

Neurocognitive Consequences of HIV Infection in Older Adults: An Evaluation of the “Cortical” Hypothesis

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Abstract The incidence and prevalence of older adults living with HIV infection is increasing. Recent reports of increased neuropathologic and metabolic alterations in older HIV+ samples, including increased cortical beta-amyloid, have led some researchers to suggest that aging with HIV may produce a neuropsychological profile akin to that which is observed in “cortical” dementias (e.g., impairment in memory consolidation). To evaluate this possibility, we examined four groups classified by HIV serostatus and age (i.e., younger ≤ 40 years and older ≥ 50 years): (1) Younger HIV– ($n = 24$); (2) Younger HIV+ ($n = 24$); (3) Older HIV– ($n = 20$); and (4) Older HIV+ ($n = 48$). Main effects of aging were observed on episodic learning and memory, executive functions, and visuoconstruction, and main effects of HIV were observed on measures of verbal learning and memory. The interaction of age and HIV was observed on a measure of verbal recognition memory, which post hoc analyses showed to be

exclusively attributed to the superior performance of the younger HIV seronegative group. Thus, in this sample of older HIV-infected individuals, the combined effects of HIV and aging do not appear to result in a “cortical” pattern of cognitive deficits.

Keywords Human immunodeficiency virus · Aging · Cognition · Neuropsychological tests · Episodic memory

Introduction

Since the introduction of combined antiretroviral therapies (cART) in 1996, the mortality rates associated with HIV infection and AIDS have decreased dramatically [1]. As a consequence, a larger proportion of individuals infected with HIV are living into increasingly later years of adulthood. At the same time, the number of incident HIV infection cases among older adults continues to grow, accounting for approximately 15% of new HIV diagnoses in 2005 [1]. These convergent factors have significantly increased the prevalence of older adults living with HIV infection over the past decade; at present, approximately 27% of HIV-infected persons are aged 50 years and older [2]. In the United States, older adults currently represent 29% of AIDS cases [1], with prevalence rates estimated to rise above 50% by 2015 [3]. Although controversy remains regarding the impact of aging on HIV disease outcomes [4], older HIV-infected adults may experience greater premorbid immune down-regulation [5], more rapid disease progression [6], and higher morbidity rates [7] than younger individuals.

Independent of one another, HIV and aging are each associated with significant neuropathological alterations (e.g., reduced synaptodentritic complexity). Increasing

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evidence also suggests that the combination of these two risk factors may have additive or synergistic effects on the central nervous system (CNS). Moreover, the neuropathological alterations associated with aging and HIV both preferentially affect the structure and function of prefronto-striato-thalamo-cortical circuits and temporolimbic networks [8, 9]. For example, several studies have found increased amyloid deposition in the hippocampus and frontal lobes in older HIV-infected individuals [10, 11], and older age has been associated with increased prevalence of ubiquitinated proteins in the temporal lobe white matter at autopsy, perhaps indicating synaptodendritic injury, inflammatory mechanisms, and gliosis [12]. Recent neuroimaging studies in HIV also indicate that older age is associated with disproportionate frontal systems alterations, including smaller frontal grey matter volumes [13], elevated markers of glial activation in frontal white matter (e.g., *myo*-inositol) [14], and reduced neuronal integrity (as measured by levels of *N*-acetylaspartate) in the basal ganglia [14], areas long recognized as being highly vulnerable to HIV-associated neuropathologies [15]. Together, the presence of these neuropathologic and metabolic alterations suggests that increased cerebral and subcortical damage may be evident in older HIV-infected individuals, thereby amplifying the risk of neurocognitive impairment [16].

Although the conceptual commonalities between the neuropsychological profiles of aging and HIV infection were first described over 20 years ago [17], only recently have investigators begun to elucidate the combined effects of these risk factors on cognition. Older adults infected with HIV are more likely than their younger counterparts to develop HIV-associated neurocognitive disorders (HAND), including HIV-associated dementia (HAD) and HIV-associated minor neurocognitive disorder (MND) [18–21]. Valcour et al. [19] reported that HIV-infected individuals aged 50 years and older had a three-fold increased risk of HAD as compared to younger adults with HIV, even after controlling for other demographic characteristics, HIV disease severity, psychiatric comorbidities, and cART use. Nondemented older adults with HIV also evidence milder forms of neuropsychological impairment at disproportionately higher levels [cf. 22], particularly in the domains of episodic memory, executive functions, and psychomotor speed [23, 24].

With the advancing age of the HIV population, greater attention has also been paid to additional conditions that have the potential to affect cognition and whose risk increases with age. For example, the aging process itself is oftentimes accompanied by a host of medical and neurological conditions including hypertension, elevated cholesterol and triglyceride levels, cerebrovascular comorbidity (e.g., stroke), and metabolic dysregulation (e.g., insulin

resistance), all of which may be accelerated in the setting of HIV infection [25–27]. Some researchers have also postulated that, in the context of aging, HIV infection may lead to increased rates of neurodegenerative disease by lowering the threshold for clinical manifestations of such disorders, via axonal injury or other mechanisms, in accordance with the cerebral reserve hypothesis [28, 29]. One frequently offered hypothesis is that older HIV-infected individuals may have an amplified risk of developing Alzheimer's disease [30–32] or evidence neurocognitive results similar to an Alzheimer's presentation (e.g., a "cortical" pattern of cognitive deficits), with findings of increased levels of brain beta amyloid and plaque-like lesions in older HIV+ cohorts supporting this hypothesis [10, 11, 33, 34, cf. 12].

With this complex combination of risk factors, some researchers have suggested that the development and expression of HAND may be evolving in older adults with HIV [28, 29, 31]. In other words, older HIV+ adults may display a qualitatively different expression of HAND from that which is observed in younger and middle-aged adults, who typically display a "subcortical" cognitive profile of bradykinesia, bradyphrenia, executive dysfunction, and deficient memory encoding and retrieval [35, 36]. More specifically, older adults with HAND may be more vulnerable to cortical dysfunction and more likely to show deficits typically associated with temporal (e.g., rapid forgetting, dysnomia) and parietal lobe functioning [31], especially given the aforementioned neuropathological alterations in mediotemporal structures that are associated with aging [10, 12]. This possibility may be even more likely considering the shifting pattern of neurocognitive disorders that may already be occurring in the cART era [37, 38]. To this end, recent studies have shown dysfunction in mediotemporal regions on positron emission tomography scans [31] and functional magnetic resonance imaging (fMRI) during memory encoding and retrieval [39], as well as cortical thinning in primary sensorimotor, premotor, and visual areas [40].

Despite the growing popularity of this hypothesis, no study to our knowledge has specifically tested the possibility of HAND evolving to reflect increased "cortical" neuropsychological deficits by examining potential interactions between aging and HIV with appropriate age and HIV comparison participants, as has been recommended [41, 42]. We therefore attempted to investigate the pattern of deficits in an older HIV seropositive sample in comparison to three other groups: (1) an older HIV seronegative sample; (2) a younger HIV seropositive sample; and (3) a younger HIV seronegative sample. We hypothesized that there would be significant main effects of HIV serostatus and age on measures of episodic learning and memory and executive functions, as well as main effects of age on semantic knowledge. In addition, we hypothesized

that a significant interaction would be observed between HIV and age on neuropsychological measures of episodic learning and memory, semantic knowledge, and visuospatial functioning.

Methods

Participants

The study sample included 116 participants who were classified with respect to HIV serostatus (HIV⁻ and HIV⁺) and age (i.e., younger ≤ 40 years and older ≥ 50 years). This yielded four groups: (1) Younger HIV⁻ ($n = 24$); (2) Younger HIV⁺ ($n = 24$); (3) Older HIV⁻ ($n = 20$); and (4) Older HIV⁺ ($n = 48$). Although the “older” adults represent a relatively youthful cohort (range = 50–79 years) in comparison to the cognitive aging literature, the use of 50 years as the cutoff age was informed both by the nature of current HIV epidemic [1] and NIMH neuroAIDS research recommendations [42]. Participants were recruited from local HIV clinics and community organizations from 2005 to 2008. HIV serostatus was determined by enzyme linked immunosorbent assays and confirmed by a Western Blot test. Study exclusion criteria included: (1) severe psychiatric illness (e.g., schizophrenia); (2) neurological disease (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 15 min, and CNS neoplasms or opportunistic infections); (3) an estimated verbal IQ score less than 70 on the Wechsler Test of Adult Reading (WTAR) [43]; (4) substance dependence within 6 months of evaluation; and

(5) a urine toxicology screen positive for illicit drugs (other than marijuana) on the day of evaluation. Note that, a positive marijuana toxicology screen was not grounds for exclusion because drug metabolites are detectable up to 30 days after last use and several medications commonly used in HIV (e.g., efavirenz, marinol) can produce positive toxicology screens.

Regarding the demographic characteristics of the study samples, Table 1 shows that the two Younger groups were comparable in age, as were the two Older groups. However, both HIV⁺ groups achieved fewer years of education and contained a smaller proportion of women compared to the Younger HIV seronegative group (P s < 0.05). In addition, the Older HIV⁺ group obtained lower scores on the HIV Dementia Scale (HDS) [44] compared to the other three samples, which is consistent with prior research [19]. Finally, the HIV⁺ groups had significantly higher proportions of individuals with lifetime diagnoses of major depression and displayed a trend-level ($P < 0.10$) difference in current affective distress as compared to the HIV⁻ groups. As concerns the general medical characteristics of the samples, Table 2 shows that the Older HIV⁺ group had the highest prevalence of hepatitis C infection, a trend-level ($P < 0.10$) difference in hypercholesterolemia, and, along with the Older HIV⁻ group, also had higher rates of hypertension. Table 2 also shows that the Younger and Older HIV⁺ groups did not differ in terms of cART status, HIV CSF RNA viral loads, or current CD4 lymphocyte counts (all P values > 0.10), although the Older HIV⁺ group had a lower nadir CD4 count ($P < 0.05$) and the Younger HIV⁺ group evidenced trends for having both a higher median viral load and a higher proportion of

Table 1 Demographic and psychiatric characteristics of the study sample

	Younger HIV ⁻ ($n = 24$)	Older HIV ⁻ ($n = 20$)	Younger HIV ⁺ ($n = 24$)	Older HIV ⁺ ($n = 48$)	F/χ^2	P	
Demographic characteristics							
Age (years)	30.1 (7.1)	56.6 (6.3)	34.3 (5.0)	55.5 (6.4)	135.21	<0.001	$Y^- = Y^+ < O^- = O^+$
Education (years)	15.4 (2.4)	14.5 (2.3)	13.4 (2.8)	13.6 (2.8)	3.15	0.028	$Y^- > Y^+, O^+$
WTAR verbal IQ	108.3 (9.8)	105.1 (10.2)	100.8 (13.4)	102.6 (14.1)	1.69	0.174	–
HIV Dementia Scale	15.8 (0.5)	15.5 (0.9)	15.6 (0.9)	14.3 (3.0)	3.77	0.01	$O^+ < O^-, Y^-, Y^+$,
Sex (% female)	66.7%	40.0%	16.7%	20.8%	18.92	<0.001	$Y^- > Y^+, O^+$
Ethnicity (% Caucasian)	50.0%	50.0%	33.3%	62.5%	18.00	0.115	–
Psychiatric characteristics							
Major depression ^a	25.0%	25.0%	50.0%	56.3%	9.73	0.021	$Y^+ = O^+ > O^- = Y^-$
Generalized anxiety ^a	0.0%	5.0%	8.3%	8.5%	2.29	0.514	–
Substance dependence ^a	25.0%	40.0%	54.2%	50.0%	5.36	0.148	–
POMS total	41.6 (24.2)	44.9 (28.6)	62.8 (33.0)	48.3 (26.6)	2.53	0.064	–

POMS Profile of Mood States, WTAR Wechsler Test of Adult Reading, Y^- Younger HIV seronegative, O^- Older HIV seronegative, Y^+ Younger HIV seropositive, O^+ Older HIV seropositive

^a Denotes a lifetime diagnosis

detectable plasma viral load ($P_s < 0.10$). As might be expected, the Older HIV+ group had a longer duration of infection and a higher prevalence of AIDS diagnoses than the Younger HIV+ group.

Materials and Procedure

All participants provided written, informed consent prior to completing a comprehensive medical, psychiatric, and neuropsychological research evaluation for which they received financial compensation. The study was approved by the university's human subjects committee.

Neuropsychological Assessment

All participants were administered a comprehensive neuropsychological assessment battery by trained research assistants. The WTAR was administered as an estimate of premorbid verbal intellectual functioning. Measures for analysis were selected from the larger battery that were known to be the most sensitive tests to cortical dysfunction, in the domains of episodic memory, semantic knowledge, executive functions, and visuospatial functioning. These measures included (1) the Boston Naming Test (BNT) [45] a standardized category (animals) verbal fluency test (Category Fluency) [46]; (2) the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test (KAIT) [47]; (3) the Logical Memory subtest from the

Wechsler Memory Scale, 3rd edition (WMS-3) [48]; (4) the California Verbal Learning Test, 2nd edition (CVLT-II) [49]; (5) the Boston Qualitative Scoring System (BQSS) for the Rey–Osterrieth Complex Figure [50]; (6) Trail-making Test, Part B [51]; and (7) Tower of London Test (Drexel Version) [52]. Table 3 indicates the specific variables that were analyzed from each measure. We also classified each individual into one of three memory profiles using a discriminant function algorithm based on three CVLT-II variables. This algorithm was originally derived for the first version of the CVLT [53] and classifies individuals as having a CVLT-II profile indicating an encoding/storage deficit, a retrieval deficit, or a normal profile. The utility of this algorithm has been shown in a number of studies examining the pattern of memory performance in various neurological groups, including HIV [54–56].

Psychiatric Assessment

All participants underwent a structured psychiatric assessment using the Composite International Diagnostic Interview (CIDI version 2.1) [57] to generate lifetime diagnoses of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Substance-Related Disorders per *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) [58] criteria. The Profile of Mood States (POMS) [59] was administered to assess overall acute (i.e., the week prior to evaluation) affective distress. The POMS is a

Table 2 HIV disease and medical characteristics of the study samples

	Younger HIV− (<i>n</i> = 24)	Older HIV− (<i>n</i> = 20)	Younger HIV+ (<i>n</i> = 24)	Older HIV+ (<i>n</i> = 48)	χ^2	<i>P</i>	
Medical characteristics							
Hepatitis C	4.2%	0.0%	4.2%	25.5%	13.50	0.004	O ⁺ > Y [−] , Y ⁺ , O [−]
Hypertension	8.3%	60.0%	25.0%	41.7%	15.08	0.002	O [−] = O ⁺ > Y [−] , Y ⁺
Hypercholesterolemia	0.0%	0.0%	0.0%	10.4%	7.40	0.060	−
Diabetes mellitus	0.0%	10.0%	4.2%	10.4%	3.28	0.350	−
HIV disease characteristics							
AIDS (%)	−	−	37.5%	68.8%	6.43	0.011	O ⁺ > Y ⁺
HAART (%)	−	−	66.7%	75.0%	1.75	0.416	−
ARV regimen duration (months)	−	−	29.4 (51.8)	12.9 (20.3)	1.54	0.216	−
HIV duration (years)	−	−	9.6 (6.7)	15.6 (7.0)	9.63	0.002	O ⁺ > Y ⁺
Nadir CD4 ^a (cells/μl)	−	−	253 [185, 344]	102 [29, 282]	4.88	0.027	Y ⁺ > O ⁺
Current CD4 ^a (cells/μl)	−	−	640 [299, 916]	512 [253, 693]	0.85	0.358	−
Plasma HIV RNA ^a (log ₁₀)	−	−	1.9 [1.7, 4.1]	1.7 [1.7, 1.8]	2.73	0.098	−
CSF HIV RNA ^{a,b} (log ₁₀)	−	−	1.7 [1.7, 1.8]	1.7 [1.7, 1.7]	0.18	0.670	−
% Detectable plasma HIV RNA	−	−	45.8%	23.9%	3.52	0.061	−
% Detectable CSF HIV RNA	−	−	20.0%	16.1%	0.11	0.745	−

Y[−] Younger HIV seronegative, O[−] Older HIV seronegative, Y⁺ Younger HIV seropositive, O⁺ Older HIV seropositive

^a Data represent medians with interquartile ranges in brackets

^b O⁺ *n* = 31 and Y⁺ *n* = 15

Table 3 Neuropsychological test performance in the four study samples

	HIV–		HIV+		Effects (<i>F</i> values)		
	Young (<i>n</i> = 24)	Old (<i>n</i> = 20)	Young (<i>n</i> = 24)	Old (<i>n</i> = 48)	HIV	Aging	HIV × Aging
Boston Naming Test (total)	55.25 (4.63)	55.55 (4.57)	53.77 (5.66)	55.00 (5.05)	0.91	0.39	0.27
KAIT Famous Faces	12.71 (3.99)	14.60 (3.33)	9.80 (3.99)	13.75 (4.63)	4.91*	11.31**	1.44
Animal fluency	22.75 (5.34)	20.47 (4.33)	21.50 (5.35)	20.77 (5.26)	0.62	1.56	0.81
WMS-3 Logical Memory							
I Total	45.29 (14.61)	48.65 (7.76)	41.50 (10.12)	38.62 (11.70)	9.38**	0.19	1.89
II Total	33.12 (7.33)	29.95 (7.16)	24.29 (8.32)	22.21 (8.92)	24.79**	1.72	0.17
Recognition	26.92 (2.06)	27.25 (1.68)	24.96 (2.69)	25.04 (2.86)	16.15**	0.10	0.10
% Retained	90.71 (9.09)	85.70 (13.23)	80.88 (16.96)	78.29 (19.25)	6.91**	1.20	0.33
CVLT-II							
Total 1–5	58.83 (9.19)	51.05 (9.75)	50.63 (12.77)	46.51 (11.99)	9.29**	4.96*	1.54
Total Cued Recall Intrusions	0.29 (0.69)	1.35 (1.57)	2.58 (2.62)	2.91 (4.09)	10.18**	1.23	0.65
Long Delay Free Recall	13.13 (2.13)	10.45 (2.46)	10.17 (4.35)	9.30 (4.13)	9.79**	3.95*	2.31
Recognition Discriminability	3.69 (0.36)	2.77 (0.71)	2.86 (0.94)	2.78 (0.95)	7.15**	7.37**	9.95**
Rey-O BQSS							
Copy Presence and Accuracy	18.08 (1.42)	17.05 (2.16)	17.92 (2.12)	17.35 (1.77)	0.01	3.15	1.65
Immediate Recall Presence and Accuracy	14.20 (3.16)	11.40 (2.39)	13.08 (3.02)	10.98 (3.45)	2.49	9.40**	1.20
Delayed Recall Presence and Accuracy	13.83 (2.85)	10.70 (3.79)	12.96 (3.68)	10.98 (3.41)	1.36	11.28**	1.71
Delayed Retention	–1.50 (10.36)	–1.40 (16.23)	–2.96 (17.57)	2.44 (27.61)	1.36	0.51	0.38
Trailmaking Test, Part B (time)	46.75 (16.10)	69.45 (17.94)	57.25 (22.57)	80.58 (52.94)	2.44	7.28**	0.03
Tower of London (Drexel) Total Moves	24.83 (13.16)	37.95 (18.56)	27.63 (17.44)	26.83 (19.65)	1.25	2.34	3.21

Note: All data are raw scores

BQSS Boston Qualitative Scoring System, CVLT-II California Verbal Learning Test, Second Edition, KAIT Kaufman Adolescent and Adult Intelligence Test, Rey-O Rey–Osterrieth Complex Figure, WMS-3 Wechsler Memory Scale, 3rd Edition

* $P < 0.05$; ** $P < 0.01$

65-item, self-report measure of current mood states on which participants rate various adjectives (e.g., “unhappy”) on a five-point Likert-type scale ranging from 0 (“not at all”) to 4 (“extremely”). The POMS Total Mood score was used for all analyses.

Medical Assessment

Finally, all participants received a neuromedical evaluation, which included a comprehensive review of medications, medical history and current symptoms, a complete physical and neurological evaluation, CDC staging, and the HDS, which is a general cognitive screening tool that evaluates memory, attention, psychomotor speed, and construction (range = 0–16). Participants also underwent a blood draw and lumbar puncture (HIV+ $n = 46$). Standard flow cytometry methods were used to count CD4+ lymphocytes in blood samples. Plasma and CSF HIV RNA levels were quantified using RT-PCR (Amplicor, Roche Diagnostics, Indianapolis, IN).

Data Analyses

Power analyses showed that the study was adequately powered (>0.80) to detect interactions of medium-to-large effect sizes, using a critical alpha at 0.05, based on our sample size ($N = 116$). The data were screened for significant outliers (i.e., data points >3.5 SD from the overall group mean) and evaluated for normality (i.e., Shapiro–Wilk W test, $P < 0.05$). A series of 2×2 ANOVAs were run to test for main effects of age (dichotomous, ≤ 40 vs. ≥ 50 years) and HIV status (dichotomous) and the potential interaction between the two variables on the neuropsychological scores of interest. Raw neuropsychological test scores were used for all analyses. To evaluate the possible effects of confounding variables on the hypothesized effects, a series of follow-up linear regressions were performed in which the four-level aging and HIV grouping variable was used as a predictor of the neuropsychological test scores, alongside the demographic, psychiatric, and medical variables upon which omnibus group differences

were observed (see Tables 1, 2). The critical alpha level was set at 0.05 for all analyses.

Results

As shown in Table 3, main effects of age were observed on select measures of learning (CVLT-II Total 1–5), memory (KAIT Famous Faces; CVLT-II Long Delay Free Recall and Recognition Discriminability; and Rey-O BQSS Immediate Recall and Delayed Recall), executive functions (Trailmaking Test, Part B), and visuoconstruction (Rey-O BQSS Copy Presence and Accuracy Score).

Main effects of HIV were observed on measures of learning (CVLT-II Total 1–5; WMS-3 Logical Memory I Total) and memory (KAIT Famous Faces; WMS-3 Logical Memory II Total, Recognition, and Percent Retained; CVLT-II Long Delay Free Recall and Recognition Discriminability). There was also a main effect of HIV on the CVLT-II classifications ($\chi^2(2) = 9.56, P = 0.008$). Full results of the classification using the CVLT-II discriminant function algorithm are presented in Table 4.

As shown in Table 3, an interaction effect was observed on a measure of verbal recognition memory (CVLT-II Recognition Discriminability). However, post hoc analyses revealed that this interactive effect was exclusively attributable to the superior performance of the younger HIV– group, such that the younger HIV– comparison group was significantly different from the other three groups, who were all roughly equivalent.

Post hoc analyses revealed no interpretive changes in the significance level of any HIV/aging interaction term when medical (e.g., hypertension, hepatitis C infection), psychiatric (e.g., depression), or demographic (i.e., sex and education) factors were included as covariates in the statistical models.

Discussion

With the advancing age of the HIV+ population and improved outlook for longevity in individuals with HIV infection, a number of clinical researchers have recently

considered whether aging in the setting of HIV might confer additional neurocognitive risks than either condition in isolation. While it is clear that HIV and aging each contribute independent deleterious effects on the CNS, resulting in decreased cognitive functioning in a subset of individuals, indirect lines of evidence have also suggested that HIV might lower the threshold for additional neurodegenerative processes that are usually seen at a later age outside of the context of HIV. While some studies have focused on enhanced cerebrovascular [26] and metabolic [27] risk in older HIV populations, the theories that have seemingly garnered the most attention recently have focused on the potential altered expression of HAND in older adults, which may reflect increased neocortical neuropathology or dysfunction, or even an early Alzheimer's process [28]. Given the promulgation of these theories, we sought to examine whether there might be detectable changes in the neuropsychological profile of older individuals with HIV infection that might provide behavioral evidence to support (or challenge) these theories.

In the present study, our findings converge with prior data showing that older age and HIV infection independently increase the risk for neurocognitive impairment, particularly in the areas of episodic learning and memory and executive functions. However, the combined effects of HIV and aging did not reflect what would classically be considered a “cortical” pattern of cognitive deficits. To this end, interaction effects were only found on a measure of verbal recognition memory, and these effects were exclusively due to the superior performance of the younger HIV– participants. Our findings, while preliminary, suggest that, even with potential changes in underlying neuropathology (e.g., brain beta amyloid deposition), older HIV-infected persons may not display neuropsychological deficits that appear “cortical” in nature compared to what might otherwise be expected in HIV disease and aging alone.

Given the often subtle effects of such neuropathological changes on cognition and the relative youth of our sample in comparison to the aging literature, it could be argued that the effects expected on neuropsychological test results in this study would be more likely to fall within the small-to-medium range. By this line of reasoning, having adequate statistical power for medium-to-large effect sizes may not be sufficient. However, we set a somewhat liberal alpha level in order to diminish this possibility, thereby decreasing our risk for Type II error (and inflating our Type I error risk). An even more liberal alpha value of 0.10 would result in one additional significant interactive effect on Tower of London Total Moves. Yet this result, surprisingly, was due to the poor performance of the older HIV seronegative sample, while the other three groups were equivalent.

Table 4 California Verbal Learning Test-II discriminant function classification results in the four study samples

	Encoding/storage profile (%)	Retrieval profile (%)	Normal profile (%)
HIV– Young	0.0	16.7	83.3
HIV– Old	15.0	10.0	75.0
HIV+ Young	25.0	20.8	54.2
HIV+ Old	17.0	23.4	59.6

Although we did not find interactive effects of HIV and aging in this sample, it is still unclear whether the combination of these factors confers an additive risk of neurocognitive impairment. While some prior studies have found additive effects in older HIV+ samples [19, 24], the profile of neuropsychological tests in our sample did not necessarily reflect an additive effect, although we did not explicitly test for additivity given the specific hypotheses being evaluated in this study. However, individuals in the older HIV+ group scored significantly lower on the HDS, a screening instrument designed specifically for the detection of HIV-associated dementia, suggesting potential additive effects. In addition, it should be noted that we did not examine a number of other cognitive domains that might be expected to show additive effects of HIV and aging, such as psychomotor/processing speed and working memory. Of note, these domains may be particularly important to examine in investigating the effect of other comorbidities on the profile of cognitive deficits in older HIV+ samples. For example, emerging evidence suggests that cerebrovascular risk factors associated with aging and HIV contribute significantly to performance on neurocognitive tests of psychomotor and processing speed [60], especially among individuals pharmacologically untreated for these risks [61]. Thus, it will be important to address issues of additivity and comorbidity in future studies of aging in the context of HIV, as added risk factor burden may increase the risk of functional impairment, including medication nonadherence [62].

The combined effects of HIV and advancing age raise clinically relevant questions regarding the effective diagnosis and treatment of neurocognitive symptoms in HIV infection, especially with the likelihood of additive deleterious effects [23]. The possibility that concomitant neurodegenerative processes are superimposed upon this clinical syndrome has the potential to challenge current models of diagnosis and treatment of HAND in older individuals. However, in this sample of older HIV+ individuals, we found minimal evidence for qualitatively distinct cognitive impairment due to alternative etiologies. Thus, clinicians and researchers may need to have sufficient cause to broaden their differential diagnosis to include other neurodegenerative causes in most individuals under 65 who are on cART treatment and have well controlled disease (i.e., adequate plasma and CSF viral control). This does not deny that some HIV+ individuals may experience comorbid processes associated with normal aging (e.g., cerebrovascular risk) that may be detrimental to their neurological health, although the extent to which HIV impacts this presentation remains uncertain. It is also still unclear what additional risk older HIV+ individuals with poorer disease management or additional risk factors (e.g., substance abuse) face.

A few limitations to this study suggest important avenues for future study. First, although the age of our older HIV+ group (mean = 55.4 years) is commensurate with other studies of aging in HIV [24], our sample was still relatively young in comparison to most studies of aging outside of the context of HIV. It is possible that as HIV-infected individuals advance in age beyond the range represented by our sample, their risk for cerebrovascular co-pathology and immune dysregulation may increase, especially with extended use of cART medications, which may result in a different pattern of cognitive impairment. The absence of interactive effects in this sample also raises the possibility that a lag occurs between when neuropathological markers appear in the cortex and when changes can be observed on neuropsychological tests. For example, it is clear that the underlying neuropathology of Alzheimer's disease is laid down many years prior to the emergence of clinical symptoms [63], and future studies using an epidemiological approach may show that age and HIV interact in older HIV+ individuals to lower the age of onset for Alzheimer's disease. However, in the case of amyloid-beta, there may be important differences in its neuropathology in HIV versus Alzheimer's disease [64] that result in unpredictable effects on the neuropsychological profile of HAND in older adults. Future studies should examine a sample of HIV+ individuals at later ages in order to further expand on these possibilities, perhaps using neuroimaging techniques that are sensitive to subtle changes in microstructure [65, 66].

Second, our study may have suffered from survival bias, in that our older HIV+ cohort may have contained a larger proportion of long-term non-progressors or individuals with slower HIV progression, whereas post-mortem studies that have reported increased neuropathology in older HIV+ individuals may have included a larger proportion of participants susceptible to dementia (and with worse immunological health). To this end, despite having a lower nadir CD4 count, a longer duration of infection, and an increased likelihood of having AIDS, our older HIV+ cohort had similar current disease markers (e.g., current CD4) compared with the younger HIV+ group, suggesting adequate current viral suppression. Thus, it would be ideal to examine a subgroup of older HIV+ individuals with a shorter duration of infection to examine the interaction of aging and HIV in those with different patterns of progression. However, our older HIV+ sample only contained 6 participants with duration of infection less than 5 years. Therefore, in an attempt to partially address this issue, we performed post hoc correlational analyses in the older HIV+ group between duration of infection and our neuropsychological outcomes. These analyses revealed that the Boston Naming Test ($r = 0.58$; $P < 0.0001$), KAIT Famous Faces Test ($r = 0.38$; $P = 0.01$), and BQSS

Delayed Retention Summary Score ($r = 0.31$; $P = 0.04$) were significantly and positively associated with duration of infection in this group. Thus, a shorter duration of infection is correlated with lower neuropsychological performances on some measures traditionally associated with a “cortical” profile of deficits in older HIV+ individuals, which is suggestive of a differential pattern of deficits in older HIV+ individuals with shorter durations of infection. Nonetheless, this finding is preliminary and awaits more detailed future analyses.

Finally, both of our HIV+ groups were relatively healthy in terms of HIV disease characteristics in comparison to many community-based samples [7]. It is possible that cognitive (and pathological) changes may be more likely to occur in individuals in later disease stages or with worse current HIV immunological health. Similarly, fewer participants evidenced HIV-associated neurocognitive disorders than might be expected—19 participants evidenced asymptomatic neuropsychological impairment, 6 participants met criteria for MND, and 1 participant met criteria for HAD. It may be that a different expression of HAND only occurs in individuals with more severe levels of cognitive impairment, such as dementia [30], which our sample failed to provide in large numbers. However, to explore this possibility, we also conducted post hoc analyses that only included individuals from the older HIV+ group with HAND diagnoses ($n = 15$). These analyses resulted in an interaction on the Trailmaking Test, Part B ($P = 0.004$), such that the Older HIV+ group with HAND had significantly greater times than the three other groups, and the Younger HIV− group had faster times than the other three groups. This finding gives some indication that older HIV+ individuals with HAND diagnoses may have increased deficits in executive functions, although these preliminary results will also need to be confirmed. Therefore, future studies should examine the pattern of neuropsychological performance in older HIV+ participants who are in later disease stages or evidence greater levels of HIV-associated neurocognitive disorders to examine for the possibility of additional neurocognitive deficits in this population.

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