Rates of non-confounded HIV-associated neurocognitive disorders in men initiating combination antiretroviral therapy during primary infection

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Objective: To determine the prevalence of HIV-associated neurocognitive disorders (HAND) in HIV-infected participants who initiated combination antiretroviral therapy (cART) during primary infection.

Design: Cross-sectional observational study.

Methods: HIV-infected men without neuropsychiatric confounds who had initiated cART during primary infection were administered a neuropsychological battery as well as questionnaires evaluating depression and quality of life. Eligibility was determined by a medical examination with history and review of records.

Results: Twenty-six primarily non-Hispanic white (73%), male (100%) participants were enrolled and underwent neurocognitive assessment. Mean age was 43 (28–71) years, with a median of 17 years of education (13–24). Median current and nadir $CD4^+$ T-cell counts were 828 (506–1411) and 359 (150–621) cells/μl. All participants had plasma HIV-1 RNA less than 50 copies/ml. Median duration of cART prior to enrolment was 5.7 years (2.2–9.9). Median global deficit score was 0.17 (0.00–0.60). Only one (4%) participant was impaired.

Conclusion: Rates of HAND in this cohort of HIV-infected men without comorbid conditions who initiated early cART are low. Our findings suggest a possible neuroprotective benefit of early cART and an important contribution of comorbidities to observed HAND prevalence.

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Keywords: central nervous system, combination antiretroviral therapy, HIV-associated neurocognitive disorder, human immunodeficiency virus (HIV-1), primary HIV infection

Introduction

HIV-associated neurocognitive disorder (HAND) is an important complication of chronic HIV-infection. The Frascati nosology delineates three major categories of HAND: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [1]. In patients with HIV-1 infection and access to care, adherence to an appropriate combination antiretroviral therapy (cART) regimen has the potential to suppress viral replication and reduce plasma HIV-1 RNA to levels

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below clinical detection [2]. These advances have resulted in a dramatic reduction in the incidence of HAD [3]. Despite these gains, cognitive impairment – most commonly in the form of ANI and MND – persists in the cART era [4,5]. Although less severe than frank dementia these disorders impact morbidity, and have been independently associated with an increased risk for mortality [6].

Recent cross-sectional studies have estimated the prevalence of HAND at approximately 40–50% in the cART era [4,7]. Several factors have been suggested to have additive or synergistic negative effects on cognitive ability in HIV-positive individuals including methamphetamine dependence [8], major depressive disorder [9] and hepatitis C [10–12]. In the CHARTER study, increased rates of HAND were seen in groups with higher degrees of comorbidities, including hepatitis C, diabetes mellitus, major depression, psychotic disorders and lifetime or current alcohol and illicit drug use disorders. These findings suggest that both HIV and comorbidity contribute to neurocognitive impairment (NCI) [4]. We hypothesized that the application of a comprehensive battery of neurocognitive tests to a cohort of non-confounded individuals who previously initiated uninterrupted, suppressive cART at acute/primary infection time points that are some of the earliest reported in the HAND literature would reveal lower rates of NCI than has been reported in cohorts with different characteristics. We also elicited comprehensive social and psychiatric histories that highlight the ongoing need for directed attention to these issues in HIV care settings.

Materials and methods

Study participants

The study was approved by the Rockefeller University Institutional Review Board. Written informed consent was obtained from all participants prior to their entering the study. Volunteers received financial compensation for participation. Approximately 200 of the active – defined as having been seen at the Aaron Diamond AIDS Research Center (ADARC) for a study visit within the past 3 years – individuals in the ADARC Primary HIV-1 Infection Cohort were invited in random order to screen for this study. Forty men completed a screening visit at ADARC/Rockefeller University Hospital (RUH) from 2010 to 2012. Participants invited for screening were those with initiation of cART during acute and early HIV-1 infection based on documentation of either a negative or indeterminate HIV enzyme immunoassay (EIA)/western blot with HIV-1 RNA greater than 5000 copies/ml, a positive HIV-1 serology with a negative, less sensitive 'detuned' ELISA, or a documented negative HIV-1 serology within 6 months of screening and a positive serology at screening.

Screen visit procedures

Participants underwent a medical history, physical and neurological examination and psychiatric and substance use history at the screening visit. Exclusion criteria adapted from Rippeth *et al.* [8] included severe neurological or *Diagnostic and Statistical Manual Fourth Edition-Text Revision* (DSM-IV-TR) [13] psychiatric illness that affects cognitive functioning (e.g. schizophrenia, bipolar affective disorder), current diagnosis of major depressive disorder as assessed by the patient health questionnaire nine item depression scale (PHQ-9) [14] and not on stable antidepressant medication greater than 30 days, a history of head injury with loss of consciousness more than 30 min, DSM-IV-TR diagnostic criteria for alcohol or illicit substance abuse or dependence, not in remission, within 1 year of the screening visit (excluding marijuana), moderate or higher efavirenz-attributable central nervous system (CNS)-related toxicity as defined in the Division of AIDS Table for grading the severity of adult and paediatric adverse events [15], or serologic evidence of untreated syphilis or positive hepatitis C serology.

Study procedures

Virologic and immunologic assessments

All participants had documented treatment for at least 1 year with cART and plasma HIV-1 RNA levels below 50 copies/ml for a minimum of 6 months prior to study entry. Participants reporting treatment interruption since cART initiation were not eligible for enrolment. Enrolled individuals were required to have a $CD4^+$ T-cell count performed and a documented plasma HIV-1 RNA below the lower limit of detection (50 copies/ml) within 6 months of study entry.

Neuropsychological evaluation

A comprehensive neuropsychological evaluation strategy was adapted from Rippeth *et al.* [8] and performed at the study visit by a neuropsychologist. The battery assessed seven cognitive domains associated with HAND [4]: verbal fluency; processing speed; attention/working memory; learning; recall; abstraction/executive functioning; and motor skills. A detailed listing of individual tests for each domain is found in results. Study participants also completed the wide range achievement test 3 (WRAT3) [16] spelling, vocabulary and arithmetic tests to provide an assessment of premorbid intellectual functioning. Raw scores for all tests were transformed into T-scores using methods that correct for age, education, sex and ethnicity where appropriate [8]. T-scores were then converted to deficit scores, which range from a minimum of 0 in the case of no impairment, to a maximum of 5 [17,18]. For each participant, calculating the sum of all deficit scores in the testing battery and then dividing by the number of administered tests allowed for determination of the global deficit score (GDS), which provides a continuous measure of NCI. Individuals were classified as neurocognitively impaired if GDS scores were at least 0.50 – a cutpoint that has been demonstrated as highly sensitive

and specific for the classification of HAND [17]. The Medical Outcomes Study (MOS) HIV Health Survey (quality of life questionnaire) [19] was completed by a subset of participants. All participants completed the Beck Depression Inventory (BDI) [20] to identify and characterize possible confounding depression at the study visit.

Study design and statistical considerations

This cross-sectional observational study was designed to determine the prevalence of neurocognitive deficits in the ADARC cohort of HIV-1 infected individuals previously initiating cART during acute and early HIV-1 infection using an objective summary score of neuropsychological impairment [18]. Associations between GDS scores and clinical parameters were evaluated using multiple linear regression. Fisher's exact test was used to determine if the prevalence rates of HAND in the ADARC cohort were statistically different from prevalence rates reported by other research groups. All other comparisons were performed using the Mann–Whitney *U* test or the Kruskal–Wallis test for single and multiple comparisons respectively. All were performed with the use of Graph Pad Prism v. 5.0d [21].

Results

Study participants

Forty men presented for screening visits between December 2010 and June 2012. A screen failure rate of 35% (14/40) was observed. The most common reasons for screen failure were active methamphetamine/other substance dependence (5/14 = 36%) and active bipolar disorder (3/14 = 21%) (Fig. 1). Two individuals with initial screen-failure due to untreated syphilis were subsequently enrolled following successful therapy. The characteristics of the cohort are shown in Table 1. Twenty-six, primarily non-Hispanic white (73%), male (100%) participants were enrolled and underwent neurocognitive assessment. The CNS penetration-effectiveness (CPE) score was calculated using predefined scoring points for each component of cART [22,23]. The median 2010 CPE score at study entry was 7 (6–10) and all participants had plasma HIV-1 RNA less than 50 copies/ml at this time. Baseline clinical and demographic characteristics of the 26 participants enrolled in the study are presented in Table 1. Individuals failing screening were demographically similar to those enrolled (Table 1).

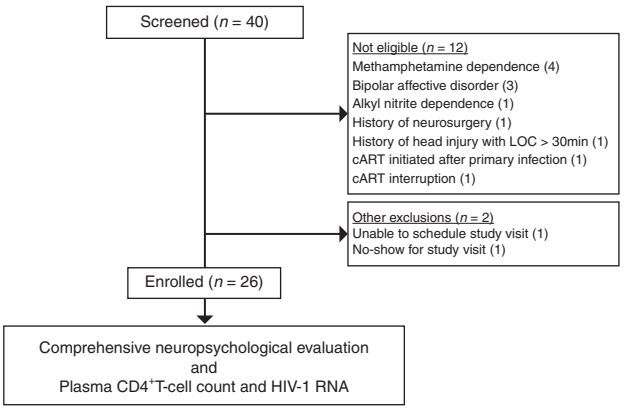

Fig. 1. Clinical flow diagram with reasons for screen failure.

The BDI was completed by all enrolled participants on the day of neurocognitive testing ($n = 26$). The median score was 1 (0–13), reflecting low overall levels of depressive symptoms in the cohort. Of the 26 individuals enrolled, three had a diagnosis of depression well controlled with buproprion ($n = 2$) or the selective serotonin reuptake inhibitor paroxetine ($n = 1$). An additional five individuals were receiving treatment for anxiety disorders with either benzodiazepines, or selective serotonin reuptake inhibitors. Four participants used, as needed, the sedative zolpidem for occasional sleep disturbance.

Recreational drug use was not uncommon amongst the study cohort, with 69% (18/26) reporting past or current use of illicit substances. Amongst those substances reported used in the past, cocaine was the most common, with 30.8% (8/26) of the entire cohort reporting its prior use. This was followed in frequency by marijuana and methamphetamine, with 11.5% (3/26) for both. Past use of intranasal heroin and ecstasy were both reported by 7.7% (2/26). Prior use of opium, alkyl nitrites and ketamine were infrequently reported at 3.8% (1/26). At the time of screening, the most commonly used illicit substance was marijuana, with 34.6% of the cohort reporting active recreational use. This was followed by cocaine at 15.3% (4/26), methamphetamine at 15.3% and ecstasy, with 7.7% of the cohort reporting its occasional use. Thirty one per cent of the enrolled cohort (8/26) reported no past or current history of recurrent illicit drug use. The three most common general medical conditions reported by study participants were hypercholesterolemia at 26.9% (7/26), seasonal allergies/allergic rhinitis at 23.1% (6/26) and anxiety disorders at 19.2% (5/26). Details of reported medical conditions are listed in Supplemental Table 1, http://links.lww.com/QAD/A780. Three individuals (11.5%) reported no significant medical history in addition to their diagnosis of HIV.

Wide range achievement test 3 test results

Raw scores for the spelling, vocabulary and arithmetic tests were converted to T-scores with a distribution mean of 100 and a standard deviation of 15 [16]. T-scores and deficit scores of the study group reflected the high education status of the group as a whole (Table 2).

Table 1. Clinical and demographic profiles for study participants.

Characteristic	Study group ($n = 26$)	Screen failure group ($n = 14$)	*P*-value
Male sex	26 (100%)	14 (100%)	1.00
Race/ethnicity			
Non-Hispanic white	19 (73%)	11 (79%)	1.00
Non-Hispanic black	2 (8%)	0 (0%)	1.00
Hispanic	5 (19%)	2 (14%)	1.00
Other	0 (0%)	1 (7%)	0.35
MSM	26 (100%)	13 (93%)	0.35
Age at screen, years, mean (range)	44 (28–71)	41 (28–52)	0.41
Education, years, mean (range)	17 (13–24)	16 (8–19)	0.55
CDC staging classification			
A1	4 (15%)	2 (14%)	1.00
A2	20 (77%)	11 (79%)	1.00
A3	2 (8%)	1 (7%)	1.00
B or C	0 (0%)	0 (0%)	1.00
$CD4^+$ T-cell nadir, cells/μl, median (range)	359 (150–621)	344 (197–846)	0.93
Estimated duration of infection prior to cART start, d, median (range)	49 (25–180)	49 (25–195)	0.38
CPE score at initiation of cART, median (range)	12 (6–13)	12 (7–13)	0.78
$CD4^+$ T-cell count at enrolment, cells/μl, median (range)	828 (506–1411)	n/a	
Plasma HIV RNA < 50 copies/ml at enrolment	26 (100%)	n/a	
Duration of cART prior to enrolment, y, median (range)	5.7 (2.2–9.9)	n/a	
CPE score at enrolment, median (range)	7 (6–10)	n/a	

Clinical and demographic profiles for study participants. Data are presented as number and percentage (%) except where specified. cART, combination antiretroviral therapy; CNS, central nervous system; CDC, Centers for Disease Control and Prevention; CPE, CNS penetration-effectiveness; n/a, not applicable. *P*-values for comparisons between study and screen failure groups were determined using Fisher's exact and Mann–Whitney tests. *P*-values less than 0.05 are considered significant.

Neurocognitive testing results

Composite raw scores and T-scores for each neurocognitive test as well as a summation of test deficit scores and the number of individuals with any measured deficit are detailed in Table 2. None of the study participants displayed any deficits in either the WAIS-III symbol search, Stroop colour and word interference or Grooved Pegboard (Dominant hand) tests, although individual deficits were occasionally noted within other tests of processing speed, abstraction/executive functioning and

Table 2. Composite raw, T and deficit scores for WRAT-3 and cognitive domain tests.

	Raw score, M (SD)	T-score, M (SD)	Deficit score, sum (range)	# (%) w/deficit
WRAT spelling	51.0 (4.5)	61.4 (9.0)	0 (0–0)	0 (0)
WRAT vocabulary	49.9 (7.8)	52.1 (10.8)	4 (0–3)	2 (8)
WRAT arithmetic	39.0 (6.5)	45.4 (9.0)	7 (0–1)	7 (27)
Cognitive domain tests				
Verbal fluency				
FAS letter fluency	45.1 (13.9)	52.3 (6.5)	1 (0–1)	1 (4)
Category fluency (animals)	21.0 (4.6)	45.4 (8.3)	10 (0–3)	5 (19)
Processing speed				
WAIS-III digit symbol	74.0 (15.1)	51.5 (8.2)	3 (0–1)	3 (12)
WAIS-III symbol search	36.4 (6.1)	56.2 (7.6)	0 (0–0)	0 (0)
Trail making test, Part A	28.1 (15.7)	47.1 (7.7)	7 (0–3)	5 (19)
Attention/working memory				
PASAT	38.4 (13.3)	50.7 (11.8)	7 (0–2)	6 (23)
WAIS-III letter-number sequencing	10.0 (2.4)	48.9 (8.3)	4 (0–1)	4 (15)
Learning				
HVLT-R Trials 1–3	25.2 (3.5)	42.3 (7.6)	10 (0–2)	9 (35)
BVMT-R Trials 1–3	22.5 (6.0)	44.8 (9.5)	8 (0–2)	7 (27)
Recall				
HVLT-R delay recall	8.8 (1.6)	42.9 (6.5)	7 (0–2)	6 (23)
Abstraction/executive functioning				
WCST-64 item (perseverations)	7.8 (6.5)	48.6 (15.6)	8 (0–2)	7 (27)
Trail making test part B (s)	59.9 (21.0)	48.6 (11.7)	8 (0–2)	7 (27)
Stroop colour and word interference[a]	32.2 (14.0)	74.8 (7.8)	0 (0–0)	0 (0)
Motor skills				
Grooved Pegboard dominant (s)	66.3 (16.2)	52.5 (14.3)	0 (0–0)	0 (0)
Grooved Pegboard nondominant (s)	71.3 (14.5)	51.1 (14.3)	3 (0–1)	3 (12)

Composite wide range achievement test 3 (WRAT3) and cognitive domain test scores for the cohort ($n = 26$). # (%) w/deficit, absolute number and percentage of individuals with deficit score greater than 0 for a particular test; (s), seconds; BVMT, brief visuospatial memory test; HVLT, Hopkins verbal learning test; M, mean; PASAT, paced auditory serial addition task; SD, standard deviation; WAIS-III, Wechsler Adult Intelligence Scale III; WCST, Wisconsin Card Sorting Test.
[a]One study participant excluded due to diagnosed colour vision deficiency.

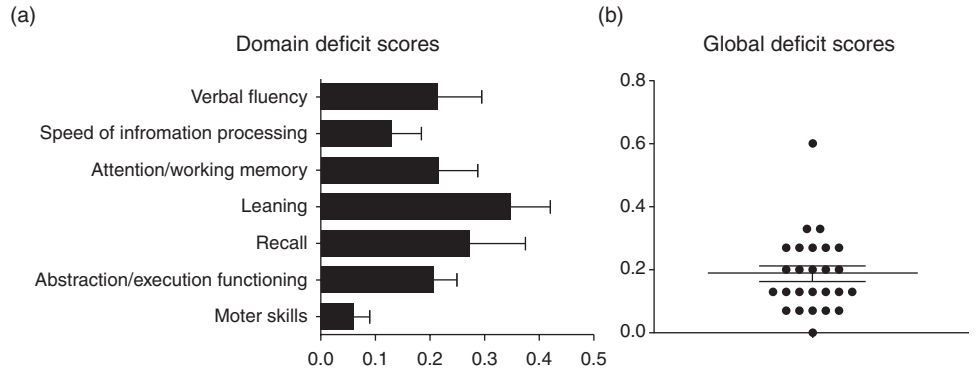

Fig. 2. Composite domain and global deficit scores. Mean composite domain (with standard deviations) (a) and individual and mean global deficit scores (b) for the study cohort ($n = 26$).

motor skills respectively. The HVLT-R Trials 1–3 test had the highest number of individuals with any deficit (9/26 = 34.6%), with deficit scores ranging from 0 to 2. Mean GDS for the study group was 0.19 (0.00–0.60). Figure 2 provides means and standard deviations for each cohort deficit score across the measured cognitive domains (Fig. 2a) as well as the GDS (Fig. 2b). Using a GDS cutpoint as at least 0.50 for impairment, only one individual was found to be impaired with a GDS of 0.60. Statistical comparison of cohort deficit scores using the Kruskal–Wallis test reveals a significant difference in performance across the cognitive domains ($P = 0.01$). Dunn's multiple comparison post-test shows the cohort performed statistically better on tests of motor skills when compared to tests of learning. No other significant differences between group performances in cognitive domains were found.

Within the study group, there was no statistical association between GDS and duration cART, duration of infection prior to initiation of cART, years of education, $CD4^+$ Nadir or $CD4^+$ at enrolment, CPE score at initiation of cART or CPE score at enrolment, ethnicity or age at screen ($P > 0.10$, all variables). Multiple linear regression was also used to assess GDS scores in each cognitive domain. Again, no association between domain-specific deficit scores and the variables listed above were found after Bonferroni correction for multiple testing (significance threshold $P < 0.0007$).

Self-perception of cognitive functioning and motor health are largely consistent with objectively measured global deficit score in this cohort

In an effort to classify individuals with ANI or MND in the presence of GDS scores indicative of NCI, participants were asked for indicators that the NCI produces some degree of interference in daily functioning as defined by self-report of the following: reduced mental acuity (such as the ability to think or reason); inefficiency in work; inefficiency in homemaking or social functioning; and motor difficulties (such as the ability to walk or hold objects) [1]. These questions were asked as above during the screening visit and participants were asked to consider the time frame covering the period since their diagnosis of HIV. Of the 26 individuals who proceeded to the study visit, one individual (4%) reported perceived inefficiencies in work, one individual (4%) reported perceived inefficiencies in homemaking. No individuals reported any perceived motor difficulties. Four individuals (15%) reported some perceived (mild) reductions in mental acuity. Of note, the one individual in our cohort with impairment in a minimum of two cognitive domains and objective evidence of NCI reported no perceived reduction in any of the queried domains, and is therefore classified as having ANI.

The Medical Outcomes Study HIV (MOS-HIV) Health Survey was applied to a subset of study participants in an effort to standardize results of subjective questions of self-perception. This tool has been used extensively in clinical trials, demonstrating sound psychometric properties in varied populations [19]. Ten dimensions of health were evaluated. The subscales of this 35-question instrument are scored as summated rating scales on a 0-to-100 scale with higher scores indicative of better health. Seventeen of the enrolled individuals completed the survey either at the time of the study visit ($n = 11$) or at time points ranging from between 2 and 26 months after the study visit ($n = 6$). Overall self-reported perceptions of general health, functional status and well-being were positive, with mean values for self-reports of cognitive, social, role and physical functioning all above 90. Although self-perceptions of cognitive health were largely consistent with the low rate of NCI in this cohort, no formal statistical correlation exists between GDS and MOS-QOL cognitive function scores ($P = 0.56$). Health transition scores indicate that the majority of respondents believed their overall physical and emotional health to have been largely unchanged or a slightly better than in the month prior to questioning. Composite MOS-HIV survey health results are shown in Table 3.

Table 3. Mean domain scores for the Medical Outcomes Study HIV *Health Survey*.

Dimension	Mean (95% CI)
Overall evaluation of health	
General health perceptions	83.8 (77.0–90.7)
Functional status	
Physical functioning	97.6 (95.1–100.1)
Role functioning	100.0 (100.0–100.0)
Social functioning	97.7 (94.2–101.1)
Cognitive functioning	90.9 (86.8–95.0)
Well-being	
Pain	91.6 (86.1–97.1)
Mental health	82.4 (77.0–87.7)
Energy/fatigue	75.6 (68.1–83.1)
Health distress	95.0 (92.0–98.0)
Quality of life	83.8 (73.7–93.9)
Change in health	
Health transition	61.8 (51.5–72.1)

Mean domain scores for the Medical Outcomes Study HIV Health Survey (MOS-HIV) with 95% confidence intervals (CI).

Discussion

As the number of people living with HIV-infection continues to grow, the prevention and mitigation of diseases that are at higher risk in infected individuals has become increasingly important. HAND persists as an important potential complication of HIV-infection [4], carrying with it the possibility of significant morbidity and mortality [24]. HIV infiltrates the CNS during primary infection, initiating complex inflammatory and viral processes that may result in neuronal damage and neurocognitive decline [25]. A recent paper by Suh *et al.* suggests that intrathecal inflammation progressively increases during primary HIV [26]. An interruption of the accrual of these inflammatory insults might therefore mitigate or abort the CNS immune activation that is widely implicated in HAND pathogenesis [27,28], resulting in decreased rates of HAND in individuals initiating cART at earlier time points. Combined with the finding that when compared to individuals without NCI, those with a diagnosis of ANI may have up to a six-fold increased risk for earlier development of symptomatic HAND [29], the need to implement clinically tested strategies to halt the initiation of NCI becomes clear. It is therefore of great clinical value to investigate if the early initiation of cART might successfully modify the risk of HAND.

Here we present data that observed rates of HAND in this cohort of HIV-infected men who initiated cART during acute/early infection are low, with only one individual (4%) in the study group meeting objective criteria for NCI following comprehensive neurocognitive testing. The finding of low rates of NCI amongst this highly educated group of individuals who have been maintained on uninterrupted, suppressive cART for several years was in-line with our clinical expectations and consistent with the largely positive self-perceptions of general and cognitive health reported amongst study participants. In an effort to identify NCI that was largely attributable to HIV-infection, we chose to investigate a cohort in which a number of comorbid illnesses thought to confound HAND diagnoses or negatively impact neurocognitive function were excluded. The observed screen failure rate in this study (35%) was largely attributed to unexpectedly high rates of substance dependence and psychiatric illness within the screening group and highlights the pervasiveness of comorbid illness in those with HIV, and the difficulty in investigating the isolated effects of HIV on cognition. It is important to note however, that a significant percentage of our study population did report the use of illicit drugs on a recreational basis that did not meet criteria for dependence or abuse. In addition, although a small number of individuals reported formal diagnoses of depression, depressive symptoms appeared well-managed pharmacologically. The decision to exclude those with comorbidities was a reasonable approach, as the potential for even a small number of individuals with confounder-attributable NCI to skew the findings within a relatively small cohort existed. However, there are reports suggesting that historic substance abuse [30] and coinfection with the hepatitis C virus [31] may not have a significant effect on observed HAND prevalence. It should also be noted that although not exclusionary, none of our enrolled participants had diabetes and although several had hypercholesterolemia, none had been diagnosed with significant cardiovascular disease.

We hypothesized that rates of HAND in the ADARC early infection cohort might be significantly lower than the approximately 40–50% reported in the CHARTER and ALLRT [4,7] studies ($n = 1316$ and 1160, respectively), in which many individuals initiated cART during chronic HIV-infection or were not on cART at the time of neurocognitive testing. Although this is true ($P < 0.0001$ by Fisher's exact test), our reported rates of NCI are also lower than that reported in the recent literature for more similar populations. Cross-sectional studies suggest that populations initiating early cART, or maintaining systemic viral suppression on cART may demonstrate decreased HAND prevalence. Crum-Cianflone *et al.* estimated a 19% prevalence of NCI in a cohort of HIV^+ patients diagnosed early in infection. In this cohort, the majority were seroconverters with a median window of 1.2 years and 64% were on cART at the time of study [32]. In a separate study, Cysique *et al.* found a similar prevalence of NCI (18%) in a chronically infected cohort of HIV^+ individuals with plasma HIV RNA levels less than 50 copies/ml [33]. In both cases, this prevalence was similar to what was found in the HIV negative control population for these studies. Although we report a 4% rate of NCI in this observational pilot study, as a result of the small size of our cohort our reported rate is not statistically different from results obtained in these two studies ($P > 0.05$ by Fisher's exact test). Although challenging, interrogation of a larger cohort would be

required to determine if rates of NCI are significantly reduced below 18–19% in non–confounded individuals initiating uninterrupted cART at the earlier time points in our study.

Study limitations include the investigation of a small, exclusively male cohort of participants and the absence of neurocognitive data from a control group. The ability to identify individuals initiating cART during primary infection is challenging and our scientific interest in investigating rates of NCI in individuals maintained on uninterrupted cART as primary infection limited the cohort available for study. However, our use of a comprehensive neurocognitive battery, with detailed medical, psychiatric and drug histories makes these data compelling. Another limitation is the cross-sectional nature of the study, which does not allow for objective longitudinal measurements of HAND. This is particularly important given the overall high educational status of the cohort. Highly educated individuals may have a higher cognitive reserve for normal neurocognitive functioning, effectively making NCI more difficult to uncover until a large amount of reserves are lost [34]. Finally, it should be noted that the median 2010 CPE score at cART initiation was 12, reflecting the fact that four participants had initiated treatment during enrolment in an ADARC study of intensified, five-drug cART [35] and an additional 12 initiated treatment with Trizivir (abacavir/lamivudine/zidovudine) containing regimens. The median 2010 CPE score of 7 at the time of entry into this pilot study reflects the fact that many had returned to standard three-drug cART by the time of enrolment. As a result, these findings may be difficult to extrapolate to individuals initiating early therapy with standard three-drug regimens. However, the extent to which the initiation of cART regimens with high median CPE scores influenced our rates of NCI is unclear. Although a recent study suggests that higher CPE regimens result in better viral suppression in the CSF [36], a randomized trial attempting to determine if treatment with CNS targeted cART regimens resulted in improved neurocognitive outcomes was inconclusive [37]. Data on CSF viral loads of enrolled participants, as well as the presence or absence of viral compartmentalization [38] or genetic signatures potentially associated with neuroadaptation [39] would be informative. Additionally, given the potential confounding interactions between HIV disease and advancing age on cognitive decline [40], it would be of interest to investigate cohorts older than the one in our study. Finally, as a result of investigating individuals with both low comorbidities and early treatment, we cannot determine the relative contribution of these two factors to the low rates of HAND observed in this cohort.

Despite the important limitations of this study, the unique nature of a comprehensive neurocognitive assessment of non-confounded men identified during primary infection with HIV makes this work relevant to greater study of HAND. Our findings, although not conclusive, are consistent with the possibility of neuroprotective benefit of initiating suppressive cART during primary infection; a benefit we hypothesize may be the result of an early decrease in CNS immune activation and/or viral replication. They also highlight the pervasiveness of comorbid illness in those with HIV, suggest an important contribution of comorbidities to observed HAND prevalence, and support the development of larger clinical trials comparing neurocognitive outcomes in individuals treated with cART during acute/primary infection as opposed to later time points.

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T.H.E. led the study, supervised the acquisition of data, analysed the data and wrote the manuscript. A.A. performed and scored all comprehensive neurocognitive assessments and edited the manuscript. M.L.M. assisted in patient recruitment and study coordination and edited the manuscript. D.G. assisted in patient recruitment and study coordination and edited the manuscript. D.D. provided input into study design, data analysis and edited the manuscript. M.M. conceived the project, created and maintained the ADARC Primary HIV-1 Infection cohort, critically reviewed the data and edited the manuscript.

Conflicts of interest

M.M. is a paid consultant for Merck and Gilead. He receives grant support from Gilead and GlaxoSmithKline and is on the Speakers Bureau for Gilead and Bristol-Myers Squibb. The remaining authors have declared that no competing interests exist.

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