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Verbal Memory Declines More Rapidly with Age in HIV Infected versus Uninfected Adults

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Abstract

Objectives—In the current era of effective antiretroviral treatment, the number of older adults living with HIV is rapidly increasing. This study investigated the combined influence of age and HIV infection on longitudinal changes in verbal and visuospatial learning and memory.

Methods—In this longitudinal, case-control design, 54 HIV seropositive and 30 seronegative individuals aged 40–74 received neurocognitive assessments at baseline visits and again one year later. Assessment included tests of verbal and visuospatial learning and memory. Linear regression was used to predict baseline performance and longitudinal change on each test using HIV serostatus, age, and their interaction as predictors. MANOVA was used to assess the effects of these predictors on overall baseline performance and overall longitudinal change.

Results—The interaction of HIV and age significantly predicted longitudinal change in verbal memory performance, as did HIV status, indicating that although the seropositive group declined more than the seronegative group overall, the rate of decline depended on age such that greater age was associated with a greater decline in this group. The regression models for visuospatial learning and memory were significant at baseline, but did not predict change over time. HIV status significantly predicted overall baseline performance and overall longitudinal change.

Conclusions—This is the first longitudinal study focused on the effects of age and HIV on memory. Findings suggest that age and HIV interact to produce larger declines in verbal memory over time. Further research is needed to gain a greater understanding of the effects of HIV on the aging brain.

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Keywords

HIV; Memory; Cognitive Aging; Autoimmune Diseases; HIV-Associated Neurocognitive Disorder

Introduction

There have been dramatic reductions in mortality and morbidity related to human immunodeficiency virus-1 (HIV) since the introduction of combination antiretroviral therapy (cART) nearly two decades ago (Detels et al., 1998). HIV associated dementia is now relatively uncommon (Sacktor et al., 2001; Woods, Moore, Weber, & Grant, 2009), and research conducted at the beginning of the cART era showed improvements in neurocognitive function following cART initiation and worsening of these functions among untreated individuals (Cohen et al., 2001). However, initial optimism that brain disturbances would soon be eradicated in people with HIV has been tempered by the persistence of HIV associated neurocognitive disorder (HAND) in about 50% of infected people (Heaton et al., 2011; Sacktor, 2002; Tozzi et al., 2007).

A variety of clinical risk factors have been linked to HAND (Cohen et al., 2011; Devlin et al., 2012). Mounting evidence suggests that advanced age is among these risk factors (Cherner et al., 2004; Cohen & Gongvatana, 2010; Harezlak et al., 2011; van Gorp et al., 1994; Vance, 2006; Wendelken & Valcour, 2012; Wilkie et al., 2003). The odds of having HAND are as much as 3 times greater in people with HIV over the age of 50 years (Becker, Lopez, Dew, & Aizenstein, 2004; Valcour et al., 2004). As effective treatment has transformed HIV into a largely manageable chronic illness, the possibility that the effects of the disease are exacerbated by age is troubling. This is especially true considering that cognitive dysfunction continues in patients treated with antiretroviral therapy (Robertson et al., 2007; Simioni et al., 2010). Neurological changes continue to occur in treated patients (Hanning et al., 2011), and even with effective control of viral replication by cART, HIV has been shown to persist in latent reservoirs in the body and brain (Finzi et al., 1997). Consequently, people with HIV face the prospect of experiencing the effects of chronic viral exposure as they age, including an increased risk of brain dysfunction. Given that the population of older HIV infected individuals is rapidly increasing (High et al., 2012; McArthur et al., 2003), there is a compelling need for prospective research aimed at delineating the effects of HIV on neurocognitive functioning in the context of the aging brain.

Learning and memory abilities are particularly vulnerable to aging effects in the general population (Peterson, 1992) and impairments in these domains are becoming more common in people living with HIV (Cysique, Maruff, & Brew, 2004; Heaton et al., 2011; Simioni et al., 2010). Furthermore, memory deficits are among the strongest neuropsychological predictors of difficulty in activities of daily living in these populations (Heaton et al., 2004; Woods et al., 2008). With such high prevalence and impact on real world functioning, memory deficits warrant specific attention in HIV related research.

Several studies have examined the role of aging in HIV associated memory deficits by comparing younger (generally aged 20 – 40 years) and older (age ≥ 50 years) participants. Sacktor et al. examined verbal and visual memory functioning in adults with HIV and found that the older group had lower scores than the younger group (Sacktor et al., 2007). Several case-controlled studies have used similar aging parameters to compare learning and memory functions among four groups – younger with HIV, older with HIV, younger without HIV, and older without HIV. Wilkie et al. found that the HIV infected participants had lower scores on a verbal learning task than participants without HIV, and the older groups performed worse on verbal learning and memory regardless of HIV status (Wilkie et al., 2003). Scott et al. also examined four groups with comparable age parameters and found that HIV status and age affected learning and memory in the same direction, with positive HIV status and older age correlating with lower scores (Scott et al., 2011). Finally, Valcour et al. had similar results, showing that positive HIV status and older age were associated with lower scores on memory assessments, with the greatest deficits seen in HIV infected groups with a lower CD4 nadir, which is the lowest historical level of CD4 T cells (V. Valcour, Paul, Neuhaus, & Shikuma, 2011).

Despite evidence that older age and positive HIV status negatively affect learning and memory, the question remains as to whether HIV and age function independently to produce neurocognitive deficits or whether their mechanisms interact. In other words, does each of these factors impair cognition independently, or does their combined effect result in greater cognitive deficits than either factor would alone? Recent research, including the three case-controlled studies discussed above, reported independent effects of age and HIV on cognition, suggesting that the magnitude of neurocognitive deficit caused by HIV is the same regardless of age, and the deficits caused by age are equal regardless of HIV status (Ciccarelli et al., 2012; Cysique, Maruff, Bain, Wright, & Brew, 2011; Kissel, Pukay-Martin, & Bornstein, 2005; V. Valcour et al., 2011; van Gorp et al., 1994). However, all but one of these studies (Sacktor et al., 2010) are cross-sectional, so they do not provide a direct means of examining the effects of HIV and age on individuals. Therefore, longitudinal case-control studies are needed to examine neurocognitive changes in young and old HIV infected and HIV uninfected individuals as they age.

The present study examines learning and memory performance and change over time in young and older adults with and without HIV. We hypothesized that older people with HIV infection would have greater baseline impairments and greater declines over time compared to younger seropositive individuals and both younger and older seronegative controls.

Methods

Participants

Participants were recruited from the outpatient Immunology Center of The Miriam Hospital and the Brown University Center for AIDS Research (CFAR), as previously described (Devlin et al., 2012). Seronegative (HIV–) controls were either recruited because they were family, friends, and visitors of the seropositive (HIV+) participants, or they responded to fliers posted in the community. All participants underwent neurological examination and a thorough medical history assessment that involved a review of medical records and a

structured clinical interview. Patients were excluded if they had any of the following: history of major head injury; neurologic condition such as dementia, seizure disorder, stroke, or opportunistic brain infections; major psychiatric illness that might effect brain function such as schizophrenia, untreated bipolar disorder, or any other psychotic or thought disorder; or current illicit drug use as defined by substance dependence in the past six months or a positive urine toxicology screen for cocaine, opiates, or illicit stimulants or sedatives. Cognitive tests were administered to all participants at baseline and again one year later. HIV infection was documented by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot. Participants were evaluated for active hepatitis C virus (HCV) infection, which was defined as detectable serum HCV by polymerase chain reaction. The study was approved by the IRB and informed consent was obtained from all participants.

The study sample consisted of 84 participants (54 HIV+ and 30 HIV-). The participants ranged in age from 40 to 74 years. Table 1 shows demographic and clinical characteristics of the sample. The HIV seronegative participants were older ($F [1, 82] = 5.582, p = .04$), had more years of education ($F [1, 82] = 9.27, p = .003$), and had lower rates of active HCV ($p = .002$) than the HIV+ group. Although there were more Caucasians without HIV than with, a Pearson's χ^2 analysis showed no significant group differences in racial and ethnic composition overall ($\chi^2 [4, N = 85] = 8.9, p > .05$). Participants were administered the Center for Epidemiologic Studies Depression Scale (CES-D) to assess for depression. HIV+ participants had a mean score of 21.5, which was higher than the mean score of 11.2 for the seronegative participants ($F [1, 82] = 13.2, p < .01$). Lifetime drug use was assessed using the Kreek-McHugh-Schluger-Kellogg (KMSK) scale. Using these criteria, the lifetime rates of substance dependence for the HIV+ participants were 55.6% for alcohol, 57.4% for cocaine, and 20.4% for opiates. For the HIV- participants, the rates of lifetime substance dependence were 40% for alcohol, 13.3% for cocaine, and 6.7% for opiates. The HIV+ participants had significantly higher rates of lifetime cocaine dependence ($p < .01$).

Among the HIV+ participants, the average time since diagnosis was 14 years, 93% were on cART, and 41% were HCV+ at the time of enrollment. While the average CD4 nadir was 153 cells/ μ L, which indicates a history of significant immunodeficiency, most participants (78%) did not have detectable plasma HIV RNA at the time of enrollment and the average current CD4 cell count was 420, which indicate a low burden of infection.

Memory Assessment

Learning and memory assessments were performed at baseline and parallel forms of the same tests were given again 1 year later (average months between assessments was 14.28; $SD = 3.09$). The testing interval did not differ between HIV- and HIV+ groups. Visuospatial learning and memory were assessed using the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996), in which participants are shown six geometric figures in a 2×3 array for ten seconds and then asked to draw as many of the figures as possible. There are three learning trials followed by a 25-minute delay free recall trial and a recognition trial, where participants identify which figures were presented initially, distinguishing those figures from new ones. Verbal learning and memory were assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R)

(Benedict, Schretlen, D., Groninger, L., Brandt, J., 1998). In this task, participants are read a list of 12 words that belong to four different semantic categories. Similar to the BVMT-R, there are three learning trials, for which the participant repeats as many words as possible after the list is read, and then a 25-minute delayed free-recall trial followed by a recognition trial. Forms 1 and 4 of the HVLT-R were used and forms 1 and 2 of the BVMT-R were used. For each test, total learning scores were calculated by adding the number of correct responses from the three learning trials for each test. Learning scores were labeled BVMT-R-sum and HVLT-R-sum for the BVMT-R and HVLT-R tests, respectively. Memory scores, the number of items correctly recalled after a 25-minute delay, were labeled BVMT-R-delay and HVLT-R-delay. Thus, the four neurocognitive indices used in subsequent analyses were BVMT-R-sum for visuospatial learning, BVMT-R-delay for visuospatial memory, HVLT-R-sum for verbal learning, and HVLT-R-delay for verbal memory.

Statistical Analysis

Analyses were performed using R statistical software (R Core Team, 2013). Alpha was set at .05, two-tailed. Differences in demographic variables between HIV groups were examined using analysis of variance (ANOVA) for continuous variables and Pearson's χ^2 tests or Fisher's Exact test for categorical variables. Repeated measures ANOVAs were used to analyze changes in clinical and cognitive variables from baseline to follow-up visits. Years of education, ethnicity, and gender were included as covariates in analyses of neurocognitive data, where ethnicity was dichotomized as white or non-white. The aging effect was modeled using both dichotomous baseline age groups (young: 40 – 54, old: 55+) and continuous age.

Primary analyses assessed for the interaction effects of HIV and aging. Multivariate analysis of covariance (MANCOVA) models were employed to assess the extent to which all baseline scores were explained by HIV status, age, and their interaction while covarying for gender, years of education, and ethnicity. Thus, the multivariate dependent variable was composed of baseline scores for all four neurocognitive tests. For analyses of longitudinal neurocognitive performance, change scores were calculated by subtracting scores at baseline from those at 12-month follow-up visits. The MANCOVA model was also applied to analyze all change scores. These models were run with age as a dichotomous variable as well a continuous variable. To assess the HIV and aging effects on each individual cognitive score at baseline and its associated change score, Analysis of Covariance (ANCOVA) models were employed to analyze each score using the same predictors and covariates as in the MANCOVA.

Our finding of interest was further analyzed to gather effect sizes. In order to calculate Cohen's d , participants were split into four groups: younger (below age 55) HIV–, older (age 55 and above) HIV–, younger HIV+ and older HIV+. Following these analyses, participants' scores were converted into T scores corrected for age, education, and gender to compare scores to established norms (R. H. B. Benedict et al., 1996; R. Benedict, Schretlen D, Groninger L, Dobraski M, Shpritz B, 1996; R. Heaton, Miller W, Taylor M, Grant I, 2004).

Results

Means and standard deviations of raw test scores by HIV status and age are presented in Table 2. Also displayed are adjusted change scores, which are derived from normalizing education, gender, and ethnicity across participants before calculating the change from baseline to follow-up. These scores more accurately reflect the final results, given that analyses controlled for these demographic variables.

There were no significant main effects of HIV or age on baseline learning and memory performance in the MANCOVA models, nor were there significant interaction effects, regardless of whether age was dichotomous or continuous. In the MANCOVA analysis with dichotomous age, the multivariate outcome was significantly associated with education (MANCOVA, $F(4, 73) = 6.58, p < .001$), gender (MANCOVA, $F(4, 73) = 3.51, p = .011$), and ethnicity (MANCOVA, $F = 3.30, p = .016$). Follow-up ANCOVA analyses revealed no significant main effects of HIV or age group on any single baseline cognitive test and no significant HIV by age group interactions. Higher education was significantly associated with higher scores on BVMT-R-Sum ($\beta = 1.08, t = 3.95, p < .001$), BVMT-R-Delay ($\beta = 0.37, t = 3.00, p = .004$), HVLT-R-Sum ($\beta = 0.95, t = 4.90, p < .001$), and HVLT-R-Delay ($\beta = 0.50, t = 4.72, p < .001$). Female gender was significantly associated with higher scores on HVLT-R-Sum ($\beta = 2.71, t = 2.68, p = .009$) and HVLT-R-Delay ($\beta = 1.40, t = 2.57, p = .012$). Finally, Caucasian participants had significantly higher scores on BVMT-R-Sum ($\beta = 4.04, t = 2.76, p = .007$) and HVLT-R-Sum ($\beta = 2.72, t = 2.63, p = .01$).

There was a significant main effect of age group on changes in learning and memory performance from baseline to year one follow-up (MANCOVA, $F(4, 73) = 4.83, p = .002$), and a significant HIV by age group interaction (MANCOVA, $F(4, 73) = 3.05, p = .02$). There were no significant effects of education, gender, or ethnicity on the multivariate change outcome. Follow-up ANCOVA analyses produced no significant associations between the predictors of interest – HIV, age group, and the HIV by age group interaction – and change in HVLT-R-sum or either of the two BVMT-R indices. However, the HIV by age group interaction was significantly associated with change in HVLT-R-Delay ($t = -2.76, p = .007$). The HIV by age interaction was also significantly associated with change in HVLT-R-Delay when age was included as a continuous predictor, ($t = -2.10, p = .04$). Figure 1 depicts the HVLT-R-delay change scores as a function of age for HIV+ and HIV– groups. Among the HIV infected participants, there was a significant effect of age ($\beta = -0.1, t = -2.09, p = .04$) such that younger participants did not show significant change in verbal memory performance over one year, but with increasing age, HIV+ participants showed increasingly greater decline. Among the seronegative controls, there was no significant effect of age on change in performance over one year, ($\beta = .05, t = .89, p = .38$), such that the younger participants did not differ significantly from the older. The difference between the effect of age on the HIV+ group and the effect of age on the HIV– group was significant ($t = -2.10, p = .04$). Large effect sizes were evident when comparing change in HVLT-R-delay scores for older HIV+ individuals with changes in scores of younger HIV+ individuals ($d = -.90$), older HIV– individuals ($d = -2.15$), and younger HIV– individuals ($d = -1.11$).

Figure 1. Change in performance on HVLT-R-Delay as a function of age for HIV+ and HIV – groups. Results are displayed as means with 95% confidence bands. Change is defined as the difference between baseline and follow-up scores (12 months – 0 months).

Examination of demographically corrected T scores revealed average performance at baseline and follow-up visits for all HIV– participants. Younger HIV+ participants had mildly impaired scores for HVLT-R-Sum and HVLT-R-Delay at baseline, but improved at follow-up. The older HIV+ group showed decline on all cognitive indices, scoring in the mildly impaired range at follow-up on BVM-T-R-Sum, BVM-T-R-Delay, and HVLT-R-Sum, and mild-to-moderately impaired on HVLT-R-Delay. Impairment descriptors are based on published research on normative deficits in HIV (Carey, et al., 2004).

Secondary analyses examined other aspects of cognition measured by the HVLT-R and BVM-T-R. The same independent variables and covariates described above were used to predict encoding (one analysis with Learning Trial 1 scores as the outcome and one with Learning Trial 3 – 1 as the outcome), consolidation (% of Learning Trial 3 retained at delayed free recall), and recognition (discriminability index). There were no significant associations between predictors and baseline performance or change over time on any of these outcome measures.

The relationships between age and HIV disease variables (duration of infection, detectable plasma HIV RNA, CD4 nadir, cART status, and HCV coinfection) were assessed in the HIV + participants for possible confounding effects of these disease variables with age, given that analyses examine the main effects of age and HIV by age interactions. Regression analyses for continuous variables and t-tests for dichotomous variables were conducted. The only significant finding was an association between younger age and detectable plasma HIV RNA ($t = 2.21, p = .04$). Therefore, detectable plasma HIV RNA and its interaction with age were included as predictors in the previously described ANCOVA analysis with our outcome of interest, change in HVLT-R-Delay, as the outcome variable. Including these predictors did not alter the result, regardless of whether age was dichotomous or continuous, and the age by HIV RNA interaction was not significant ($p = 0.17$).

There were significant group differences in rates of active HCV infection. However, only three seronegative participants had active HCV, so we could not include presence of HCV as a covariate. Therefore, all analyses of neurocognitive variables were run without data from these 3 participants and outcomes were compared with analyses that did involve these participants. There were no significant differences between the two sets of analyses, so the reported results include data from these three participants.

Baseline depression and lifetime history of cocaine dependence were also significantly different between HIV groups, so their change over time and influence on cognitive variables were examined. A repeated-measures ANOVA revealed that, while both HIV groups had decreased levels of depression at follow-up, there was no significant interaction with HIV, signifying that the HIV+ and HIV– groups improved in depression scores at the same rate. Another repeated-measures ANOVA showed that rates of lifetime history of cocaine dependence, as defined by KMSK scores, did not change from baseline to follow-up.

visits for either the HIV+ or the HIV- group. Mixed between-within ANOVAs assessed for influence of these variables on cognitive performance. There was no significant effect of depression or lifetime history of cocaine dependence on testing scores, nor was there any significant interaction of cocaine dependence by HIV status or age. This indicated that neither depression nor lifetime history of cocaine dependence had any significant effect on test performance for participants, regardless of age or HIV status.

Similar analyses were conducted to examine whether changes in learning and memory varied as a function of race or ethnicity. Changes in learning and memory over time were not significantly influenced by race/ethnicity, nor were they influenced by the interaction of HIV by race/ethnicity.

Of the 131 participants enrolled in the study, 47 people (31 HIV+, 16 HIV-) dropped out prior to the second visit. Participants were grouped according to attrition status, and demographic, clinical, and cognitive characteristics were compared between groups using Fisher's exact tests for categorical variables and t-tests for continuous variables. Groups did not differ significantly on any demographic or HIV-associated clinical characteristics except lifetime history of alcohol dependence, which was more prevalent in the attrition group (Fisher's exact test, $p = .03$). To examine the influence of alcohol dependence on the outcome of interest, lifetime history of alcohol dependence was included as a covariate in the previously described ANCOVA analysis with change in HVLT-R-Delay as the outcome variable. The HIV by age interaction remained significant regardless of whether age was dichotomous ($t = -2.72$, $p = .008$) or continuous ($t = -2.04$, $p = .04$). Attrition groups also differed significantly on cognitive performance at baseline. Raw scores indicate that participants who dropped out before the second visit performed worse on BVMT-R-Sum ($p = .023$), BVMT-R-Delay ($p = .024$), HVLT-R-Sum ($p = .024$), and HVLT-R-Delay ($p = .039$).

Discussion

Findings from this study are among the first to demonstrate greater declines in verbal memory performance among older HIV+ adults compared to younger HIV+ adults, and also compared to younger and older seronegative controls. In fact, declines on verbal memory performance were only evident among the older participants with HIV, and increasing age exacerbated this effect. Younger people infected with HIV did not show a decline in HVLT-R delayed recall score at one-year follow-up, and neither did seronegative controls, regardless of age, supporting our hypothesis that HIV accelerates age-associated memory impairments. It is noteworthy that the HIV by age interaction was a significant predictor of verbal memory decline, indicating that HIV affects cognitive performance differentially depending on age. Large effect sizes were evident when comparing older HIV+ participants to all others, indicating that verbal memory decline was dramatically different in this group. In sum, HIV and age effects appear to interact and result in verbal memory decline among older people with HIV.

Several past studies have examined cognition as a function of age and serostatus (Ciccarelli et al., 2012; Cysique et al., 2011; Kissel et al., 2005; Scott et al., 2011; Valcour et al., 2011;

van Gorp et al., 1994), but none to date have studied longitudinal change in memory. While cross-sectional studies provide useful information regarding the relationship between HIV, age, and cognition, they can only be used to make inferences about how abilities change over time in individuals based on age and HIV status. Longitudinal methods are necessary to directly address whether cognition differentially declines as a function of HIV status and age because they allow for measurement of individuals as they age rather than comparing younger and older groups. This likely explains why our data show a significant interaction between HIV and age effects while previous studies did not. In fact, the HIV by age interaction did not significantly explain baseline performance on any task, which is in accordance with the lack of an interaction effect in previous cross-sectional research (Ciccarelli et al., 2012; Cysique et al., 2011; Kissel et al., 2005; Scott et al., 2011; Valcour et al., 2011; van Gorp et al., 1994; Wilkie et al., 2003). It is probable that the interactive relationship between the effects of serostatus and age, where the impact of one depends on the level of the other, can only be observed in longitudinal data. This notion is further supported by the results of another longitudinal study examining the effects of HIV and age on cognition. Sacktor et al. compared change in psychomotor performance between HIV+ and HIV- individuals and found that while the seronegative group did not decline in ability, the HIV+ group declined more with advancing age (Sacktor et al., 2010). This interaction effect coincides with our own longitudinal data.

Demographically corrected T scores, displayed in Table 3, show average learning and memory performance among all HIV- participants. HIV+ participants, however, showed mildly impaired performance on several neurocognitive tests. Test scores in this range have been associated with functional deficits in HIV+ populations (Heaton et al., 2004). Furthermore, T scores in the range of 35 – 39 are linked with deficit scores of 1, which are associated with clinically significant neuropsychological impairment (Carey et al., 2004). Thus, our results suggest that younger HIV+ adults exhibited clinically significant impairment relative to normative data on baseline verbal learning and memory. Older HIV+ adults showed clinically significant impairment on only verbal memory at baseline, but on all four cognitive conditions at follow-up. Given that the older HIV+ adults showed decline on all cognitive tests from baseline to follow-up, it may be concluded that changes in this group were clinically significant. However, based on the scope of the current study, it was not possible to derive reliable change indices, as we did not have an adequate reference sample of older adults.

Studies examining the main effects of HIV and age on memory function have found significant group differences in verbal and visuospatial learning and memory performance (Ciccarelli et al., 2012; Kissel et al., 2005; Scott et al., 2011), whereas the present study did not. This study's lack of group differences in baseline testing may be attributed to the test scores of the younger participants, which were higher than expected in the younger HIV+ adults and lower than expected in the younger seronegative controls. This further supports the need for longitudinal research, in which individuals are compared to their own baseline performance rather than to a different, younger group of participants, as longitudinal research reduces the amount of statistical error and provides greater sensitivity for detecting differences in learning and memory performance as a function of age and HIV status.

This study adds to a growing body of literature showing increasing prevalence of memory deficits in asymptomatic people with HIV (Cysique et al., 2004; Heaton et al., 2011). While problems with learning and memory have been described in people with HIV and AIDS since the early days of the disease (Navia, Jordan, & Price, 1986), they were uncommon in asymptomatic individuals, and HIV was typically associated with impairments in attention, executive, and psychomotor functions. Still, the articles showing increased prevalence of memory deficits conclude that the dysexecutive pattern of deficits in asymptomatic HIV+ individuals remains the same, as memory deficits stem from difficulties with encoding and learning new information. The current study shows that in the younger group with HIV, there is indeed evidence of both learning and memory impairment. However, the older HIV+ group lacked impairment in encoding/learning paradigms of memory tests at baseline and exhibited mild impairment on verbal memory delayed recall. At follow-up, the same group exhibited deficits in both verbal and visuospatial learning, but deficits were greater on verbal memory delayed recall. This suggests that older individuals with HIV are presenting memory problems that are not entirely related to initial learning and are difficult to explain solely on the basis of attention and executive factors. Subjects were also unimpaired in recognition performance despite deficits in delayed recall, providing evidence that they do not have a primarily amnesic disturbance or severe mesial temporal lobe dysfunction. It is not uncommon for people with mild cognitive impairment (MCI), regardless of the etiology, to show difficulties with delayed memory in the absence of recognition impairments, which go on to be affected at later stages. It is still unclear if that pattern will be the same in HIV, and whether these deficits are reflecting an amnesic MCI or a mix of mesial temporal and frontal system involvement. This effect of greater forgetting was only evident in the older HIV+ participants, implying that both HIV and age are contributing to memory loss in asymptomatic individuals with HIV.

Both HIV and advancing age affect cognition on their own, and it is likely that these risk factors work in combination to produce greater deficits in older infected individuals. Supporting evidence comes from earlier findings that suggest an increased prevalence of neurocognitive impairments among older people with HIV than would be expected from either aging or HIV infection alone (Bhatia, Ryscavage, & Taiwo, 2012). Also, the significant interaction of age by HIV status observed in the current study provides compelling evidence that verbal memory recall worsens disproportionately with age in people with HIV compared to those without the virus, further supporting the notion that the effects of HIV and age are synergistic rather than independent.

Several mechanisms may account for the interactive effects of age and HIV. Studies show that HIV may increase the brain's susceptibility to neurodegeneration (Lawrence & Major, 2002; Valcour, Shikuma, Watters, & Sacktor, 2004). HIV causes chronic inflammation in the brain, which may contribute to the pathogenesis of central nervous system disorders (Minghetti, 2005). Neuroimaging and neuropathological studies provide further evidence. Older age has been associated with white matter abnormalities across many brain regions in people with HIV (Gongvatana et al., 2011). Other changes associated with cognitive deficits that are similar to those occurring in age-associated neurodegenerative diseases have been found to occur in HIV, including increased tau protein and beta amyloid deposition in the brain and abnormal biomarker levels in the cerebrospinal fluid (Anthony, Ramage, Carnie,

Simmonds, & Bell, 2006; Brew, Pemberton, Blennow, Wallin, & Hagberg, 2005; Gisslen et al., 2009; Steinbrink et al., 2013). Increasing age was shown to be a risk factor for amyloid plaque deposition in HIV+ patients (Esiri, Biddolph, & Morris, 1998), and research suggests that the hippocampus is preferentially affected, along with the frontal lobes (Brew, Crowe, Landay, Cysique, & Guillemin, 2009). Whether such pathology reflects neurodegeneration occurring as a manifestation of chronic HIV infection in the context of aging or whether it reflects comorbid neurological brain disease in a proportion of HIV– infected populations as they reach advanced age remains an open question. Some recent findings suggest that tau protein and beta amyloid occur differently in HIV and Alzheimer’s disease (Ances et al., 2012).

Research comparing HIV+ and HIV– participants found decreased volumes of the hippocampus, an important brain structure for learning and memory, in seropositive adults (Archibald et al., 2004; Chang et al., 2011). Furthermore, volume differences in this region correlate with performance on neuropsychological testing in HIV infected individuals (Chang et al., 2011; Kuper et al., 2011). Cohen et al. previously showed that in people with HIV, reduced hippocampal volume is associated with disease history factors (CD4 nadir and duration of infection) (Cohen, Harezlak, Schifitto, et al., 2010) and N-acetylaspartate, a cerebral metabolite that indicates neuronal loss (Cohen, Harezlak, Gongvatana, et al., 2010). These findings are especially salient given the increasing memory problems in elderly HIV+ individuals.

While it is possible that HIV associated neurodegenerative changes account for the observed findings, other age-related comorbidities could play a role. HIV infected adults experience an increase in cardiovascular disease, diabetes mellitus, and metabolic disturbances (Guaraldi et al., 2011). Each of these comorbidities can cause cerebral dysfunction in its own right. As people with HIV are now reaching advanced age, they are subject to prolonged exposure to cART, which may cause toxicities that contribute to abnormal adiposity, renal and kidney dysfunction, neuropathy, and perhaps cerebral dysfunction as well (High et al., 2012). Each of these factors may contribute to HAND and explain the interaction of age and HIV as risk factors for cognitive decline.

There are a few potential limitations to this study. Some of the seronegative participants were as old as 74, whereas the oldest participant with HIV was 64. Given that significant declines were found in such a young HIV+ population, however, it seems likely that these effects will be even greater when looking at older people with a more prolonged duration of HIV infection. Second, longitudinal measurements spanned only one year. Despite the restricted time frame, current significant findings raise concern that older HIV infected people may experience ongoing memory decline, though future studies with longer follow-up periods are needed to determine whether this is the case..

Patients who dropped out of the study after the baseline visit had poorer neurocognitive functioning than those who remained in the study. This effect is not surprising, as greater study attrition is common among participants with the greatest illness severity or functional impairment(Chatfield, Brayne, & Matthews, 2005). The age of participants who dropped out did not differ significantly from those who completed both visits. Also, there were almost

twice as many HIV+ subjects who dropped out than HIV-. Thus, while definitive conclusions cannot be reached regarding how these individuals would have performed over time, interaction effects of HIV by age on decline in verbal memory would likely have been even greater had analyses included data from those participants who dropped out of the study.

The clinical sample examined in this study closely resembled the demographic characteristics of seropositive people from Southeastern New England. It is possible that people from this region differ in demographic and clinical characteristics from people in other parts of the world, which should be considered for generalization of results.

In conclusion, HIV and age act in combination to produce greater memory declines in older infected individuals. These findings are relevant for individuals aging with HIV, as cognitive status is predictive of functional ability in everyday activities as well as morbidity and mortality. Given that the populations studied were non-demented, these results show early cognitive changes that precede functional decline, thus exposing opportunities for intervention. As the population with HIV ages, it is important to investigate the effects of the disease, comorbid conditions, and age on cognition. Future research is needed to delineate the individual contributions of these risk factors to cognitive decline, as well as their combined effect, and potentially answer the question of whether or not HIV is accelerating the aging process. Further research is also warranted to examine the mechanisms producing these observed cognitive changes, including investigations of structural and functional neurological biomarkers.

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Figure 1. Change in performance on HVL T-R-Delay as a function of age for HIV+ and HIV- groups. Results are displayed as means with 95% confidence bands. Change is defined as the difference between baseline and follow-up scores (12 months – 0 months).

Table 1

Demographic and Clinical Characteristics

Demographic Characteristics	HIV+ (<i>n</i> = 54)	HIV- (<i>n</i> = 30)
Age (years)	49.4 (6.3)	53.3 (8.6) *
Education (years)	12.7 (2.3)	14.5 (3.3) *
% Male	64.8	53.3
Race/Ethnicity		
% Caucasian	55.6	80.0
% African American	20.4	13.3
% Latino	11.1	0
% Asian	1.9	0
% Other Race	11.1	6.7
Psychiatric Characteristics		
CES-D Score	21.5 (13.9)	11.2 (8.9) *
% Lifetime Alcohol Dependence	55.6	40.0
% Lifetime Cocaine Dependence	57.4	13.3 by
% Lifetime Opiate Dependence	20.4	6.7
Clinical Characteristics		
% with active HCV	40.7	6.7 *
HIV Duration (years)	14.3 (6.4)	
% Undetectable HIV RNA	77.8	
Current CD4	420 (252)	
CD4 Nadir (cells/ μ L)	153 (154)	
% on cART	92.6	

Note. Results are presented as means. Standard deviations in parentheses. CES-D = Center for Epidemiologic Studies Depression Scale; HCV = Hepatitis C Virus; cART = Combination Antiretroviral Therapy

*
 $p < .05$

Table 2

Neurocognitive Performance by HIV Status and Age Group

HIV Status	Age Group	Test	Baseline	Follow-Up	Change
HIV –	Younger N=21	BVMT-R-Sum	20.86 (8.65)	22.67 (7.11)	1.81 (4.92)
		BVMT-R-Delay	8.14 (3.53)	9.10 (2.43)	0.95 (1.66)*
		HVLT-R-Sum	24.14 (5.92)	26.19 (5.26)	2.05 (3.68)*
	Older N=9	HVLT-R-Delay	8.24 (3.05)	8.71 (2.74)	0.48 (2.18)
		BVMT-R-Sum	23.33 (5.07)	23.67 (5.77)	0.33 (4.90)
		BVMT-R-Delay	9.33 (1.66)	9.44 (2.13)	0.11 (1.90)
HIV +	Younger N=40	HVLT-R-Sum	25.33 (3.17)	28.33 (0.73)	3.00 (3.57)*
		HVLT-R-Delay	9.56 (1.59)	10.44 (1.24)	0.89 (1.17)
		BVMT-R-Sum	21.13 (6.65)	22.73 (6.44)	1.60 (5.41)
	Older N=14	BVMT-R-Delay	8.50 (2.89)	9.43 (1.91)	0.93 (2.47)*
		HVLT-R-Sum	23.25 (4.70)	24.50 (5.28)	1.25 (4.02)
		HVLT-R-Delay	7.73 (2.66)	8.65 (2.84)	0.93 (2.13)*
		BVMT-R-Sum	18.21 (4.69)	15.14 (8.51)	-3.07 (7.58)
		BVMT-R-Delay	7.71 (2.92)	6.57 (4.16)	-1.14 (3.13)
		HVLT-R-Sum	23.50 (5.35)	26.79 (15.45)	3.29 (16.48)
		HVLT-R-Delay	7.85 (2.30)	7.43 (4.96)	-0.62 (4.66)

Note. Results are presented as means (with standard deviations in parentheses) of raw uncorrected scores. BVMT-R = Brief Visuospatial Memory Test – Revised; HVLT-R = Hopkins Verbal Learning Test – Revised. Young = 40–54 years; old = 55 years and above. Adjusted change score = raw scores based on normalized education, gender, and ethnicity.

* Significant mean change (paired *t* test, *p* < .05, two-sided)

Table 3

Demographically corrected T scores for neurocognitive performance by HIV status and age group

HIV Status	Age Group	Test	Baseline	Impairment Severity	Follow-Up	Impairment Severity
HIV –	Younger N=21	BVMT-R-Sum	43.25 (17.21)	Normal	47.00 (14.18)	Normal
		BVMT-R-Delay	44.52 (18.45)	Normal	49.63 (12.91)	Normal
		HVLT-R-Sum	40.37 (14.84)	Normal	45.58 (13.03)	Normal
		HVLT-R-Delay	40.45 (16.24)	Normal	42.94 (14.45)	Normal
	Older N=9	BVMT-R-Sum	52.17 (9.40)	Normal	53.30 (10.19)	Normal
		BVMT-R-Delay	52.55 (8.09)	Normal	53.10 (10.38)	Normal
		HVLT-R-Sum	47.98 (7.65)	Normal	55.13 (11.09)	Normal
		HVLT-R-Delay	50.56 (8.50)	Normal	55.32 (6.28)	Normal
HIV +	Younger N=40	BVMT-R-Sum	43.00 (13.37)	Normal	46.57 (12.82)	Normal
		BVMT-R-Delay	45.63 (15.77)	Normal	50.89 (10.24)	Normal
		HVLT-R-Sum	37.94 (11.59)	Mild	41.09 (13.05)	Normal
		HVLT-R-Delay	37.62 (13.84)	Mild	42.21 (15.41)	Normal
	Older N=14	BVMT-R-Sum	41.10 (8.81)	Normal	36.17 (15.84)	Mild
		BVMT-R-Delay	44.66 (14.24)	Normal	36.29 (16.57)	Mild
		HVLT-R-Sum	40.49 (12.73)	Normal	38.87 (13.17)	Mild
		HVLT-R-Delay	39.81 (12.05)	Mild	34.04 (18.17)	Mild-Moderate

Note. Results are presented as Mean (Standard Deviation)

Young = 40 – 54; Old = 55 and above

Impairment severity based on published research on normative deficits in HIV (Carey, et al., 2004).