocognitive impairment.^{79,80} The performance in executive function and processing speed tasks correlated with reduced psychologic wellbeing defined by variables such as recreational drugs, irritability, and somatic complaints.⁷⁹ Impairment of processing speed could be associated with high levels of anxiety and depression and with reduced psychologic wellbeing.⁸⁰ However, in another study, the central executive, but not other cognitive functions, was significantly impaired in a sample of people with HIV, but this was not predictive of patients' psychologic wellbeing.⁷⁸

Mental Health

Depression

Depression was targeted in 10 of 52 studies.^{36,57,72,80-86} An association between neurocognitive impairment and depression was reported in 7 studies.^{57,72,80,81,83,85,86} In Chartier and colleagues' study, attention and central executive performance emerged as predictors of depression.⁸¹ In another study, central executive and processing speed performance were associated with depression.⁷² Processing speed was also associated with depression in the investigation by Janssen and colleagues.⁸⁰ Four other studies documented an association between depression and neurocognitive impairment, including testing functions responsible for supervisory control.^{57,83,85,86} However, one study did not find a correlation between impairment of attention or executive control and depression in a sample of people with HIV aged 50 to 59 years.³⁶ Similar results were obtained by Kamat and colleagues, who reported that neurocognitive function was not associated with depression.⁴⁴ Lifetime alcohol and marijuana consumption did not predict performance in tasks involving activation of the central executive, and there was no association with depression,

but there was an association with adverse medical outcomes.⁸² Intellectual and central executive function, age, and somatic symptoms of depression (but not education) were significant predictors of HIV disease progression and survival, but the association between neurocognitive impairment and depression was unclear.⁸⁴

Apathy

Apathy was considered by 4 of 52 studies⁴¹⁻⁴⁴; association with neurocognitive impairment was found in 2 of the 4.^{42,43} Castellon and colleagues reported association of central executive and executive function performance with apathy,⁴³ although in a study by Shapiro and colleagues, processing speed and attention, not central executive performance, were associated with apathy.⁴² However, 2 studies did not find an association between neurocognitive performance and apathy.^{41,44}

Anxiety

Anxiety was considered in 3 of 52 studies^{80,85,86}; all of these studies documented the association under investigation. A correlation between neurocognitive performance and anxiety, with no specific involvement of the central executive, was found in a follow-up study on the effects of efavirenz.⁸⁶ According to Robertson and colleagues, neurocognitive status, including testing of functions involved in the supervisory control, was associated with anxiety.⁸⁵ In another study, impairment of processing speed correlated with anxiety.⁸⁰

Discussion

Neurocognitive impairment in people with HIV persists in the ART era.^{87,88} A large-sample multisite study⁸⁹ demonstrated the presence of deficits in cognition in approximately 52% of people with HIV. About 33% of participants had asymptomatic cognitive disorders, 12% had mild neurocognitive impairment, and 2% had HIV-associated dementia. Although poor neuropsychologic function is a significant predictor

of mortality in people with HIV,⁹⁰ the picture is less clear concerning the sequelae of neurocognitive impairment in patients' everyday life functions. Central executive, attention, executive, and processing speed functions have often been described as impaired in people with HIV,^{78,91} but the consequences of such deficits, in terms of everyday life outcomes, are far from understood.

Autonomy in Everyday Life

From the current literature review, 7 studies^{24,38-40,47,48,52} documented an association between neurocognitive impairment and deficit in ADL. In one of these studies,⁵² although participants were young (mean age, 39.3 [standard deviation, 7.5]), they had relatively advanced stages of disease (34% had Centers for Disease Control and Prevention [CDC] stage C disease, 58% had AIDS, and the mean CD4+ count was 365.5 [standard deviation, 267]). Other studies described uncertain or nonsignificant relationship between neurocognitive impairment and ADL or iADL.^{44,49-51,53} Three of these studies^{44,49,53} reported an association between mental health and performance in ADL or iADL. Based on current evidence, we may assume that in patients treated with ART and with restored immunologic function, neurocognitive impairment may be associated with ADL or iADL. The relationship could be mediated by mental health or other unmeasured factors. For patients with relatively advanced disease or who are older, neurocognitive impairment could likely lead to a reduction of performance in ADL or iADL. Both aging and HIV disease progress may independently impact neurocognitive function, including a person's central executive, processing speed, and executive function.²²

Aging is particularly important in contemporary ART research because currently more than 50% of people with HIV are 50 years or older. In the large MACS (Multicenter AIDS Cohort Study) investigation,²² age was described as a variable independently associated with episodic memory and motor function performance. The relationship between

neurocognition and ADL or iADL in people with HIV in the transition phase (ie, 50-60 years of age) or older was examined by 3 studies reviewed herein.^{24,39,40} These studies described the association as under investigation.²⁴

One study reported that advances in ART contributed to decreases in disability rates in people with HIV.⁹² Nevertheless, these rates remain higher than those reported in the general population. Thus, people with HIV are still potentially at risk for problems in ADL or iADL, especially at age 50 years and older, and should be prospectively monitored. Results of the neuropsychologic literature reported herein are in conflict in that no specific role of the central executive, attention, executive function, or processing speed has been demonstrated in determining a decline in ADL or iADL. One possible explanation was provided by Scott and colleagues, who showed that multitasking, not the activation of a single neuropsychologic function, is crucial in predicting iADL impairment in people with HIV.⁹⁵

It has been suggested that health, not HIV status, could be related to performance at work among people with HIV.⁹⁴ Contrary to this position, a national survey conducted in France concluded that even though the conditions among people with HIV in 2015 were far better than those observed in 2000 or before, unemployment is still an issue in this subpopulation.⁹⁵ Further, financial hardship may be relevant for people with HIV, especially among ethnic minorities.⁹⁶ Job security, not only employment, is an important predictor of mental health in people with HIV.⁵⁴ In this regard, university graduation and being 40 years of age or older are protective factors for successful employment. A recent study highlighted the positive relationship between being employed and mood in people with HIV.⁹⁷ By contrast, 3 risk factors for lower job security include frailty, HIV disease severity, and HCV coinfection⁹⁸; the specific role of CD4+ cell count has not been determined.⁹⁹

In the pre-ART era, people with HIV experienced several limitations restricting their ability to work and were

frequently on work disability.⁹⁷ In the ART era, many patients can continue working or return to work, or they are now transitioning to retirement.¹⁰⁰ Unemployment is still associated with higher AIDS-related or non-AIDS-related mortality.¹⁰¹ Nevertheless, employment among people with HIV should be carefully considered, given that the proportion of people with HIV receiving disability benefit awards may affect the measurement. From the present review, it emerged that neurocognitive function, especially in terms of the central executive, attention, and executive function, is correlated with employment status.^{47,48,52-54,56,59,60} This result was not confirmed by data from the TREVI project,⁵⁵ but such discrepancy could be explained by the fact that different studies tested patients of different age cohorts (eg, Kordovski et al⁵⁶ and van Gorp et al⁵⁹ considered patients in their 30s and early 40s years of age, while Wagener et al⁵⁵ enrolled patients in their late 40s and 50s years of age). We also remark that the impact of the central executive, attention, and executive function in predicting the employment status of people with HIV should be studied in conjunction with the role of prospective memory, another predictor of employment status¹⁰² not targeted in this review. It has also been shown how less educated people with HIV could be at higher risk of unemployment,¹⁰³ which might suggest a protective effect of cognitive reserve.

Capacity to Make Decisions and Adherence to Treatment

A noteworthy result of this review is that the central executive, processing speed, and executive function performance of a person are predictive of their decision-making ability.⁶¹⁻⁶⁴ As such, it may provide a neurocognitive hypothesis of why some people with HIV are exposed to certain risk behaviors, such as substance use and gambling. Apart from mental health and social factors, there could be a purely cognitive component that explains why these patients are impaired in their risk behaviors and decision-making skills.

This finding also highlights the importance of early psychologic intervention in people with HIV who show risky behaviors in everyday life.

In the literature, low CD4+ cell count, anxiety,¹⁰⁴ and depression^{105,106} have already been associated with poor adherence to ART. An important question concerns whether or not neurocognitive impairment could directly impact treatment adherence. Results from this review are not converging. On the one hand, 2 studies documented a possible effect of neurocognitive performance, in particular the central executive.^{67,69} On the other hand, 3 studies found a null or uncertain effect of the central executive, attention, or supervisory control.^{66,68,70} We suggest that the interplay with other neuropsychologic functions, such as prospective memory, could be important in this regard. We also note that one study found that cognitive performance was associated with patients' abilities to navigate the Internet to complete important health-related tasks (eg, online pharmacy and health records navigation). These activities require central executive, attention, processing speed, and executive function integrity, which may be related to adherence to ART.¹⁰⁷

Quality of Life and Psychologic Wellbeing

Recent research has focused on the roles of mental health¹⁰⁸ and social support¹⁰⁹ in determining quality of life in people with HIV. Important conditions such as the presence of depressive symptoms or pain have been associated with reduced quality of life.¹¹⁰ One study also reported that time since HIV diagnosis is more important than a person's age in defining quality of life in people with HIV.¹¹¹ Biologic parameters, such as immune activation and viral load, also seem to be related to this outcome.¹¹² However, the role of neurocognitive impairment, which was addressed in this review, seems uncertain.

Three studies reviewed herein showed the specific role of neurocognitive impairment on quality of life.^{72,74,76} In particular, Harrison and colleagues

found an association between central executive, attention, and processing speed performance and quality of life,⁷² and Osowiecki and colleagues documented the contribution of executive control and processing speed.⁷⁴ However, other studies failed to find a specific and independent role of these functions in quality of life.^{37,73,75} This discrepancy may be explained by the different tasks used by different authors, by the different strategies of controlling for confounding, and by the possibility of residual or unmeasured confounding.

Two studies reported an association between psychologic wellbeing and performance in executive function and processing speed.^{79,80} Although testing for neuropsychologic performance and psychologic wellbeing, one study did not describe an association.⁷⁸ We may assume a mediating effect played by mental health (which was not explicitly tested by the authors). Indeed, absence of depressive or anxiety symptoms could protect the psychologic wellbeing of patients with mild or well-controlled neurocognitive problems.

Mental Health

Depression is a common comorbidity in people with HIV and is associated with the presence of other chronic diseases¹¹³ and anxiety.¹¹⁴ In the ART era, both depression and neurocognitive impairment remain prevalent and are associated conditions in people with HIV. This was recently confirmed by data from the European-Canadian network sCReen for Anxiety, depression, and Neurocognitive Impairment in HIV+ patients (CRANIum), where about 40% of screened participants tested positive for neurocognitive impairment and about 16% had depression.⁸⁵ According to Todd and colleagues, depressive symptoms are commonly reported in about 30% of people with HIV and are associated with mortality.¹¹⁵ HAND can arise relatively independent of depression and is not a simply reactive disturbance.¹¹⁶ A longitudinal study found that lifetime major depressive disorders were associated with cognitive problems in everyday life, and

difficulty increased at times of incident major depressive episodes. Individuals with incident major depressive episodes did not show consistent neuropsychologic decline.¹¹⁷

Results of this review indicate an association between neurocognitive impairment and depression.^{57,72,80,81,83,85,86} In particular, an association between attention, central executive performance,^{72,80} and processing speed was documented.^{72,80} Although negative results have been reported in the literature,^{36,44,82} most studies described a correlation. It is difficult to ascertain the prevalent direction of this association, for which more evidence coming from large-sample longitudinal studies is needed. With the current state of knowledge, we may assume that targeting neurocognitive function as a specific goal of an intervention with people with HIV could also lead to benefits in terms of mental health.

Presence of depressive symptoms and impairment in executive control emerged as 2 independent predictors of meta-memory performance,¹¹⁸ which may explain why people with HIV who report both neurocognitive impairment and depressive symptoms have difficulty managing several tasks of everyday life, such as keeping track of medical appointments and drug adherence. Though potentially meaningful, to our knowledge this possible explanation has not been explored in depth. It is also worth observing that from 1 study reviewed herein,⁸² important factors related to mental health, such as current and lifetime alcohol use and marijuana consumption, although associated with adverse medical outcomes, were not associated with performance in central executive and attention tasks.

The correlation between neurocognitive impairment and depression in people with HIV is well documented; however, the picture is much more fragmented in regards to apathy. Apathy was described in association with neurocognitive performance in 2 of the reviewed studies,^{42,43} but not in others.^{41,44} Apathy is related to the activity of the motivational system,¹¹⁹ which is relatively independent of the central executive, attention, or processing

speed performance. This may explain the negative results (ie, no association of apathy with the neuropsychologic performance) reported in the literature.

All studies analyzed in this review described an association between neurocognitive impairment and anxiety.^{80,85,86} This provides converging evidence with the early findings by Hestad and colleagues,¹²⁰ who reported that central executive and processing speed difficulties were associated with anxiety in people with HIV. Even though the direction of the association is uncertain, the presence of anxiety symptoms should be specifically targeted by clinicians, which may lead to careful longitudinal monitoring for presence of cognitive decline. A factor related to anxiety that has not been specifically addressed in this review is stress and post-traumatic stress. A study conducted with the WIHS (Women's Interagency HIV Study) cohort¹²¹ showed that stress and post-traumatic stress correlate negatively with neurocognitive performance, even though the outcomes on everyday life function have not been explored. Early childhood trauma should be discussed in relation to cognitive impairment, mental health, and everyday life outcomes. Another WIHS investigation found that for women who have experienced early life trauma, resilience can be protective in terms of depression and quality of life.¹²² However, the relationship between early childhood trauma and neurocognitive impairment is still to be clarified.

Fatigue is another important variable, well known to many people with HIV and clinicians. One study documented the association of neurocognitive impairment with fatigue in people with HIV.¹²³ Because fatigue has also been described as associated with depression and anxiety in people with HIV,¹²⁴ all these variables should be studied together and inserted in a dynamic model to understand possible pathways toward personalized care. The role of HCV coinfection should also be explored more in depth,¹²⁵ as well as its association with fatigue and ADL or iADL performance.¹²⁶

Substance use is another relevant factor related to mental health that is connected with everyday life outcomes. A study conducted on the MACS cohort¹²⁷ found that cocaine use in people with HIV led to a 3-fold-increased risk of depressive symptoms. Another MACS investigation¹²⁸ showed that in the years 1984 to 2013, marijuana use decreased in people with HIV, but daily use among users increased; cigarette smoking and alcohol consumption were positively correlated with marijuana use. Together, these findings indicate the importance of substance use as a plausible mediating or moderating factor between neurocognition and everyday life outcomes.

Limitations

In the last 20 years, knowledge of everyday life outcomes in people with HIV has progressed considerably; nevertheless, there are still many issues open for future research. Limitations of the current literature include scarce consideration of disease stage, nadir CD4+ cell count, virologic suppression, illness consequent to opportunistic infection and inflammation, blood parameters such as dyslipidemia or insulin resistance,⁵⁹ and brain measures such as axonal injury.¹²⁹ The relationship and interplay of these parameters with neurocognitive impairment and everyday life outcomes are still unclear. Sex also appears to play a role in neurocognition in people with HIV; women seem more affected by neurocognitive impairment than men,²¹ but the relationship to everyday life function is not clear. Other important variables that should be assessed in conjunction with neurocognitive performance and everyday life outcomes are quality of sleep,¹³⁰ pain,¹³¹ presence of cumulative stressful events,¹³² physical performance,⁴⁰ social support, and quality of intimate relationships. The role of polypharmacy in relation to cognition and ADL or iADL should be assessed. A recent study found that people with HIV aged 50 years or older are at risk for increased and sustained polypharmacy. This could have a relevant impact on

neurocognition and autonomy in daily living.¹⁵³ Finally, most studies mainly enrolled patients aged 30 to 59 years, so everyday life outcomes of people with HIV who are 20 to 29 years old should be specifically targeted for future research.

Conclusion

In general, neurocognitive impairment in people with HIV is associated with everyday life outcomes, particularly with ADL or iADL, problems at work and employment status, decision-making ability, and psychologic wellbeing. The relationship between quality of life and adherence to treatment is debated because nonconverging results have emerged in the contemporary literature. Other intervening factors, such as mental health, could have an impact and mediate the relationship. Moreover, even though there is converging evidence suggesting correlation of neurocognitive impairment with everyday life outcomes in chronic HIV disease, the strength of this association, the relationship with specific biomarkers, and the effect of existing modifiers are still to be clarified. Together, these findings imply the need for policy makers to invest more resources into the investigation of the neuropsychology of HIV, especially considering progress in life expectancy of people with HIV. This should also be studied in light of the effects of SARS-CoV-2 infection in those with HIV.¹⁵⁴ The multidisciplinary intervention strategy for people with HIV may be remodulated, particularly in terms of longitudinally monitoring the neuropsychologic function and its interaction with mental health. Ecologic outcomes, such as quality of life and psychologic wellbeing, should be routinely assessed. 

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