

# Neuropsychological Characteristics of Adults with HIV: A Systematic Review

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## Summary

**Introduction:** HIV-Associated Neurocognitive Disorder (HAND) is frequently reported even in patients undergoing Antiretroviral Therapy (ART), however, its severity, the main affected domains, and its relationship with ART are not well understood.

**Objective:** Through a systematic review, to identify the prevalence of HAND, the most affected cognitive domains, and determine the possible role of ART.

**Method:** PubMed database was consulted using the keywords "HIV" AND "HAND" OR "cognitive impairment", OR "neuropsychological impairment", OR "dementia", OR "cognitive decline" including papers published between 2019-2020. Initially, 460 papers were identified, meeting 11 the inclusion and exclusion criteria. A narrative synthesis was used to analyze the selected studies.

**Results:** The sample size, criteria used to establish HAND, and neuropsychological assessment instruments varied widely between the studies. Asymptomatic neurocognitive disorder (ANI) was the most frequent form of HAND, ranging from 25 to 57%, followed by mild neurocognitive disorder (0.8-38%) and HIV-associated dementia (HAD) (0.6-6%). The main domains affected were processing speed, attention, memory, working memory, verbal fluency and motor skills. Cognitive ability did not differ depending on ART status. The use of a single database and the absence of a quantitative analysis limited this review.

**Conclusion:** Despite the consensus on criteria for HAND diagnosis, studies show high variability in assessment and diagnostic methods. Variable percentages of HAND are reported in the analyzed studies, ANI being the most and HAD the least frequent. Patients on ART can still present cognitive deficits although HAD is uncommon. Low education level was frequently associated with cognitive dysfunction.

**Keywords:** HIV; HAND; ADL; Neuropsychological assessment

## Introduction

The relationship between Human Immunodeficiency Virus (HIV) and the central nervous system was initially identified in patients with Acquired Immunodeficiency Syndrome (AIDS) presenting opportunistic diseases such as encephalitis, leukoencephalopathy, toxoplasmosis, or meningitis [1]. Afterwards, the virus was detected in neuronal cells, macrophages, and microglia of HIV-infected patients in the absence of opportunistic diseases, indicating that HIV could directly alter the Central Nervous System (CNS) and, consequently, cognitive functions [2]. Antiretroviral therapy (ART) makes it possible to slow down the progression of the infection and lessen the effect of HIV in the CNS [3-5], although the effect of ART on cognitive functioning is not yet clear.

### HIV-associated neurocognitive disorder

Since the beginning of the epidemic, cases with varying degrees of cognitive impairment were reported in HIV-infected persons [6].

This cognitive impairment was initially termed AIDS-associated dementia complex when it was identified in AIDS phases and was later named HIV-associated dementia (HAD [6]), when it was determined that cognitive impairment could be detected even in the absence of opportunistic diseases. However, due to the existence of cases with cognitive impairment that did not meet dementia criteria, the terms Mild Neurocognitive Disorder (MND) and Minor Cognitive-Motor Disorder (MCMD) were proposed [4,5]. There is currently a consensus to use the Frascati criteria and the generic term HIV-Associated Neurocognitive Disorder (HAND), which includes the entire spectrum of cognitive impairment [3]: Asymptomatic Neurocognitive Impairment (ANI), MND and HAD, of which ANI is the most frequent [6].

ANI and MND are generally characterized by subtle changes in working memory, speed of information processing, difficulty in verbal fluency, decreased learning ability, or altered verbal memory

[4]. Specifically, the Frascati criteria [3] indicate that ANI is diagnosed when the performance in neuropsychological tasks is 1SD below the mean for age-educational appropriate norms in two or more cognitive domains in the absence of functional impairment. MND is defined by impairment in two or more cognitive domains, with performance 1SD below the mean and mild to moderate interference in activities of daily living (ADL) or in mental acuity. HAD usually develops in advanced stages of infection and is characterized by cognitive performance 2SD below the mean in two or more cognitive-motor domains and significant functional impairment [3]. HAD is described as a subcortical dementia, with severe memory loss, impaired attention, motor (speed and precision), and executive dysfunction [4]. Psychotic symptoms or mood disorders can also be observed [4]. Neurological signs such as altered saccadic eye movements, adiadochokinesia, hyperreflexia, and frontal release signs (e.g., sniffing or glabellar reflex) may also be present in HAD [4,6]. Furthermore, according to Frascati criteria the diagnosis of any degree of HAND should include assessment of the following domains (with at least two measures per domain): verbal/language, attention/working memory, abstraction/executive, memory, speed of information processing, sensory-perceptual, and motor skills. Also, cognitive impairment should not be explained by delirium or other preexisting causes, including other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse [3]. The use of mood and ADL scales is also recommended [4].

### Despite ART, HAND can still occur

The role of ART in the maintenance of cognitive ability is not fully understood. To date, several lines of research suggest that HAND may still occur despite ART. For example, Kramer-Hämmerle S, et al., [7] found that HIV can remain in the CNS even after successful ART. In concordance, HAND has continued to be reported even as ART options advance [3,4]. Furthermore, it has been reported that some ART can cause neurotoxicity contributing to the presence of HAND [8]. Interestingly, in the pre-ART era, reports indicated the presence of HAD in patients with a CD4 cell count less than 200. In contrast, after the introduction of ART, the incidence of milder forms of HAND has been observed more frequently in patients with a normal or near-normal CD4 cell count [3]. In sum, ART seems not to be sufficient to fully prevent or manage HAND [9].

In a previous systematic review and meta-analysis, Habib AG, et al., [10] analyzed 16 papers from Sub-Saharan Africa, finding that 42.37% of HIV+ patients without ART and 30.39% HIV+ patients on ART for at least 6 months had cognitive impairment. Such impairment was more common in patients with psychiatric comorbidities in the HIV+ without ART group. The authors concluded that HIV predisposes patients to cognitive impairment, although ART can substantially reduce it. An important limitation of the study is that it only analyzed papers that used the International HIV Dementia Scale, a screening tool that assesses memory, motor and psychomotor speed only, and thus, could not accurately determine the severity of HAND.

Additionally, time of initiation of ART after diagnosis and treatment adherence are other factors suggested as playing an important role in CNS disease manifestations. For example, Ellis R, et al., [11] identified that initiating ART as early as possible could reduce the risk of developing HAND. It has also been suggested that ART interruptions may have a relationship with the development of HAND [12].

Heterogeneity of the HIV and different methodological approximations contribute to the difficulty in obtaining clarity about the cognitive characteristics of the disease. Moreover, there is

still much to understand regarding ART and its effect on CNS and cognitive health [13]. Therefore, the aim of this systematic review was to examine the most recent neuropsychological findings in adults with HIV to identify the prevalence of HAND, which cognitive domains are affected, and its association to ART.

## Method

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [14] was used for the preparation of this systematic review.

### Search strategy

An electronic search of the PubMed database via Medline was conducted in October 2020 using the keywords “HIV” AND “HAND” OR “cognitive impairment”, OR “neuropsychological impairment”, OR “dementia”, OR “cognitive decline”. Some of these search keywords were taken from a previous systematic review [10] which focused exclusively on cognitive aspects, and not on other HIV-related aspects. The general term HAND was used, which includes HAD, MND, and ANI.

### Eligibility of studies

Inclusion criteria were studies published between 2019 and 2020 addressing cognitive aspects of HIV in adults aged 18-59 years and describing the prevalence of HAND, the affected cognitive domains, and/or the relationship between ART and HAND. Studies in English or Spanish that were already published or accepted for publication were included. Exclusion criteria included only addressing the neurobiological or physiological aspects of HIV or ART, general aspects of HIV infection (e.g. prevention, transmission), opportunistic diseases, studies whose main topic did not consider neuropsychological characteristics in HIV, and those that studied only seronegative, non-human, older adult, children, or adolescent samples.

### Selection of studies

The studies were organized in a Microsoft Excel spreadsheet to rule out duplications. The initial review of titles and abstracts permitted the identification of studies that could be eligible based on the pre-established inclusion criteria. The complete articles were read for final selection and data extraction.

### Qualitative evaluation and data synthesis

The Joanna Briggs Institute [15] critical checklist was used to assess the methodological quality and risk of bias of the studies. Studies were classified according to their quality scores obtained from the JBI criteria into low quality (<50% of criteria met), moderate quality (50-75% of criteria met) and high-quality studies (>75% of criteria met). Given the small number of studies that met the inclusion criteria, we did not predefine the exclusion of studies based on study quality.

Although the PRISMA model proposes a quantitative analysis, this was not possible due to the use of different assessment instruments, different methods and statistical analyses, and because the sample size of the studies was relatively small. For this reason, a narrative synthesis method was used, describing the main methodological characteristics and findings of the studies in text and tables.

## Results and Discussion

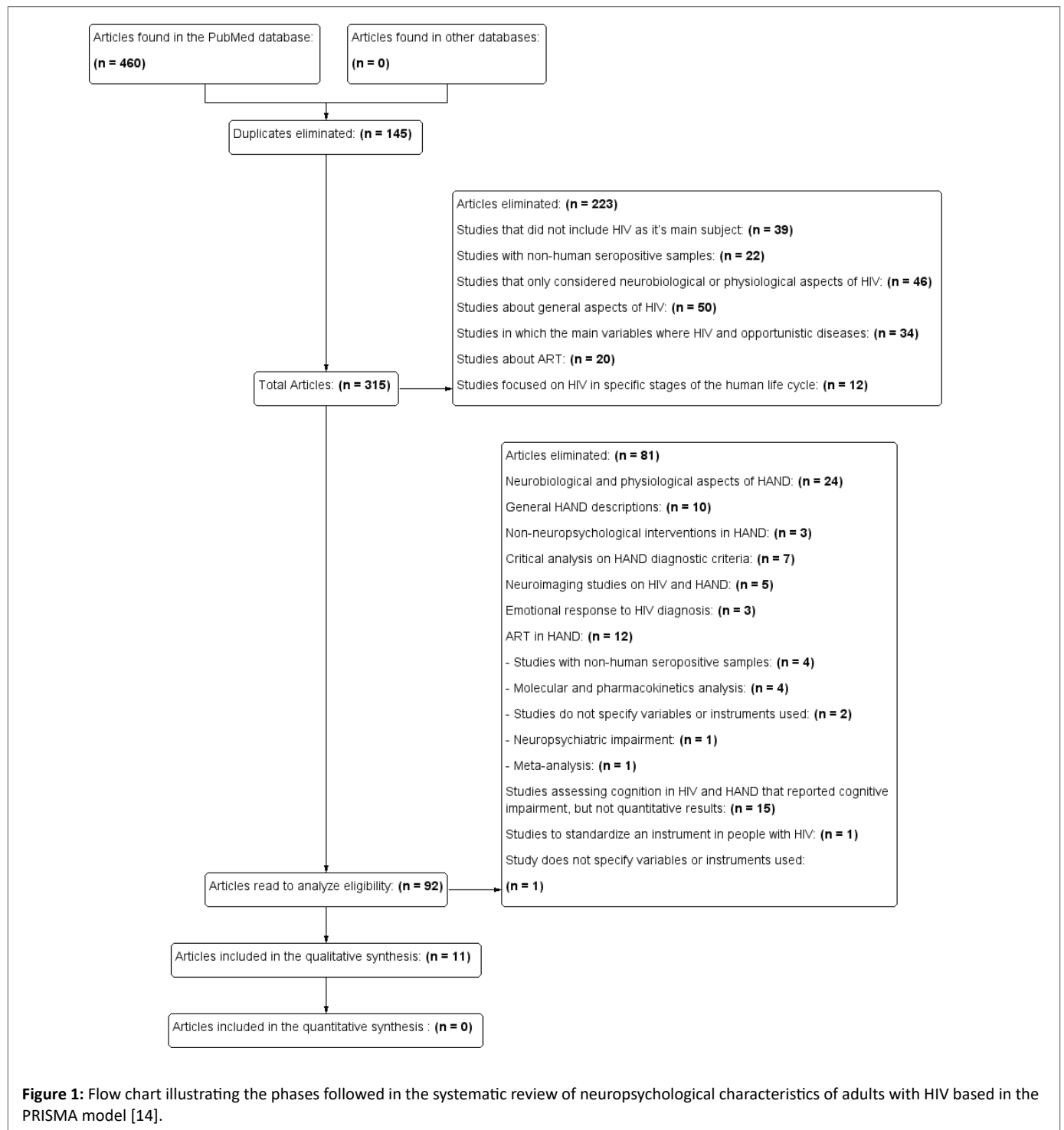
A total of 460 studies were identified in the first phase of the search. After eliminating duplicates, reviewing the abstracts based on the inclusion criteria, and qualitatively analyzing the remaining studies,

11 studies were included in the present review as they described the prevalence of HAND, the affected cognitive domains of the studied population, and/or the relationship between ART and HAND. Figure 1 shows in a flow chart the process used in the selection of the works analyzed.

### Qualitative evaluation of selected studies

Due to their descriptive nature and the impossibility of establishing causal relations, the studies included in this systematic

review correspond to a 4b JBI (2014) evidence level, this level is low. Nonetheless, four of the studies can be considered of high methodological quality (>75%) [16-19] according to the JBI checklist and three with moderate quality (50-75%) [20-26] (Table 1). Regarding the evaluation of possible biases, we identified differences in age and formal education between the HIV+/HIV- groups in some comparative studies that could have influenced the results. Figure 2 shows the qualitative evaluation of the selected studies in this review according to JBI critical checklist.



**Figure 1:** Flow chart illustrating the phases followed in the systematic review of neuropsychological characteristics of adults with HIV based in the PRISMA model [14].

	Inclusion criteria	Study subjects	Measurement	Valid measurement	Confounding factors	Strategies for confounding factors	Outcomes measurement	Statistical analysis
Agarwal et al. 2020	+	+	+	+	-	-	?	+
Costaggu et al. 2020	-	+	+	+	?	?	-	+
Forno et al. 2020	-	+	+	+	?	?	?	+
Kanmogne et al. 2020	-	+	+	+	?	?	?	+
Liang et al. 2020	-	+	+	?	+	+	+	+
Métral et al. 2019	-	+	+	+	+	+	+	+
Milanini et al. 2020	+	+	+	?	-	-	+	+
Nakao et al. 2019	?	+	+	+	?	?	+	+
Nyamayaro et al. 2020	?	+	+	?	+	+	+	+
Paolillo et al. 2019	?	+	+	+	?	?	+	+
Zaegel et al., 2020	+	+	+	+	+	+	+	+

**Figure 2:** Qualitative evaluation of risk of bias for methodological aspects of the reviewed studies. The graph shows the evaluation of the main methodological aspects of each study as follows: green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias. For detailed information as to the guidelines for assessing each methodological aspect, please refer to Joanna Briggs Institute [15].

### Place of origin of studies

Most studies were conducted in Africa, including Sub-Saharan Africa [26], Zimbabwe [17], and a multicenter study from Kenya, Tanzania, and Uganda [22]; as well as Europe, including Italy [24], France [19], and a multicenter study from Switzerland [21]. The remaining studies originated in the USA [18], India [23], and Japan [16].

### Methodological aspects

The comparison groups among the studies varied considerably, some studies only compared cognitive performance to the normative data included in the tests while some included control groups (Table 2). Sample size was also variable, ranging from 68 to 472 participants.

The average age ranged from 37.9 to 54.3 and from 34.6 to 50.4 years for HIV+ and HIV- participants, respectively. Table 2 summarizes the main characteristics and results of the studies analyzed. One study

was longitudinal [18] and the remaining 10 were cross-sectional; in the case of studies by Métral M, et al., [21] and Milanini B, et al., [22], although they are part of a longitudinal multicenter projects, results reported in the analyzed papers are cross-sectional.

### Diagnosis and severity of HAND: ANI was the most prevalent among studies

Although not all studies reviewed aimed at determining the percentage of participants with HAND as a main objective, the proportion of participants with cognitive impairment in eight studies varied from 26.3 to 58.2% [16,17,19,21-25]. The highest proportion, described in Zaegel-Faucher O, et al., [19] in France, is similar to the 46.9% reported by Heaton RK, et al., [27] in a large sample in the US.

Regarding the clinical criteria used for HAND diagnosis, from the seven studies, six explicitly described using the Frascati criteria [3] that classifies HAND into ANI, MND, and HAD [16,19,21,23-25]. Nonetheless, alignment to such criteria was in general lax: only two

**Table 1:** Cognitive domains assessed and number of tests used per study.

Cognitive domains		Domains assessed and number of tests per study										
		Agarwal R, et al. [23]	Costaggu D, et al. [24]	Forno G, et al. [25]	Kanmogne GD, et al. [26]	Liang HJ, et al. [20]	Métral M, et al. [21]	Milanini B, et al. [22]	Nakao A, et al. [16] <sup>a</sup>	Nyamayaro P, et al. [17]	Paolillo EW, et al. [18]	Zaegel-Faucher O, et al. [19] <sup>b</sup>
Cognitive screening		1	1						1			
Verbal/Language			2	1		1	2	1	ns	2	2	ns
Attention/ Working memory			1	1	2	4	1	1	ns	3	3	ns
Executive Function	US					3	2		ns			ns
	Flexibility			1						2	1	
	Problem solving			1							1	
	Decision making								1			
Memory			2	1	2	2	1	1	ns	2	2	ns
Processing speed			1			4	2	1	ns	3	2	ns
Sensory-perceptual skills			2				2					ns
Motor skills				1		1	2	1		2	1	ns
Others	Depressive symptomatology	1	1			1	1	1		1		1
	ADL	1	1				1				1	1
	Neurological Soft Signs			1								
	Mental and physical health					1			1		1	

Note: US, unspecified (assessment of specific executive functions is not reported); ns, number of tests used to assess each cognitive domain is not specified; ADL, activities of daily living.  
 Numbers represent the number of tests used to assess each domain; missing entries represent absence of assessment.  
<sup>a</sup>Authors report the use of four neuropsychological instruments but do not specify which subtests were used as measures of each domain.  
<sup>b</sup>Authors report that at least one test was used to assess each domain, reporting a range of 1-9 possible tests per domain.

studies [19,21] assessed all seven domains plus ADL and depressive symptomatology as recommended by the criteria. From the remaining studies, two do not specify whether ADL were measured [16,25] to establish an adequate HAND classification; another study uses the combination of ADL and global scores on a screening test to determine HAND classification; and one study based HAND classification only on the severity of cognitive impairment [24], thus only being able to suggest a mild or severe form of HAND. Although differing in their assessment methods and alignment with said criteria, such studies consistently reported a lower proportion of HAD (0.6-5.2%) and a higher proportion of ANI (25.4-47.5%), while the proportion of MND was highly variable (0.8-38.5%), with only one study reporting a greater frequency of MND than ANI [25]. Consistent with our findings, Heaton RK, et al., [27] described that 70% of their patients with HAND reported impairment in cognitive abilities that did not interfere with their daily activities, suggesting ANI. Such findings indicate that in most cases with HAND, subtle cognitive deficits are only detected by neuropsychological evaluation and given the lack of impact on ADL, the person would hardly notice any change in their cognitive abilities.

Only two studies describe in detail the affectation of ADL in their participants with different degrees of HAND [23,24]. In the first study, slight difficulties were found in food preparation, transportation, medication intake and money management; and in the second one,

the instrumental ADL measurement reported that 13.3% of the participants showed scores suggesting dependency, however, the authors acknowledged that some participants had never performed certain activities on which they were questioned (cleaning, food preparation, laundry) so the results are not clear. Additionally, when dividing the sample based on cognitive ability into two groups (<-1SD and >-1SD), the group that scored <-1SD showed moderate to severe depressive symptomatology, which could in some cases exclude the diagnosis of HAND according to Frascati criteria. In general, few information is given by studies as to how cognitive impairment affects the daily lives of people living with HIV in aspects such as work, family, recreational, social, and health-related aspects. Such void of information could limit the ability of health professionals to design and implement intervention strategies to ameliorate or compensate cognitive decline.

Findings suggest that the application of the Frascati criteria is not consistent and represents a limitation when attempting to establish the prevalence of HAND across studies. Additionally, other factors that may have contributed to the variability in HAND prevalence between studies include sample size, domains assessed, duration of HIV infection, and the instruments used. Furthermore, greater care should be put on reporting the impact of HAND in daily lives of people living with HIV.



**Table 2:** Summary of the methodological characteristics (sample and instruments) and main findings on frequency of HAND, cognitive functioning, and affectionation of ADL of the reviewed articles.

Authors (year)	Sample Characteristics	ART characteristics of the sample	Main Results		
			Frequency of HAND	Affected Domains	Affectionation of ADL
Agarwal R, et al. [23]	160 HIV+, 4.27 DD	50% of participants were pre-ART and 50% of participants on ART	52.5% had HAND (47.5% ANI and 5% MND)*	Memory, visuospatial skills, language, calculation, naming, and abstraction are significantly associated with HAND	5% of the participants had mild difficulties in ADL
Costagguio D, et al. [24]	166 HIV+, 18DD	100% of participants on ART	44.5% had HAND (38.5% mild form and 6% probable HAD)*	The most affected domains were immediate and delayed memory and attention	9.6% needed help with ADL
Forno G, et al. [25]	3 HIV+ groups: 18 ANI, 21 MND, 28 cognitively healthy	89% of ANI participants on ART, 95% of MND and 93% of cognitively healthy	58.2% had HAND (26.9% ANI, 31.3% MND)*	When compared to the cognitively healthy HIV+ group, significantly lower scores on the neurological soft signs test (spatial orientation and right/left orientation) were identified in the ANI and MND groups	NA
Kanmogne GD, et al. [26]	347 HIV+ and 395 HIV-	55.39% on ART, 43.1% naive, 1.46% no current treatment	ND	Attention/working memory deficits were identified in 17.5% of HIV+ subjects versus 12.7% in HIV-. A significant difference was observed in learning between HIV+ (altered in 18.7%) and HIV- (altered in 12.4%). Memory performance was significantly worse in HIV+ subjects versus HIV-	NA
Liang HJ, et al. [20]	39 HIV+ (21 males, 8DD; 18 females, 7DD) 45 HIV- (20 males, 25 females)	89% on ART	ND	The HIV+ group performed significantly worse in fluency, attention/working memory, and processing speed	NA
Métral M, et al. [21]	981 HIV+	100% of participants on ART	26.8% had HAND (25.4% ANI, 0.8% MND, and 0.6% HAD)*	41% had errors in motor skills, 33.1% in processing speed, 33% in attention/working memory, 17.2% in verbal episodic memory, 7% in language, and 5.8% in sensory-perceptual skills	ADL were evaluated to diagnose HAND, but the impairment is not reported
Milanini B, et al. [22]	2 472 HIV+ and 429 HIV-	68% on ART	38% had cognitive impairment	The most affected domains were speed of information processing, manual dexterity and verbal fluency	NA
Nakao A, et al. [16]	38 HIV+ and 30 HIV-	42% on ART	26.3% had HAND (10.5% ANI, 10.5% MND, and 5.2% HAD)*	Not reported	NA
Nyamayaro P, et al. [17]	155 HIV+, 7DD; 76 HIV-	100% of participants on ART	49.7% of HIV+ had cognitive impairment	HIV+ subjects had significantly lower performance than the HIV- group in attention, processing speed, learning, memory, and verbal fluency. 50% of HIV+ subjects had memory and attention errors	NA
Paolillo EW, et al. [18]	6 groups: non-frail (18 HIV+, 8DD /39 HIV-), pre-frail (25 HIV+, 8DD /20 HIV-), and frail (7 HIV+, 8DD /1 HIV-).	94% of non-frail on ART, 84% of pre-frail and 86% of frail	ND	After 2 years of follow-up, pre-frail HIV+ showed significant decline in processing speed, motor skills, and delayed recovery	Frail HIV+ group had a significant decline in ADL compared to all groups and reported poorer physical and mental health
Zaegel-Faucher O, et al. [19]	121 HIV+, 21DD	100% of participants on ART	57% had HAND (28.9% ANI, 24.8% MND, and 3.3% HAD)*	The most affected domains were attention, working memory, executive function, and processing speed	ADL were evaluated to diagnose HAND, but the impairment is not reported

\*Based on Frascati criteria; DD, years since HIV diagnosis; ND, not determined; NA, not assessed

## Processing speed and attention were the most reported affected cognitive domains

Frascati criteria establish that the assessment of HAND should include verbal/language, attention/working memory, abstraction/executive, memory, speed of information processing, sensory-perceptual, and motor skills domains [3]. Despite this specification, the reviewed studies, including those which aimed at establishing the prevalence of HAND, show a high variability in the specific cognitive domains that were assessed, the number of tests used to assess each domain, and the instruments used to assess the cognitive functions. The most frequently assessed domains were attention/working memory (ten studies) and memory; followed by verbal/language (nine studies) and processing speed (eight studies), with only three studies assessing sensory-perceptual skills.

The most commonly affected cognitive domains across studies were processing speed [18-22] and attention [19-21,24]; followed by memory [18,21,24], working memory [19-21] verbal fluency [21-23], and motor skills [21,22].

Specifically, studies analyzing affected cognitive domains in comparison to HIV- participants identified that the HIV+ group performed significantly worse than the HIV- group mainly in attention/working memory [17,20,26], learning/memory [16,25], speed of information processing, and verbal/ non-verbal fluency [17,20]. Additionally, Liang HJ, et al., [20], found that HIV+ women, but not HIV+ men, were slower than sex-matched controls on sensorimotor function.

Nakao A, et al., [16] report deficient decision-making ability in HIV+ participants. Specifically, the authors report that the amount of money at the end of the game was less and the Iowa Gambling Task (IGT) total score was significantly lower in the HIV+ group than in controls. Moreover, worse IGT performance was associated with the presence of HAND. Social cognition deficiencies including decision-making have been consistently associated to decreased quality of life, mental health, functional disability, and impaired social relations in other neurological and psychiatric populations [28]. Future studies should explore the affectation of decision-making and other social cognitive abilities, and their effects on daily lives of people living with HIV+.

## Studies reported no differences in cognitive ability between patients with or without ART

The specific treatment regimens and proportion of HIV+ participants on ART varied across studies, from only 42% to 100% (Table 2). Only Zaegel-Faucher O, et al., [19] specify that participants with poor treatment adherence were excluded from the study. In addition to such variability in sample characteristics, not all studies consider the association between HAND and ART treatment duration, type or status (being treated or not).

Some studies analyze whether participants on/off ART differ in their cognitive status, finding no differences in general. For example, Forno G, et al., [25] report no significant differences in the proportion of participants on ART depending on the degree of HAND (cognitively healthy, ANI and MND). In the same line, Agarwal R, et al., [23] and Milanini B, et al., [22] do not find significant differences in the proportion of participants with or without HAND/cognitive impairment depending on whether they were receiving ART or not. Also, Nakao A, et al., [16] found no differences on decision-making ability, and Kanmogne GD, et al., [26] on attention/working memory or memory/learning, depending on ART status.

In the study by Milanini B, et al., [22], the authors found that neither ART status nor ART duration were significant predictors of cognitive impairment. In contrast, Métral M, et al., [21] identified that the odds of having cognitive impairment increased with ART duration, nonetheless, it stabilized with longer ART durations; also, several authors conclude that despite advances in ART, people living with HIV are still at risk of cognitive impairment [22,26].

Such findings are consistent with a longitudinal study in which ART had no effect on cognitive dysfunction and on the risk of progression to symptomatic forms of HAND despite having an effect on the infectious process [29], as the effects on the CNS, and therefore on cognition, continue to be present in varying degrees despite treatment [27]. This is also pointed out in a previous systematic review describing that although ART has enabled the reduction of cognitive disorders, particularly HAD, the mildest forms of HAND are still frequent [10].

In the ART era, confounding and aggravating factors, mainly opportunistic diseases that affect CNS function, are less common [3] and were controlled in the reviewed studies. Available treatments have allowed HIV to be considered a chronic disease, providing greater time, health, and quality of life [4]. However, receiving ART or its success in terms of immunological indicators seems not to be consistently associated to maintenance of cognitive ability.

## Other findings

**Assessment instruments:** The most frequently used instruments for cognitive assessment were the Wechsler Memory Scale (WMS III and IV), the Wechsler Adult Intelligence Scale (WAIS III and IV), and the Grooved Pegboard Test (GPT). However, the neuropsychological instruments used in each study varied widely, possibly depending on the availability in each country, with one study having to translate instruments prior to their use, but without reporting a standardization/validation process or the availability of adequate normative data [17]. Findings demonstrate that there is no consensus on a specific neuropsychological battery to evaluate HAND. Reaching such consensus could facilitate the identification of HAND and the comparison of studies carried out in different parts of the world.

## Other variables associated to HAND

**Serological, immunological and other biological variables:** Although we did not specifically search for variables associated to HAND, some of the included studies did report several. For example, two studies [22,26] found that even with an adequate CD4 cell count, there is still risk of developing cognitive impairment. Additionally, Milanini B, et al., [22] found that higher levels of plasma HIV RNA, current nadir CD4 cell count, and higher WHO stage are associated with increased risk of cognitive dysfunction. Kanmogne GD, et al., [26] reported that carriers of CRF02\_AG viruses showed reduced deficits in attention/WM in comparison with those infected with other subtypes in Cameroonians. Finally, Paolillo EW, et al., [18] identified pre-frailty state as predictive of cognitive decline in HIV+ population

Forno G, et al., [25] found that, compared to the cognitively healthy HIV+ group, ANI and MND groups had moderate to severe impairment in two neurological soft signs, right-left and spatial orientation on the Heidelberg scale.

**Sociodemographic variables:** Several studies find that poorer education is associated with cognitive impairment [17,21,22]. Métral M, et al., [21] found that cognitive impairment was associated with older age, non-caucasian ethnicity and unemployment together with longer antiretroviral therapy duration. Additionally, Related with gender, Liang HJ, et al., [20], found that cognitive impairment on

HIV+ people may be greater in women than in men, specifically on sensorimotor function.

**Longitudinal studies:** The longitudinal study by Paolillo EW, et al., [18], divided the sample into six HIV+/- groups (non-frail, pre-frail, and frail). At the baseline assessment it was reported that the HIV-non-frail group performed better in learning, memory, and motor domains compared to the other groups. In ADL, the HIV+ frail group had a significant decline in a period of two years in relation to the rest of the groups, in addition to identifying a decrease in physical health. At the 2-year follow-up, pre-frail HIV+ participants had a significant decrease in overall cognitive performance, specifically in processing speed and motor skills. Significant differences in processing speed were observed in the pre-frail HIV+ group when compared to the non-frail HIV+ group, and in motor skills when compared to the frail HIV+ group. Some studies have suggested that HAND could have a progressive nature, with ANI conveying a two to six-fold increase in risk for developing symptomatic forms of HAND in a shorter time [29]. Moreover, other studies have also pointed a relevant association between frailty and cognitive decline in HIV population [30].

### Limitations

Our review included articles from a single database and the inclusion criteria focused purely on cognitive aspects in adults with HIV, excluding other specific populations such as children, older adults or pregnant women, resulting in a small sample of articles. Therefore, the amount of information reviewed was limited, reducing the ability to generalize conclusions and limiting the analysis to a narrative synthesis. Due to methodological differences and heterogeneity in the studies, no statistical analysis was performed to assess the consistency of the results and establish estimates to detect any effect.

### Conclusion

Although specific criteria have been published to identify different degrees of HAND, including the cognitive domains to be assessed, recently published studies still demonstrate broad variability in the methods used to assess and diagnose cognitive decline in HIV, limiting the ability to compare and generalize findings on HAND prevalence. Despite such limitations, HAD is the least and ANI the most reported form of HAND. Most studies find no association between ART and the presence of HAND but identify lower education level as a risk factor for cognitive impairment. Finally, there is no consensus on a specific neuropsychological battery to evaluate HAND. Such consensus could facilitate the identification of HAND and the comparison of studies carried out in different parts of the world.

### Conflict of Interest

The authors report no conflicts of interest with respect to the materials, methods, and results presented in this article.

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