

# Cognitive function in treated HIV patients

Valerio Tozzi  
Pietro Balestra  
Raffaella Libertone  
Andrea Antinori

Lazzaro Spallanzani National Institute  
for Infectious Diseases, Rome, Italy

**Abstract:** Although highly active antiretroviral therapy (HAART) has reduced the incidence of HIV-associated dementia, the overall prevalence of HIV-associated neurocognitive disorders (HAND) has increased. Since treatment and prevention of HAND are becoming an increasing concern, management strategies for cognitive impairment in patients living with HIV are expected to play an important role in the near future. This review summarizes the existing literature on studies investigating cognitive functions in patients receiving antiretroviral (ARV) treatment. Most studies indicate that HAART use results in improvement of neurocognitive functions, yet milder forms of HAND are not only prevalent, but also incident in patients with persistently undetectable plasma HIV RNA. We performed a systematic review on all studies performed in patients receiving ARV treatment that included neurocognitive evaluations as study end points. Thirty-six studies were examined. Study methodology varied from cross-sectional to double-blind, randomized, controlled designs. Aside from historic zidovudine monotherapy trials, in most studies, ARV schemes varied considerably, and in some cases, ARV regimens were not reported in detail. Only a few articles included virological studies on cerebrospinal fluid. Study duration was <2 years in most cases. Differences in study design and presence of study limitations may account for difficulties in understanding the impact of HAART on cognition and in evaluating the effect of an individual agent or ARV regimen on cognitive functioning. The aim of the present article is to provide HIV clinicians with a comprehensive review of recent achievements and future prospects for ARV treatment and prevention of cognitive dysfunctions in HIV-infected patients.

**Keywords:** highly active antiretroviral therapy, neurocognitive disorders, HIV dementia, central nervous system

## Introduction to cognitive impairment in HIV patients

The central nervous system (CNS) is a major target of HIV-1 infection. HIV invades the CNS during the primary infection period and establishes a protected viral reservoir. In a consistent proportion of patients, chronic CNS HIV infection can lead to neurodegenerative complications that have recently been characterized as HIV-associated neurocognitive disorders (HAND). HAND defines three categories of dysfunction: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).<sup>1</sup>

The introduction of highly active antiretroviral therapy (HAART) as a standard of care has considerably enhanced the life expectancy among HIV-infected individuals. Over the last 20 years, antiretroviral (ARV) therapy has moved from an almost

Correspondence: Valerio Tozzi  
Lazzaro Spallanzani National Institute  
for Infectious Diseases, Via Portuense  
270, 00149 Rome, Italy  
Tel +39 06 55170427  
Fax +39 06 55170405  
Email [valerio.tozzi@inmi.it](mailto:valerio.tozzi@inmi.it)

ineffective monotherapy to combination multidrug regimens able to suppress plasma viral load to undetectable levels in most HIV-infected patients. Consequently, the natural history of HIV infection has been changed into a manageable chronic disease requiring long-term ARV treatment. However, despite this success, there are a number of important issues that needs to be addressed. Nowadays, the incidence of the most severe form of HAND and HAD has declined.<sup>2-4</sup> However, HAND represents an unresolved clinical issue. First of all, while HAD has become less frequent, MND and ANI may persist in a relevant proportion of patients.<sup>5-7</sup> Second, consistent literature has demonstrated strong relationships between HAND and employment, medication adherence, mood, fatigue, interpersonal functioning, quality of life, survival, and use of healthcare resources.<sup>8-11</sup> Finally, because the HIV-infected population is aging, patients are exposed to a growing number of comorbidities with negative impact on cognitive functioning.<sup>12</sup> Thus, identifying patients at risk of HAND and developing treatment strategies able to prevent and effectively treat HIV-associated cognitive dysfunctions should become a priority.

This review summarizes the existing literature on prevalence, clinical presentation, and treatment strategies of HAND.

## Methods

### Search strategy

The search was conducted using different strategies. First, a literature search was performed using the PubMed database. Search terms that might indicate cognitive function (cognitive impairment, HIV-associated dementia, AIDS dementia complex, cognition, and neuropsychological tests) and ARV treatment (antiretroviral therapy, treatment, and HAART) were used as keywords. Second, the names of key researchers in the topic were used as authors for PubMed database searches. Third, the reference sections of relevant studies on the topic were screened.

### Eligibility criteria, inclusion and exclusion criteria

All studies assessing neuropsychological (NP) measures as primary or secondary end points in patients receiving ARV therapy were included. We defined ARV therapy as any treatment with ARV drugs, either alone like zidovudine monotherapy or in combination. We defined NP measures as a NP battery that included at least three NP tests. The time period covered was from 1987 to June 2010. Studies on children and adolescents were excluded.

## Clinical presentation and prevalence of cognitive impairment in HIV

### Clinical presentation

The diagnostic criteria for HAND were updated in 2007.<sup>1</sup> These criteria recognize 3 categories of HAND: the asymptomatic form (ANI), the mild form (MND), and the severe form (HAD). Patients with ANI show an acquired impairment in cognitive functioning, documented by detailed NP testing exploring at least 5 cognitive domains, in at least 2 domains. The cognitive impairment is asymptomatic and does not interfere with everyday functioning.

HAD lies on the opposite side of the clinical spectrum. HAD is among the most devastating consequences of HIV infection due to its progressive impact on everyday life. It is characterized by moderate to severe neurocognitive impairment, affecting at least 2 cognitive domains.<sup>1</sup> Early clinical features include a combination of a triad of manifestations: cognitive (forgetfulness, poor concentration, and attention deficits), motor (tremor, ataxia, and spasticity), and behavioral (agitation and apathy).<sup>9</sup> In patients with HAD, the impairment is moderate to severe and produces a marked interface with daily functioning (work, home life, and social activities).<sup>1</sup> Later in the course of the disease, global dementia, paraplegia, and mutism may occur. Typically, in untreated HIV-infected patients, HAD evolves insidiously over a period of weeks or months.<sup>9</sup>

The intermediate form of HAND is MND. MND is often an antecedent syndrome and can precede the onset of frank dementia. Clinical features of MND are similar to HAD, although with less severe signs and symptoms. The cognitive impairment, involving at least 2 cognitive domains, produces a mild interface in daily functioning.<sup>1</sup>

### Incidence and prevalence

Epidemiological and clinical studies have provided evidence for a change in HAND in the era of HAART. Since the introduction of HAART as a standard of care, there has been a decline in the incidence of HAD as presenting manifestation of AIDS.<sup>2-4</sup>

However, despite this improvement, cognitive decline remains a common feature of HIV infection. Data from the literature consistently indicate that, compared to the pre-HAART era, the overall prevalence of HAND is still considerably high. In the early HAART era, Ferrando et al<sup>5</sup> performed a cross-sectional study of 130 symptomatic HIV-positive patients. A battery of six NP tests assessing the domains of attention, concentration, learning, memory, psychomotor speed, and executive function was used. Among

the 69 patients taking HAART, the overall prevalence of less severe forms of cognitive impairment was 22%. Subsequent reports indicated that, compared to the pre-HAART era, the prevalence of HAD could be unchanged or even increasing.<sup>13,14</sup> A total of 202 HIV-positive patients enrolled in the Hawaii Aging with HIV Cohort underwent a cross-sectional evaluation with a comprehensive NP battery of 12 tests assessing multiple cognitive domains.<sup>15</sup> HAD was diagnosed in 25.2% of older (>50 years) and in 13.7% of younger subjects, and mild forms of cognitive impairment were observed in 44.7% of older and in 26.3% of younger participants. In more recent estimates, the prevalence of HAND, especially in its less severe forms of MND and ANI, is still considerably high. Robertson et al performed a prospective cohort study among 1160 subjects enrolled in the ALLRT study. ALLRT is a prospective observational cohort enrolling patients participating in AIDS Clinical Trials Group (ACTG) who have been randomly assigned to ARV therapies, immune-based therapies, or strategies for anti-HIV interventions. Every 48 weeks, subjects performed tests to screen for HIV-related neurological diseases. A brief neurocognitive screen battery, consisting of 3 NP tests, was used. Raw test scores were standardized using demographic-adjusted normative means. Relative to the normative data, 2 levels of impairment were defined: mild and mild to moderate. A total of 458 subjects out of 1160 (39%) were classified as having at least mild neurocognitive impairment. Using the most conservative estimate, 304 of 1160 (26%) patients had at least mild to moderate impairment. Moreover, among patients classified impaired at baseline, 56% remained impaired at follow-up visits. Finally, of 615 subjects who were unimpaired at baseline, 128 (21%) became impaired at subsequent visits.<sup>6</sup> HAD was observed at similar frequencies in sub-Saharan Africa.<sup>16</sup> Wong et al performed a cross-sectional study in an ambulatory clinic in Uganda. A battery of eight NP tests exploring 5 cognitive domains was administered to 78 HIV-infected patients. The results of NP testing of 100 HIV-negative subjects were used to construct normative data. Standardized neurologic assessment, medical history, functional status assessment, and normatively adjusted NP test scores were used to classify patients as having HIV dementia. Overall, the frequency of HIV dementia was 31%.<sup>16</sup> More recently, the prevalence of cognitive deficits was explored in a cohort of 200 patients with long-standing undetectable plasma HIV RNA.<sup>7</sup> Patients with confounding comorbid conditions were excluded. Subcortical functions were evaluated using a battery of 9 tests exploring a wide range of cognitive domains. Mood disorders, behavioural changes, and functional impairment were assessed using

standardized instruments. The updated research nosology for HAND was used to define patients as having ANI, MND, or HAD.<sup>1</sup> Overall, the estimated prevalence of HAND in this cohort of HAART-treated patients with an undetectable viral load was 69%. More in details, the proportion of patients with ANI, MND, and HAD was 42%, 28%, and 4%, respectively.<sup>7</sup> These data indicate that although HAND without functional repercussion on daily life was the most frequent subtype of HAND, neurocognitive impairment may be present in more than 50% of patients on successful HAART.

In summary, current estimates indicate that HAND can develop in a considerable portion of HIV-infected patients despite effective viral suppression in the periphery.

### Risk factors

Risk factors for HAND include current or past low CD4 cell count,<sup>6,15–18</sup> advanced age,<sup>15,16,19</sup> coinfection with hepatitis C virus,<sup>18,20</sup> insulin resistance or diabetes,<sup>19</sup> and cardiovascular risk factors.<sup>21</sup> Advanced immune suppression, either current or historical, and older age are strong risk factors for HAND, being reported in most published studies. Among the 202 patients enrolled in the Hawaii Aging with HIV Cohort, HAD was more frequent in older (>50 years)<sup>15</sup> compared to younger individuals (25.2% and 13.7%, respectively;  $P = 0.04$ ). Among older individuals, meeting HAD criteria was significantly associated with low CD4 cell count (OR = 7.13; 95% CI = 1.8–28.2).<sup>15</sup> Within the ALLRT study, after adjusting for race, education, age, sex, and ARV therapy, both previous and current CD4 cell count <200/uL were significantly associated with neurocognitive impairment.<sup>6</sup> Wong et al examined frequency and risk factors for HAD in an HIV clinic in Uganda.<sup>16</sup> At regression analysis, older age and lower CD4 cell count were significantly associated with the diagnosis of HAD. Each additional 10 years of age conferred a greater than twofold risk of HAD ( $P < 0.05$ ), and reduced levels of CD4 count (100 cells/uL decrement) was associated with a 60% increase in the odds of having HAD ( $P < 0.05$ ). Nadir CD4 counts <200 cells/uL had been associated not only with a higher prevalence of neurocognitive deficits, but also with decreased functioning in selected neurocognitive areas such as attention, working memory, and executive function.<sup>17</sup>

Insulin resistance, diabetes,<sup>19</sup> and cardiovascular risk factors may also be detrimental to neurocognitive functioning, especially in patients with high CD4 cell count.<sup>21</sup> Wright et al assessed risk factors associated with baseline neurocognitive performance in HIV-infected patients enrolled in the SMART substudy.<sup>21</sup> A total of 292 subjects were administered a five-test

NP battery. Median CD4 cell count was 536/uL. Overall, 14% of patients had neurocognitive impairment. Prior cardiovascular disease (OR = 6.2;  $P = 0.01$ ), hypercholesterolemia ( $P = 0.02$ ), and hypertension ( $P = 0.03$ ) were associated with poorer neurocognitive performance, but low CD4 cell count and other risk factors for HAD were not.

### Role of comorbidities

Since HIV-infected patients are living longer, they are exposed to an increasing number of comorbidities that could have a relevant impact on cognition. These include hepatitis C, current or previous substance abuse (methamphetamine, narcotics, alcohol, and cocaine), major psychiatric disorders (bipolar illness, schizophrenia, and major depression), CNS opportunistic infections and/or tumors, major stroke, transient ischemic attacks, head injury, multiple sclerosis, and other dementing disorders (Alzheimer's disease).<sup>1,20,22</sup> Finally, aging itself could play a role in contributing to cognitive impairment in patients with HIV infection.<sup>9,12,23</sup>

The role of comorbidities has been recently categorized as incidental, contributing, and confounding.<sup>1</sup> An incidental comorbidity may have minor effects on NP test results, but is unlikely to cause even mild global impairment. Incidental comorbidity does not preclude diagnosis of HAD. A contributing comorbidity is likely to have at least mild effects on NP test results, but is unlikely to cause clinically significant global impairment by itself. A contributing comorbidity does not preclude diagnosis of HAD. Finally, a confounding comorbidity is more severe and is likely to have major effects on NP test results, with significant neurocognitive impairment and functional disability, or is likely to cause invalid NP test results. A confounding comorbidity precludes diagnosis of HAD.

Moreover, while comorbidities may act as confounders to accurate diagnosis of HAND, they could also have an additive effect if HAND is already present. Thus, cognitive impairment in patients on HAART may also occur as a consequence of multifactorial etiology, with neurocognitive consequences of HIV infection sometimes overlapping with aging and with comorbidities directly affecting cognition.

### Efficacy of commonly used treatments such as ARV therapy

The optimal treatment for HAND has not been established, but there is strong evidence that ARV therapy can improve cognitive dysfunction. Here, we summarize the existing literature on the topic. Study design, patients' characteristics, NP test batteries, cognitive domains, ARV treatment, and

main findings of studies evaluating the effects of ARV therapy on cognition are reported in Table 1.

#### Mono-ARV therapy

Several studies were performed with zidovudine monotherapy. The importance of these historical studies is that they first documented the beneficial effect of ARV therapy on the course of HAD. Moreover, at that time, 2 large, double-blinded, placebo-controlled studies clearly demonstrated the superiority of zidovudine monotherapy versus placebo on end points exploring cognition.<sup>24,25</sup> These are among the few randomized, controlled studies on HAD ever performed. Schmitt et al first demonstrated that advanced HIV-infected patients receiving zidovudine showed improved cognition, in measures exploring attention, memory, and motor functioning compared with patients receiving placebo.<sup>24</sup> Subsequently, the same was shown in patients fulfilling the criteria for HAD.<sup>25</sup> Finally, it was reported that in some patients, the neurological benefits associated with zidovudine use could sometimes be transient.<sup>26</sup>

#### HAART improves neurocognitive function

In 1998, a cross-sectional study on advanced HIV-infected patients first reported that subjects taking HAART performed significantly better on tests of attention, concentration, learning, memory, and psychomotor speed than those not taking HAART.<sup>5</sup> A bit later, by incorporating serial NP evaluations in a randomized, multicenter trial enrolling 1031 patients, it was shown that a combination therapy of zidovudine–didanosine–nevirapine preserved or improved NP performance compared to alternating zidovudine–didanosine and zidovudine–zalcitabine combination regimens.<sup>8</sup> Subsequently, several observational studies independently reported significant NP improvements in patients receiving protease inhibitor (PI)-based HAART (Table 1).<sup>27,28</sup>

Additional studies confirmed the finding in different populations including women<sup>29,30</sup> and patients in sub-Saharan Africa (Table 1).<sup>31</sup> Moreover, it was shown that the cognitive domains enhanced with HAART were psychomotor speed, verbal anterograde memory, and executive functions, thus supporting the idea that HAART could revert cognitive dysfunction by improving subcortical cognitive functions.<sup>32</sup> To further assess the pattern and durability of neurocognitive benefits, Ferrando et al performed a prospective evaluation of 141 patients over a 2.5-year period. They found that the impairment rate decreased from 62% to 33%. Moreover, after controlling for multiple factors including the potential effects of practice, the use of potent HAART was associated

**Table 1** Studies on effects of ARV therapy on cognition

References	Design	Diagnoses (baseline mean CD4 cell count/crmm)	No. of patients (% with NCI)	NP tests	Cognitive domains	Study duration	ARV drugs	Main findings
Schmitt <sup>24</sup>	Double blind, placebo controlled	Advanced HIV+ (CD4 = n.r.)	n = 281 (NCI = n.r.)	Trail Making A and B, Ruff's Two and Seven, Buschke's Selective Reminding Procedure, Digit Span, Finger Oscillation (a modification of), Symbol Digit	Information processing speed, attention, working memory, executive functioning, verbal memory, motor functioning	16 weeks	ZDV, placebo	Compared with patients receiving placebo, patients receiving ZDV showed improvements in measures exploring attention ( $P = 0.0004$ ), memory ( $P = 0.031$ and $0.0003$ ), and motor functioning ( $P < 0.0001$ )
Sidtis <sup>25</sup>	Double blind, placebo controlled	HAD (CD4 = 491)	n = 40 (NCI = 100%)	Trail Making A and B, Digit Symbol, Verbal Fluency, Timed Gait, Finger Tapping	Information processing speed, attention, working memory, executive functioning, verbal memory, motor functioning	64 weeks	ZDV 2000 mg, ZDV 1000 mg, placebo	Significant improvement in the combined treatment groups compared to the placebo group (at week 16, mean NPZ change scores for 2000 mg, 1000 mg, and placebo groups were +0.88, +0.72, and -0.11, respectively ( $P = 0.03$ ))
Tozzi <sup>26</sup>	Observational, single site	HAD (CD4 = 165)	n = 30 (NCI = 100%)	Trail Making A and B, Digit Span, Digit Symbol, Digit Span, Corsi Cube, Rey Auditory Verbal Learning, Babcock Story Recall, Grooved Pegboard, Rey Complex Figure, Stroop Color	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, motor functioning, visuospatial abilities	12 months	ZDV 1000 mg, ZDV 750 mg, ZDV 500 mg	With ZDV use, a reversal to less severe stages of HAD was seen in most patients with mild to end-stage dementia. The benefit was sometimes only transient
Ferrando <sup>5</sup>	Cross-sectional	Advanced HIV+ (CD4 = 296)	n = 130 (NCI = 37%)	Trail Making A and B, Digit Symbol, California Learning Verbal, Stroop Color-Word, North American Adult Reading	Information processing speed, executive functioning, verbal memory, motor functioning	n.a.	Taking HAART (n = 69), not taking HAART (n = 61)	Subjects taking HAART performed significantly better on tests of attention ( $P < 0.01$ ), concentration ( $P < 0.01$ ), memory ( $P < 0.01$ ), and psychomotor speed ( $P < 0.0001$ ) than those not taking HAART
Price <sup>8</sup>	Double blind, randomized	Advanced HIV+ (CD4 = 25)	n = 1313 (NCI = n.r.)	Digit Symbol, Timed Gait, Finger Tapping, Grooved Pegboard (dominant hand)	Information processing speed, gross motor functioning, fine motor speed	52 weeks	ZDV/ddl alternating, ZDV + ddC, ZDV + ddl, ZDV + ddl + NVP	Compared to ZDV/ddl alternating monotherapy and ZDV + ddC combination, patients on ZDV + ddl + NVP and ZDV + ddl combination arms showed significant improvements in NPZ-4 scores across the 52-week observation ( $P < 0.001$ )

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References	Design	Diagnoses (baseline mean CD4 cell count/crmm)	No. of patients (% with NCI)	NP tests	Cognitive domains	Study duration	ARV drugs	Main findings
Tozzi <sup>27</sup>	Observational, single site	Advanced HIV+, PI naive (CD4 = 17)	n = 26 (NCI = 81%)	Trail Making A and B, Digit-Span, Digit-Symbol, Corsi Cube, Rey Auditory Verbal Learning, Babcock Story Recall, Grooved Pegboard, Rey Complex Figure, Stroop Color	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, motor functioning, visuospatial abilities	15 months	One PI + two NRTIs	Significant improvements, up to 15 months, in measures of concentration and speed of mental processing ( $P < 0.05$ ), mental flexibility ( $P < 0.05$ ), memory ( $P < 0.05$ ), fine motor functions ( $P < 0.05$ ), and visuospatial and constructional abilities ( $P < 0.01$ )
Sacktor <sup>28</sup>	Observational, multicenter	HIV+ (CD4 = 364)	n = 411 (NCI = 87%)	Trail Making B, Symbol Digit, Grooved Pegboard	Information processing speed, executive functioning, fine motor functioning	2 years	No therapy (n = 183), monotherapy (n = 69), combo without PI (n = 142), combo with PI (n = 17)	For the Symbol Digit Test, compared to monotherapy and no therapy groups, both combo + PI (difference +0.26; $P = 0.03$ ) and combo - no PI (difference +0.29; $P = 0.01$ ) improved significantly
Tozzi <sup>42</sup>	Observational, single site	Advanced HIV+ (CD4 = 114)	n = 28, (NCI = 57%)	Trail Making A and B, Digit-Span, Digit-Symbol, Corsi Cube, Rey Auditory Verbal Learning, Babcock Story Recall, Grooved Pegboard, Rey Complex Figure, Stroop Color	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, fine motor functioning, visuospatial abilities	45 months	One PI + two NRTIs	Significant improvements up to month 45 in measures of mental flexibility (Trail Making B: $P = 0.04$ ) and motor functioning (Grooved Pegboard: $P < 0.001$ ). Seven of 16 (44%) patients remained impaired despite 3 years of HAART
Suarez <sup>22</sup>	Observational, single site	Advanced HIV+ (CD4 = 100)	n = 91, (NCI = 58%)	Trail Making A and B, Grober and Buschke, Purdue Pegboard	Information processing speed, executive functioning, episodic memory, fine motor functioning	39 months	Various HAART regimens	Compared to baseline, HAART use was associated with improvements in cognitive functions (Trail Making A: $P = 0.02$ ; Grooved Pegboard: $P < 0.001$ ), especially during the first year of treatment
Cohen <sup>29</sup>	Observational, single site	Advanced HIV+ women (CD4 = 65)	n = 126 (NCI = n.r.)	Color Trail Making I and 2, Controlled Oral Word Generation, Four-word Learning, Grooved Pegboard	Information processing speed, executive functioning, verbal fluency, verbal memory, fine motor functioning	36 months	Non-HAART (n = 70), HAART (n = 55)	Compared to baseline, HAART-treated patients showed improved performance on Color Trails ( $P < 0.01$ ), Grooved Pegboard ( $P < 0.01$ ), and Controlled Oral Word ( $P < 0.01$ ) tests, while non-HAART patients showed significant worsening

Sacktor <sup>13</sup>	Cross-sectional, Dana and NEAD Cohorts	Advanced HIV+ (CD4 = 178)	n = 523 (NCI = 75%)	Trail Making A and B, Digit-Symbol, Grooved Pegboard, Rey Auditory Verbal Learning, Rey Complex Figure, Odd Man Out, Californian Computerized Assessment Package, National Adult Reading	Information processing speed, executive functioning, verbal fluency, verbal memory, visuospatial memory, constructional abilities, fine motor functioning, reaction time	n.a.	Pre-HAART (n = 272), HAART (n = 251)	No differences in the occurrence of NP abnormalities and of HAD between pre-HAART and HAART cohorts (prevalence of HAD 27.3% and 32.1%, respectively; $P = 0.17$ )
Richardson <sup>30</sup>	Cross-sectional, multicenter	Advanced HIV+ (CD4 = 416)	n = 149 (NCI = 42%)	Color Trail Making I and 2, WHO-UCLA Auditory Verbal Learning, Grooved Pegboard, Symbol Digit Modality, Visual Reproduction (subtest of WVMMS), Mental Alternation, Simple and Choice Reaction Time	Information processing speed, attention, working memory, executive functioning, verbal memory, visuospatial memory, fine motor functioning, constructional abilities, reaction time	n.a.	Off HAART (n = 67), on HAART (n = 82)	Compared to HIV-positive women on HAART, patients off HAART were at increased risk of having impaired NP test scores (Color Trails 2: $P = 0.04$ ; Grooved Pegboard: $P = 0.03$ ; Symbol Digit: $P = 0.003$ )
Marra <sup>40</sup>	Prospective treatment effect trial, single site	PI naive (CD4 = 259)	n = 25 (NCI = n.r.)	Digit-Symbol, Timed Gait, Grooved Pegboard, Finger Tapping	Information processing speed, gross motor functioning, fine motor functioning, motor speed	8 weeks	Mostly IDV-based HAART	Significant improvements in NPZ-4 at week 4 ( $P = 0.003$ ) and week 8 ( $P = 0.01$ ) in patients treated with ZDV or IDV. NPZ-4 improvement was associated with decline in CSF HIV-1 RNA at both visits ( $P = 0.001$ and $P = 0.02$ )
Ferrando <sup>33</sup>	Observational, single center	Advanced HIV+ (CD4 = 249)	n = 141 (NCI = 62%)	Digit-Symbol, Stroop Color Word, California Verbal Learning, Grooved Pegboard	Information processing speed, executive functioning, verbal memory, fine motor functioning	2.5 years	Mostly PI-based HAART	The prevalence of NCI decreased from 62% to 33% ( $P < 0.0001$ ). The use of PI-based HAART was associated with improvements in Digit Symbol ( $P < 0.01$ ) and Grooved Pegboard ( $P < 0.01$ ) tests
Sacktor <sup>37</sup>	Prospective study within the MACS cohort	Cognitively impaired HIV+ (CD4 = 281)	n = 49 (NCI = 100%)	Trail Making B, Symbol Digit Modalities Test	Information processing speed, executive functioning	1.5 years	Various HAART regimens	Systemic virologic suppression associated with improved psychomotor speed performance (changes in Digit Symbol and Trail Making B tests: 0.56, $P < 0.05$ and 0.68, $P < 0.05$ , respectively) and virologic rebound with psychomotor speed performance decline

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Table 1 (Continued)

References	Design	Diagnoses (baseline mean CD4 cell count/crmm)	No. of patients (% with NCI)	NP tests	Cognitive domains	Study duration	ARV drugs	Main findings
Letendre <sup>39</sup>	Prospective treatment effect trial, single site	Cognitively impaired HIV+ (CD4 = 117)	n = 31 (NCI = 100%)	Trail Making A and B, Symbol Digit Modalities, Figural Visual Scanning, Digit-Symbol, Grooved Pegboard, WAIS-R Block Design, Paced Auditory Serial Addition, WAIS-III Letter-Number Sequencing, WMS-Visual Span, WAIS-R Digit-Span, Rey Auditory Verbal Learning, Hopkins Verbal Learning Test-R, WMS-R Visual Reproductions, Semantic Verbal Fluency, Controlled Oral Word Association, Stroop Color-word, Wisconsin Card Sorting, Halstead Category	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, visuospatial memory, motor functioning and praxis, constructional abilities	15 months	Various HAART regimens	Significant improvement in NP performance (median decrease in global deficit score: 0.44, $P < 0.0001$ ) CSF HIV RNA suppression was an independent predictor of NP improvement. Number of CSF-penetrating drugs associated with greater reductions in CSF viral load
Robertson <sup>41</sup>	Prospective observational, single site	Advanced HIV+ (CD4 = 226)	n = 48 (NCI = 62%)	Trail Making A and B, Digit-Symbol, Stroop Color-word, Paced Auditory Serial Addition Test, Rey Complex Figure, Rey Auditory Verbal Learning, Timed Gait, Grooved Pegboard, Finger Tapping, WAIS-R Vocabulary, Computerized Simple and Choice reaction time	Information processing speed, executive functioning, verbal memory, working memory, visuospatial memory, fine motor functioning, gross motor functioning, constructional abilities, language, reaction time	6 months	Various HAART regimens	Significant improvement in neurologic and NP functioning (global NPZ scores pretreatment: $-0.74$ , during HAART: $-0.52$ , $P < 0.0001$ ). All NP domains showed improvements ( $P < 0.01$ ) with exception of gross motor. Significant decline in CSF HIV RNA
Cysique <sup>43</sup>	Cross-sectional analyses of two cohort studies	Advanced HIV+ (CD4 = 229)	n = 141 (NCI = 40%)	Trail Making A and B, Digit-Span, Symbol Digit Modalities, Purdue	Information processing speed, attention, working memory,	n.a.	Monotherapy cohort (n = 51),	The prevalence of NP impairment was 41% (21/51) in the monotherapy and 38.8% (35/90) in the HAART cohort,

	HAART cohort (n = 90)	executive functioning, verbal fluency, language, verbal memory, visuospatial memory, motor functioning, constructional abilities, reasoning	Pegboard, Grooved Pegboard, Rey Complex Figure, Controlled Oral Word Generation, WAIS-R Similarities, California Verbal Learning, Grooved Pegboard	with no difference across pre-HAART and HAART eras
Clifford <sup>36</sup>	HIV+ naive (CD4 = 219)	Information processing speed, executive functioning	Trail Making A and B, Digit-Symbol	Improvement in NP performance (Trail Making A and B) was comparable in patients who were receiving EFV and those who were not
Cysique <sup>38</sup>	Advanced HIV+ (CD4 = 352)	Information processing speed, attention, working memory, executive functioning, verbal fluency, language, verbal memory, visuospatial memory, motor functioning, constructional abilities, reasoning	Trail Making A and B, Digit Span, Symbol Digit Modalities, Purdue Pegboard, Grooved Pegboard, Rey Complex Figure, Controlled Oral Word Generation, WAIS-R Similarities, California Verbal Learning, Grooved Pegboard	Although the majority of patients improved (global cognitive score changes from baseline at month 6, 15, and 27: 0.22 ( $P < 0.05$ ), 0.41 ( $P < 0.01$ ), and 0.21 (n.s.), respectively), over the long term, 30% of patients showed reliable cognitive decline. Neuroactive HAART regimens were associated with NP improvement
Sacktor <sup>31</sup>	Advanced naive HIV+ (CD4 = 71)	Information processing speed, attention, working memory, executive functioning, verbal memory, fine motor functioning, gross motor functioning	WHO-UCLA Auditory Verbal Learning, Timed Gait, Grooved Pegboard, Symbol Digit, Color Trails, Digit-Span	Improvements in tests of verbal memory (Auditory Verbal Learning, $P < 0.001$ ), psychomotor speed (Symbol Digit, $P < 0.001$ ), and executive functioning (Color Trails I and 2, $P < 0.003$ ) after 3 and 6 months
Gibbie <sup>22</sup>	HIV+ (CD4 = 458)	Attention, working memory, visuospatial memory, executive functioning, fine motor functioning, reaction time	Grooved Pegboard, CANTAB	Overall improvements in neurocognitive performance (baseline and follow-up z-scores: Grooved Pegboard -1.74 and -0.47, mental flexibility -1.19 and -0.54, reaction time -0.71 and +0.35, working memory -0.61 and -0.31). NP improvements were more pronounced in patients without depression at baseline

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Table 1 (Continued)

References	Design	Diagnoses (baseline mean CD4 cell count/crmm)	No. of patients (% with NCI)	NP tests	Cognitive domains	Study duration	ARV drugs	Main findings
Carvalho <sup>45</sup>	Observational, single site	Naive, minor cognitive dysfunction (CD4 = 134)	n = 14 (NCI = 100%)	Verbal Fluency, Logical Memory, Visual Recognition, Word Span, Stroop Color Word	Attention, memory, executive functioning, verbal fluency, verbal memory	6 months	EFV + ZDV + 3TC	No improvement in the neurocognitive status ( $P = n.s.$ for all comparisons) despite CSF and plasma HIV viral load suppression
McCutchan <sup>35</sup>	Observational, multicenter	Advanced AIDS with immune reconstitution (CD4 = 230)	n = 286 (NCI = 27%)	Trail Making A and B, Digit-Symbol	Information processing speed, executive functioning	96 weeks	Various HAART regimens	Most advanced AIDS patients responding to HAART have stable or improving cognition (prevalence of NCI at baseline, week 48, week 96: 27%, 16%, and 14%, respectively) but were more likely to be impaired than the general population
Tozzi <sup>46</sup>	Observational, single site	HIV+, cognitively impaired (CD4 = 257)	n = 94 (NCI = 100%)	Trail Making A and B, Digit-Span, Digit-Symbol, Corsi Cube, Rey Auditory Verbal Learning, Grooved Pegboard, Rey Complex Figure, Stroop Color	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, fine motor functioning, visuospatial abilities	63 months	Various HAART regimens	Overall, 59/94 (63%) patients remained impaired despite long-term HAART (65-month probability of persistent impairment: 53%). The severity of cognitive impairment at baseline was the strongest predictor of persistent impairment (OR for baseline NPZ-8 score 3.07; $P = 0.001$ )
Cole <sup>34</sup>	Observational, multicenter within the MACS cohort	Asymptomatic HIV+ (CD4 = 399)	n = 316 (NCI = 0%)	Trail Making A and B, Symbol Digit modalities	Information processing speed, executive functioning, attention	5 years	Various HAART regimens	NP tests remained stable in the long-term asymptomatic patients (compared to HIV-negative controls, Trail Making A and B and Digit Symbol tests did not decline over 5 years)
Robertson <sup>6</sup>	Observational, multicenter within the ALLRT study	HIV+ (CD4 = 424)	n = 1160 (NCI = 39%)	Trail Making A and B, Digit-Symbol	Information processing speed, executive functioning, attention	At least 48 weeks	Various HAART regimens	Prevalent NC impairment was 39% (458/1160 patients). Incident NC impairment was 21% (458/1160 patients). Low CD4 cell counts were associated with prevalent sustained impairment
Brew <sup>44</sup>	Phase III, randomized, double-blind placebo-controlled trial	HIV+ with HAD (CD4 = 168)	n = 105 (NCI = 100%)	Trail Making A and B, Symbol Digit, Grooved Pegboard, Verbal Fluency, Rey Auditory Verbal Learning, Cal Cap Reaction Time	Information processing speed, executive functioning, verbal fluency, verbal memory, reaction time	12 weeks	Stable HAART + ABC (n = 52), stable HAART + placebo (n = 53)	Both groups showed improvements in NP performance (global NPZ score changes from baseline at week 6 and 12: +0.58 and +0.72, respectively) without any additional benefit from ABC ( $P = 0.735$ )

Childers <sup>56</sup>	Observational	Advanced HIV+ (CD4 = 363)	n = 11 (NCI = 27%)	Trail Making A and B, Digit-Symbol, Paced Auditory Serial Addition, Hopkins Verbal Learning, Brief Visuospatial Memory, Controlled Oral Word Association, Grooved Pegboard, Stroop Color-word, Wisconsin Card Sorting, Halstead Category	Information processing speed, executive functioning, verbal fluency, verbal memory, working memory, visuospatial memory, fine motor functioning	1 year	Either PI or NNRTI + NRTIs	During HAART interruption, NP performance did not change (global deficit score: from 0.31 to 0.31; $P = 0.72$ ). Significant improvement in NP performance following HAART reinitiation (global deficit score from 0.31 to 0.16; $P = 0.005$ )
Marra <sup>54</sup>	Observational, multisite	Advanced HIV+ (CD4 = 111)	n = 79 (NCI = 33%)	Trail Making A and B, Digit-Symbol, Finger Tapping, Grooved Pegboard, Timed Gait, Rey Auditory Verbal Learning	Information processing speed, executive functioning, verbal memory, fine motor functioning, gross motor functioning	Up to 52 weeks	Various HAART regimens	Among the 26 NP-impaired patients, overall NP improvement (estimate 0.86 over study course higher NPZ4, $P < 0.001$ ), but no improvement in patients receiving regimens with higher ( $\geq 2$ ) CPE ranks ( $P = 0.86$ ). CPE ranks $\geq 2$ were associated with higher odds of suppression of CSF HIV (OR = 4.1; $P = 0.04$ )
Cysique <sup>68</sup>	Prospective treatment effect trial, single site	HIV+, cognitively impaired (CD4 = 196)	n = 37 (NCI = 100%)	Trail Making A and B, Paced Auditory Serial Addition Test, Grooved Pegboard	Information processing speed, executive functioning, working memory, fine motor functioning	48 weeks	Various HAART regimens	NP performance improved at week 12, 24, 36, and 48 (proportion of patients improving: 13.5% ( $P < 0.001$ ), 32.1%, 40.9%, 33.3% ( $P < 0.001$ at each study point)). CNS penetration capacity (CPE $\geq 2$ ) was the strongest predictor of cognitive improvement ( $P = 0.002$ )
Tozzi <sup>55</sup>	Observational, single site	Advanced HIV+ (CD4 = 292)	n = 185 (NCI = 50%)	Trail Making A and B, Digit-Span, Digit-Symbol, Corsi Cube, Rey Auditory Verbal Learning, Babcock Story Recall, Grooved Pegboard, Rey Complex Figure, Stroop Color	Information processing speed, attention, working memory, executive functioning, verbal fluency, verbal memory, fine motor functioning, visuospatial abilities	Up to 7 years	Various HAART regimens	Higher CPE scores were associated with NP improvements (NPZ8 changes at first and second visit: $P = 0.012$ and $P = 0.001$ , respectively). In contrast, higher estimates of neuropenetration with previously published score systems were not
Valcour <sup>49</sup>	Observational, single site	HIV+ (CD4 = 23)	n = 27 (NCI = 44%)	Digit-Symbol, Rey Auditory Verbal Learning, Timed Gait	Information processing speed, verbal memory, gross motor functioning	48 weeks	Various HAART regimens	Both patients with HAD and patients without HAD exhibited a robust NP improvement in all measures (ie, NPZ-global: from $-0.43$ to $+0.06$ , $P < 0.001$ ). Baseline monocyte HIV DNA predicted 48 weeks NP performance ( $P < 0.001$ )

(Continued)

Table 1 (Continued)

References	Design	Diagnoses (baseline mean CD4 cell count/crmm)	No. of patients (% with NCI)	NP tests	Cognitive domains	Study duration	ARV drugs	Main findings
Clifford <sup>51</sup>	Randomized, double-blinded, controlled trial (ACTG 5097s)	HIV+ naive (CD4 = 219)	n = 303 (NCI = 25%)	Trail Making A and B, Digit-Symbol	Information processing speed, executive functioning	46 months	EFV + ZDV + 3TC ± ABC (n = 200); ABC + ZDV + 3TC (n = 103)	Compared to baseline, NP improvements maintained up to week 184 in all study arms (mean change in NPZ3 score +0.81; $P < 0.01$ ). The same was observed in patients of the EFV arms (mean change in NPZ3 score +0.57; $P < 0.01$ )
Winston <sup>50</sup>	Randomized, controlled study	HIV+ naive (CD4 = 215)	n = 30 (NCI = n.r.)	CogState	Learning, working memory, executive functioning	48 weeks	EFV + TDF + FTC (n = 9); ATV/rit + TDF + FTC (n = 9); ZDV + ABC + TDF + FTC (n = 12)	Overall improvements in all NP testing parameters. Greater improvements in neuronal recovery in NP testing for AZT-ABC-TDF-FTC (identification, executive function, and speed performance tasks: $P = 0.04$ , $P = 0.02$ , and $P = 0.02$ , respectively) and at proton magnetic resonance spectroscopy for EFV-TDF-FTC (changes in NAA/Cr ratio $P = 0.041$ )
Robertson <sup>57</sup>	Prospective treatment effect trial, ACTG A5170	Not advanced HIV+ (CD4 = 833)	n = 167 (NCI = 41%)	Trail Making A and B, Digit-Symbol	Information processing speed, executive functioning	96 weeks	Various HAART regimens	NP performance improved significantly following HAART discontinuation (NP score improvements of 0.22, 0.39, 0.53, and 0.74 at week 24, 48, 72, and 96; $P < 0.001$ )

**Abbreviations:** ABC, abacavir; ACTG, AIDS Clinical Trials Group; ADC, AIDS dementia complex; ALLRT, Longitudinal Linked Randomized Trials; ATV/rit, atazanavir/ritonavir; CANTAB, Cambridge Neuropsychological Test Automated Battery; CNS, central nervous system; CogState, computerized cognitive test battery; CPE, CNS penetration effectiveness; CSF, cerebrospinal fluid; Dana, The Dana Consortium; ddC, didanosine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorders; IDV, indinavir; MACS, Multicenter AIDS Cohort Study; n.a., not applicable; NCI, neurocognitive impairment; NEAD, Northeastern AIDS Dementia Consortium; NP, neuropsychological; NPZ, neuropsychological z score; n.r., not reported; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; TDF, tenofovir; ZDV, zidovudine; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition; WHO-UCLA AVLT, World Health Organization—University of California Los Angeles Auditory Verbal Learning Test; WJMS, Wechsler Visual Memory Scale-Revised.

with longitudinal improvement in psychomotor speed, suggesting that subcortical brain structures mediating psychomotor speed might be sensitive not only to HIV-related neuropathological changes, but also to sustained benefits from HAART.<sup>33</sup> Among participants in the MACS cohort monitored over a 5-year follow-up period, no decline in cognitive functions was reported.<sup>34</sup> While confirming the overall improvements in several neurocognitive domains with HAART, Gibbie et al also reported a decline in depression scores. Interestingly, several interactions with depression scores were noted in this study since patients without depression improved significantly at cognitive testing while those with depression did not.<sup>22</sup> Stable or improving cognition over a 2-year period was also reported in advanced HIV-infected patients.<sup>35</sup> Within the randomized, double-blinded, controlled ACTG 5095 trial, a battery of three NP tests was administered to 303 ARV-naive patients randomly assigned to zidovudine–lamivudine–abacavir or zidovudine–lamivudine–efavirenz or zidovudine–lamivudine–abacavir–efavirenz. NP measures were collected at baseline and at weeks 1, 4, 12, and 24. Symptoms that might be associated with efavirenz use (neurologic symptoms, sleep disorders, anxiety, and depression) were assessed by standardized questionnaires. Overall, NP performance, as measured by standardized NPZ3 scores, improved in all study arms, with greater changes occurring in the first week of treatment. Efavirenz use was associated with neurologic symptoms distinct from depression and anxiety. However, despite neurologic symptoms, improvement in NP performance was comparable in patients who were receiving efavirenz and those who were not.<sup>36</sup>

Improvement in psychomotor speed performance was also reported in association with systemic virologic suppression and decline in psychomotor speed performance with virologic rebound.<sup>37</sup> However, the association of cognitive improvement with plasma HIV RNA decline was not confirmed in most subsequent studies.<sup>6,38,39</sup>

The notion that HAART is beneficial for cognitive functions was reinforced by prospective studies demonstrating that improvements in cognition were associated with HIV RNA decline in cerebrospinal fluid (CSF). Marra et al first reported the association of cognitive improvement with CSF viral load reductions.<sup>40</sup> Similarly, significant improvement in neurologic and NP functioning and significant decline in CSF HIV RNA after HAART initiation or HAART change were reported.<sup>41</sup> These observations were extended by Letendre et al<sup>39</sup> who demonstrated that CSF HIV RNA suppression was an independent predictor of cognitive improvement. These data support the concept that inhibition

of HIV replication within the CNS could be a critical step in arresting the neurodegenerative process.

### Variable benefits from HAART

However, despite this success, accumulating evidences started to suggest that standard HAART regimens were often insufficient to fully reverse the cognitive dysfunction. A prospective observational study in advanced HIV-positive patients treated with HAART demonstrated that, aside from overall improvements in measures exploring different cognitive domains, more than 40% of cognitively impaired patients remained impaired despite more than 3 years of HAART.<sup>42</sup> Other authors reported similar findings in different populations of HIV-infected patients treated with HAART (Table 1).<sup>22,33,35</sup> These observations were supported by the analysis of two cohorts performed before and after the advent of HAART showing no difference in the overall occurrence of HIV dementia and NP abnormalities.<sup>13</sup> Similarly, Cysique et al reported that the prevalence of NP impairment was not different across pre-HAART and HAART eras.<sup>43</sup>

In the HAART era, only a few randomized trials have been performed. A Phase III randomized, double-blinded, placebo-controlled trial of adding abacavir to optimal stable background therapy failed to find any differences in cognitive performance between the placebo and the abacavir group at week 12.<sup>44</sup> This was in contrast with placebo-controlled trials performed in the monotherapy era.

To assess the extent to which cognitive functions changed overtime in patients with advanced disease, Cysique et al performed a prospective evaluation of 101 patients with CDC stage C3 disease. They found that although the majority of subjects improved, over the long term, 30% of patients showed reliable cognitive decline. Cognitive decline was related to lower nadir CD4 cell counts, past depressive episode, past HIV-related brain diseases, and number of previous AIDS-defining events.<sup>38</sup> No improvement in neurocognitive status was reported in 14 naive patients with minor cognitive dysfunction treated with zidovudine–lamivudine–efavirenz, despite CSF and plasma HIV suppression.<sup>45</sup> Moreover, a nonreversible component of cognitive impairment was noted in 63% of cognitively impaired patients treated with HAART for a mean of 63 months, with severity of cognitive impairment at enrolment being (at multivariable analyses) the strongest predictor of persistent impairment.<sup>46</sup> These data confirmed that the NP benefits from HAART could be variable from patient to patient. Incidence and prevalence of neurocognitive impairment was examined among 1160 subjects within the ALLRT study. At least mild impairment

was noted in 39% of patients with low (either current or nadir) CD4 cell counts being significantly associated with prevalent impairment.<sup>6</sup> This suggests the presence of a nonreversible component of neural injury and that neural injury continues in some patients regardless of the success of ARV therapy. Studies demonstrating impaired cognitive functions despite HAART are supported by virological studies indicating that despite successful suppression of plasma viremia, HIV may replicate within the CNS at detectable levels and that detectable CSF HIV RNA may be associated with considerable levels of ARV drug resistance.<sup>47</sup>

Taken together, these data consistently indicate that current HAART regimens may be insufficient to fully treat and/or to fully prevent the development of HIV-associated cognitive impairment.

### Recent findings

Recent achievements on ARV therapy and HAND expanded our knowledge and answered some important questions on the dynamics of cognitive changes, predictors of responses, and the outcome of different regimens.

Cysique et al performed a prospective study on patients with HAND retested with NP examinations at several targeted time points after HAART initiation. NP performance changes were standardized against comparison groups to account for practice effects. They found that rapid cognitive improvements could be observed in 13% of subjects within the first 12 weeks after HAART initiation or HAART change. The proportion of patients improving increased over time to 41% at week 48. While providing the first evidence of short-term cognitive improvement as a marker of neurologic outcome of treatment, these findings also suggested that the window opportunity for NP improvement might be relatively long.<sup>48</sup> Moreover, the extent of improvements was greater in patients with severe NP impairment at baseline, pointing to the reversibility of cognitive dysfunctions. Finally, the CNS penetration capacity was found to be the strongest predictor of cognitive improvement supporting the use of neuropenetrating ARV drugs to treat patients with HAND.

The SEARCH 001 Cohort Study was a prospective study to determine immunological and virological factors influencing cognition after first-time HAART in 15 individuals with HAD and in 15 HIV-infected patients without HAD. Variables were examined longitudinally to determine factors predictive of degree of cognitive recovery, and NP data of patients with HAD were compared to those of 230 HIV-negative controls to account for practice effects on repeated testing. Patients with HAD and patients without

HAD exhibited a robust cognitive response to HAART. Moreover, monocyte HIV DNA level correlates to cognitive performance before HAART and 48 weeks after HAART. The relationship between monocyte HIV DNA and the NP performance remained present in a multivariate model that included age, education, and baseline CD4 count. The authors concluded that baseline monocyte HIV DNA may predict 48-week cognitive performance.<sup>49</sup> While confirming the improvement in NP performance after HAART initiation, these findings raise the possibility that short-term incomplete cognitive recovery with HAART may be a consequence of an active process related to HIV monocyte reservoir in the periphery.

The results of two randomized studies comparing different HAART regimens in measures of cerebral functioning tests were recently reported. Winston et al performed a randomized, controlled study of tenofovir–emtricitabine plus either efavirenz, or atazanavir–ritonavir or zidovudine–abacavir on 30 treatment-naïve patients. Cerebral function tests included neurocognitive testing and assessment of cerebral metabolites using proton magnetic resonance spectroscopy with calculations of N-acetylaspartate-to-creatine (NAA/Cr) ratios in several anatomical voxels, at baseline and after 48 weeks. Overall, improvements in all neurocognitive testing parameters and increases of NAA/Cr ratios were observed during the study period and significant differences between treatment arms emerged. Over the 48 week of the study, greater improvements at cerebral metabolites assessment were observed for recipients of tenofovir–emtricitabine plus efavirenz and greater improvements in neurocognitive function testing were observed for recipients of tenofovir–emtricitabine plus zidovudine–abacavir. The authors concluded that quadruple nucleoside reverse transcriptase inhibitor (NRTI) might have had superior positive effects on cognition as a consequence of optimal CNS drug penetration of these drugs and that NP improvements in the efavirenz arm might have been blunted by neuropsychiatric side effects of the drug.<sup>50</sup> Finally, the results of the ACTG 5097s trial, a large, randomized, double-blind trial of 3 ARV regimens of zidovudine–lamivudine in combination with blinded efavirenz, abacavir, or efavirenz plus abacavir on long-term impact of efavirenz on NP performance, were recently published.<sup>51</sup> A total of 117 patients were studied. Improvements were seen at week 184 in all groups compared to baseline performance ( $P < 0.01$ ). Each of the three component tests (Trail Making A and B, Digit Symbol test) showed statistically significant improvements during the interval of the study in all study arms. Interestingly, although

in efavirenz-based arms NP performance improvements were maintained over 3 years, higher efavirenz plasma levels were correlated with a small but significant negative impact on NPZ3 summary score ( $r = -0.29$ ;  $P < 0.01$ ).

### Data on cognition and ARV penetration into the CNS

ARV drugs differ in their ability to cross blood–CNS interfaces and to reach the CNS at therapeutically effective levels. ARV drugs are considerably different not only in their CSF levels, but also in their capacity to reduce CSF HIV RNA to undetectable levels<sup>40,52</sup> and improve cognition.<sup>8,24,50</sup> The optimal treatment for HAND has not been established, but the general consensus is that the ability of ARV drugs to reach the CNS is a critical factor for patients' neurological response.<sup>9</sup> Several ARV drugs, or drug combinations, have been shown to be more neurologically active than others on the basis of their capacity to suppress CSF viral load<sup>40,52</sup> and improve NP performance.<sup>8,24,50</sup> Moreover, it has been shown that virologic suppression in the CSF is associated with significant NP improvement.<sup>39–41</sup> However, how to estimate the effectiveness of different ARV drug combinations in suppressing viral replication within the CNS and improving cognition remains controversial. Until recently, zidovudine, stavudine, abacavir, lamivudine, indinavir, efavirenz, and nevirapine were considered ARV drugs with good CNS effectiveness,<sup>9</sup> generally on the bases of their CSF concentration from human studies. Recently, when trying to develop a clinically useful approach to estimating CNS effectiveness, a CNS-penetration-effectiveness (CPE) ranking system was proposed. This ranking system was based not only on CSF drug concentration, but also on the chemical properties of ARV drugs and clinical studies on drug ability to reduce CSF viral load and improve cognition.<sup>23,53</sup> The authors found that HAART schemes with higher CPE ranks were associated with greater reductions of CSF HIV RNA levels.<sup>53</sup> These data have been subsequently confirmed in independent studies.<sup>54</sup> The ACTG 736 was a prospective study aimed to examine changes in CSF HIV RNA and in NP function in patients who begin or change an ARV regimen. A total of 79 patients were studied. Overall, participants took 48 different ARV regimens. Patients who were prescribed a regimen with CPE rank of at least 2 had significantly higher odds of suppression of CSF HIV RNA (OR = 4.1;  $P = 0.04$ ).<sup>54</sup>

Whether or not higher CPE ranks are also associated with greater improvement in NP test has been recently investigated by different groups. Cysique et al performed a prospective evaluation of 101 patients with stage C3 disease. They found

that neuroactive HAART regimens, defined according to the CPE rank, were associated with NP improvement.<sup>48</sup> In a retrospective analysis of an observational cohort, Tozzi et al compared the CPE score and other scores that were used in previous published studies. The main outcome criterion was changes in cognition in five cognitive domains. Higher CPE scores, consistent with higher estimates of neuropenetration, were consistently and significantly associated with NP improvements, while higher estimates of neuropenetration with alternative scores were not.<sup>55</sup> In contrast, Marra et al showed that ARV with good CNS penetration, as assessed by CPE rank, while more effective in reducing CSF viral load, were associated with poorer neurocognitive performance. Among 26 patients with impaired NP performance at entry, patients who were prescribed ARV regimens with CPE ranks of  $<2$  ( $n = 12$ ) showed significant improvements in NPZ4 scores ( $P = 0.002$ ), while patients who were prescribed regimens with a CPE rank of at least 2 showed no changes in NP measures.<sup>54</sup> Among potential explanations of this unexpected finding, the authors mention the hypothesis of CNS toxicity of some ARV drugs or drug combinations.<sup>54</sup>

Thus, ARV regimens with estimated good CNS penetration seem more effective in controlling CSF viral replication. However, the question of whether drug combinations with better estimates of CNS penetration are associated with better cognition remains controversial and larger controlled trials are needed to address the topic.

### Data on structured treatment interruption

Although no longer considered therapeutically beneficial, the neurocognitive effects of treatment interruption were examined in two independent studies. Childers et al reported that during structured treatment interruption (STI), NP performance did not change. Following reinitiation of HAART, improved viral suppression and immune restoration resulted in significant improvement in neurocognitive performance.<sup>56</sup> In contrast, more recently, it has been reported that among asymptomatic patients who initiated HAART at CD4 counts  $>350$  cells/uL, neurocognition improved significantly following ARV treatment discontinuation, suggesting a potential neurotoxicity associated with ARV drug use.<sup>57</sup> Potential explanations of these inconsistent results include differences regarding degrees of immune function at baseline, nadir CD4 counts, and HAART regimens.

### Adjuvant therapies

Aside from ARV therapy, ongoing work has focused on the potential role of adjuvant and neuroprotective therapies.

However, although neuroprotective therapies might be needed over time, especially in patients not responding neurologically to HAART, their role appears to have unproven or limited benefits. The ability of minocycline, an antibiotic with potent anti-inflammatory and neuroprotective properties, to protect against HIV-associated neurodegeneration is supported mainly by studies on animal models.<sup>55</sup> Recently, a placebo-controlled trial to assess the effectiveness of the selegiline transdermal system in patients with HIV-associated cognitive impairment failed to show any effect on cognitive performance and on HIV-induced metabolic brain injury as measured by proton magnetic resonance spectroscopy.<sup>59</sup>

### NP testing as an end point

NP testing is routinely used to quantify the severity of cognitive impairment, define the pattern of involvement, and assess the impact of treatment. For these reasons, they have been included as an end point in most published studies on cognitive function in treated patients. However, regarding the use of NP testing as an end point, several questions remain. First, it is not easy to determine the potential role of practice effects because some studies did not include comparison groups; however, a consistent number of studies included methodological interventions to account for practice effects.<sup>8,24,25,33,48–50</sup> Second, NP test batteries differ widely across studies. While a consistent number of studies utilized comprehensive NP batteries examining a relevant number of cognitive domains, some studies were performed with brief NP batteries exploring a limited range of NP functions, with limited sensitivity and specificity. Third, the presence of potential confounders, although carefully evaluated in most studies, was not universally examined.

With all the above mentioned limitations, NP testing should be included as an end point in all studies. Ideally, NP evaluation should be accompanied by careful assessment of confounders, structured neurological evaluation, assessment of depression, assessment of functional consequences of NP impairment, CSF examination with virological and biomarker studies, and functional neuroimaging.

## Discussion

We have examined the existing literature on the effects of HAART on NP functions. A great number of studies on NP outcomes in patients receiving ARV therapy have been published to date. However, several methodological and statistical issues should be considered in evaluating the existing literature. The strength of the evidences of studies reported in this review varies widely and a hierarchy of evidences

exists. Small study size and lack of adequate statistical power could represent important limitations of some studies, especially those with a cross-sectional design. In general, observational cohorts may provide more information, but observational studies tend to include patients who are already on HAART and examine NP end points at nonplanned intervals. Unfortunately, most published studies are either cross-sectional or observational in design. Some carefully planned prospective treatment effect cohorts have also been conducted and provided a consistent body of knowledge on the topic. However, only a few randomized, controlled studies have been performed to date, making it difficult to draw definitive conclusions on some aspects. Thus, differences between study designs may account for a number of discrepancies between results.

Moreover, there are also remarkable differences among patients' characteristics. Only a few studies examined exclusively patients with documented cognitive impairment. Some studies examined patients with advanced diseases including subjects with normal cognition. Other studies enrolled neurologically asymptomatic patients at an early disease stage and with high CD4 cell counts. ARV therapy schemes and treatment duration also varied considerably. The presence and nature of comorbid conditions were not consistently examined in all studies. Finally, nature and length of NP batteries varied broadly, making NP test results difficult to compare.

With all the above-mentioned considerations, it is rather clear that most studies indicate that use of HAART results in improvement of neurocognitive functions. Two randomized clinical trials clearly showed the superiority of zidovudine monotherapy over placebo in improving cognition both in advanced HIV-infected patients<sup>24</sup> and in patients with HAD.<sup>25</sup> A randomized trial performed in the early HAART era showed that zidovudine–didanosine–nevirapine therapy improved NP performance compared to dual NRTI therapy.<sup>8</sup> Recently, in a randomized, controlled study, greater improvement in neurocognitive function testing was reported in naive patients treated with tenofovir–emtricitabine–zidovudine–abacavir compared to tenofovir–emtricitabine–atazanavir–ritonavir.<sup>50</sup> Finally, the randomized, double-blind trial ACTG 5097s showed statistically significant improvements over 3 years of study duration in all study arms.<sup>51</sup> Most cohort studies also indicate that use of HAART is associated with improved cognition.<sup>3,6,26–35,37,38,40–42,45,46,48,49,55,56</sup> Interestingly, almost all randomized studies<sup>8,24,25,36,50,51</sup> and carefully designed prospective cohorts on advanced and/or cognitively impaired patients<sup>30,31,37,40,41,48</sup> reported improvements

in cognition with HAART use. Improvements were more pronounced in severely cognitively impaired subjects<sup>48</sup> and occur within a few weeks of ARV therapy initiation or change.<sup>24,25,36,48,51</sup> These data clearly indicate that there is a reversible component of HIV-associated cognitive impairment linked to HAART-induced reduction of viral replication within the CNS.<sup>39–41</sup>

However, a great variability of treatment responses was reported since improvements in NP functions were neither full<sup>6,38,42,43,45,46,55</sup> nor universal.<sup>54,57</sup> It is evident that a consistent proportion of patients failed to fully revert the cognitive dysfunction. Persistent NP impairment despite HAART was reported in a consistent number of patients.<sup>6,46</sup> The severity of NP impairment<sup>46</sup> and previous advanced immunosuppression<sup>6</sup> were reported as associated with persistent impairment. The presence of a nonreversible component of NCI suggests the presence of nonreversible neural injury that presumably derives from residual damage secondary to neurotoxic cascades within the CNS. In fact, in vivo cognitive impairment has been associated with postmortem neuropathologic changes<sup>60</sup> and with in vivo evidences at magnetic resonance imaging studies of white matter tract injury consistent with axonal or neuronal loss<sup>61</sup> and gray and white matter brain loss.<sup>62</sup>

Other potential explanations of persistent cognitive impairment in patients treated with successful HAART include ongoing viral replication of compartmentalized HIV within the CNS<sup>47</sup> and insufficient penetration of some ARV drugs within the CNS.<sup>9</sup> Moreover, ongoing chronic inflammatory processes within the CNS and vascular factors might also contribute to persistent cognitive impairment in patients treated with HAART. Risk factors for cardiovascular disease (ie, smoking, hypertension, dyslipidemia, obesity, and diabetes) contribute to the pathogenesis of both vascular dementia and Alzheimer disease.<sup>63,64</sup> Cardiovascular risk factors<sup>21</sup> and insulin resistance<sup>19</sup> are also associated with cognitive impairment in HIV-infected patients. Raised inflammatory markers are common to cardiovascular disease,<sup>65</sup> metabolic syndrome,<sup>66</sup> dementia,<sup>67</sup> and accelerated aging in HIV-infected patients.<sup>68</sup> Recently, increased plasma levels of markers of vascular dysfunction have been associated with impairment in verbal comprehension and perceptual reasoning in perinatally HIV-infected youth.<sup>69</sup> High levels of immune activation markers, like  $\beta$ -2-microglobuline, neopterin, quinolonic acid, and monocyte chemoattractant protein-1 (MCP-1) within the CSF are frequently found in patients with HAD.<sup>70</sup> Persistent intrathecal immune activation was described in HIV-infected patients on ARV therapy having CSF HIV RNA between 2.5 and 49 copies/mL.<sup>71</sup> The same was reported in patients

successfully treated with HAART for more than 4 years.<sup>72</sup> Taken together, these data suggest that inflammatory mediators released within the CNS could initiate and maintain the neurodegenerative process resulting in neuronal dysfunction and death in patients treated with HAART.<sup>73</sup>

Finally, a few studies indicate no changes in neurocognitive performance or even NP deterioration with HAART use, suggesting potential toxicity from ARV drug use. One report observed no changes in NPZ4 scores in patients receiving neuropenetrating ARV drugs and significant improvements in patients receiving ARV combination with lower estimate of CNS penetration.<sup>54</sup> A second article reported NP improvement after HAART discontinuation.<sup>57</sup> However, the first study had a relatively small number of patients, and the second included a very short battery of NP tests. Moreover, both studies have not been confirmed. However, although evidence of CNS ARV toxicity is relatively low, the concern is rather reasonable, and randomized, controlled trials on the topic are needed.

In conclusion, remarkable progress has been made on our understanding prevalence, risk factors, and response to treatment of HIV-associated cognitive disturbances. However, a number of open questions and unresolved clinical needs still remain. There is a need for randomized prospective trials and carefully planned large prospective cohort studies to answer unresolved issues.

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## Disclosure

The authors report no conflicts of interest in this work.

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