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A History of Alcohol Dependence Augments HIV-associated Neurocognitive Deficits in Persons Aged 60 and Older

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Abstract

Background—Excessive alcohol use is common among people living with HIV. Given the growing prevalence of older HIV+ adults, and observations indicating higher risk for neurocognitive impairment in older adults with either HIV infection or alcoholism, an increased understanding of their combined impact in the context of this increasingly aged population is crucial.

Methods—We conducted comprehensive neurocognitive assessment in 112 older HIV+ individuals aged 50 to 69 years. Regression analyses were conducted to examine the interaction between age and the presence of lifetime alcohol dependence on neurocognitive measures, controlling for years of education, hepatitis C serostatus, and lifetime non-alcohol substance use disorder.

Results—Significant interactions of age and alcohol dependence history were found for global neurocognitive function, which was driven by the domains of executive function, processing speed, and semantic memory. Follow-up analyses indicated adverse effects of alcohol use history on neurocognitive measures that were evident only in HIV+ individuals 60 years and older.

Conclusions—While mounting evidence in younger cohorts indicates adverse synergistic HIV/alcohol effects on neurocognitive function, our novel preliminary findings in this elderly HIV+ cohort demonstrated the importance of even a relatively distant alcohol use history on the expression of HIV-associated neurocognitive disorders that may not become apparent until much later in life.

Keywords

HIV infection; alcohol use disorder; aging; neurocognitive impairment

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INTRODUCTION

Older adults constitute an increasing proportion of people living with HIV disease. The most recent CDC report indicates that 35% of HIV-infected individuals in the US are age 50 and above, which represents a significant rise from 17% in 2001 (Centers for Disease Control and Prevention, 2013). This steady increase has been attributed to both the success of combination antiretroviral therapy (cART) in reducing the rate of mortality associated with HIV/AIDS, and recent findings indicating increasing rates of HIV seroconversion among older adults (Antiretroviral Therapy Cohort Collaboration, 2008; Centers for Disease Control and Prevention, 2013; Department of Health and Human Services, 2012). This demographic shift presents a significant public health concern given mounting evidence indicating that health burden typically affecting older adults may be augmented in the context of HIV disease. Increased risks for cardiovascular, liver, kidney, and bone diseases, and non-AIDS cancers have been reported in cART-receiving cohorts (Brown and Qaqish, 2006; Currier *et al*, 2008; Kirk *et al*, 2007; Neuhaus *et al*, 2010; Weber *et al*, 2006). Importantly, individuals with chronic HIV disease still have a shorter expected lifespan than the general population despite potent antiretroviral therapy (ART) (Bhaskaran *et al*, 2008). Moreover, the rate of HIV-associated neurocognitive disorders (HAND) appears to be higher in older adults (Valcour *et al*, 2004). The mechanisms underlying age-related complications in chronic HIV disease remain inadequately understood, although possible contributors include chronic inflammation, use of certain ART drugs, metabolic disorders, in addition to the high prevalence of behavioral risk factors such as alcohol and substance abuse observed in HIV-infected people (Deeks, 2011; Justice, 2010).

Excessive alcohol use is common among HIV-infected individuals, with an estimated prevalence of current heavy drinking of at least 8%, which is almost twice the rate of the general population (Galvan *et al*, 2002). A recent national cohort study found that nearly half of persons living with HIV have a lifetime history of an alcohol use disorder (Byrd *et al*, 2011). Alcohol consumption in the context of HIV disease has been linked to higher viral replication, adverse interaction with ART drugs, poor ART adherence, accelerated disease progression, and greater blood-brain barrier permeability (Bryant, 2006; Cook *et al*, 1997; Hendershot *et al*, 2009; Meyerhoff, 2001; Purcell *et al*, 2001; Samet *et al*, 2007; Shiu *et al*, 2007). While the impact of HIV disease and alcoholism on the brain is each well established (Grant, 1987; Heaton *et al*, 1995), relatively few studies have examined their combined effects on neurocognitive and brain abnormalities. Available studies conducted in young and middle-age cohorts have indicated adverse synergistic effects on structural and metabolic brain integrity, in addition to neurocognitive function involving working and episodic memory, verbal reasoning, and reaction time (Fama *et al*, 2009; Green *et al*, 2004; Moore *et al*, 2014; Pfefferbaum *et al*, 2005; Pfefferbaum *et al*, 2007; Pfefferbaum *et al*, 2006; Pfefferbaum *et al*, 2012). Existing findings in seronegative adults with alcoholism indicate increased risk of abnormal neurocognitive and brain alterations with older age (Oscar-Berman and Marinkovic, 2007), while such relationships remain to be examined in the context of HIV disease. Alcohol use disorders have been related to worse everyday functioning among immunocompetent HIV+ individuals and greater neuropsychiatric distress in acute and early infection (Blackstone *et al*, 2013; Weber *et al*, 2013). Whether a

history of excessive alcohol use combines with HIV disease to exacerbate brain injury in older persons is currently unknown. Given the increasingly aged HIV population, better understanding of the neurocognitive impact of alcohol use is crucial. This may be particularly important as people living with HIV reach their seventh decade, during which declines in frontotemporal brain systems and accompanying deficits in memory and executive functions typically occur (Hedden and Gabrieli, 2004). Thus while the existing literature on older HIV-infected adults shows at least additive effects on brain structure and function for persons in their 50s, the combined impact of aging and HIV disease may expand to the point of synergy in the seventh decade and beyond, perhaps especially for individuals with additional risk factors such as alcohol dependence.

To this end, we examined the combined neurocognitive impact of alcohol use history and older age in a cohort of 112 HIV-infected individuals age 50–69 with or without lifetime histories of alcohol dependence. Participants were stratified in age by decades to specifically contrast the effects of alcohol use history in those younger and older than 60 years. We hypothesized that the adverse impact of alcohol use history on global and domain-specific neurocognitive function would be more pronounced in HIV-infected individuals over the age of 60 relative to their younger counterparts.

METHODS

Participants

The 112 participants in this study were recruited from HIV clinics and the local community as part of NIH-sponsored studies at the UC San Diego HIV Neurobehavioral Research Program. The UC San Diego Human Research Protections Program approved all study procedures, and all participants provided written informed consent prior to enrollment. HIV serostatus was confirmed with standard Western blot and/or a point-of-care test (MedMira Inc., Nova Scotia, Canada). Exclusion criteria included estimated verbal IQ score below 70 on the Wechsler Test of Adult Reading (WTAR), history of chronic medical or neurological conditions such as active CNS opportunistic infections, seizure disorders, head injury with loss of consciousness > 30 minutes, stroke with persistent neurological sequelae, non-HIV-associated dementias, or history of severe psychiatric disorders such as schizophrenia. Participants were also excluded if they met DSM-IV criteria for substance use disorders other than alcohol dependence within 30 days prior to evaluation. Participants were not assessed if they screened positive on alcohol breathalyzer or urine drug screen except cannabis on the day of testing.

The participant cohort consisted of HIV-seropositive individuals between 50 to 69 years of age (mean = 56.14, SD = 5.19). Mean estimated duration of HIV disease was 17 years (range = 1, 28). Most participants (90%) were prescribed combination antiretroviral therapy (cART), had suppressed (< 50 copies/mL) HIV RNA in blood (83%), and were not severely immunosuppressed [median current CD4⁺ T-cell count 511/mm³ (range = 33, 1695)]. A majority (63%) of the participants reported nadir CD4⁺ T-cell counts below 200/mm³, indicating history of AIDS. Nearly a third (32%) of the cohort was hepatitis C virus (HCV) seropositive, similar to other reported HIV⁺ cohorts in the US (Devlin *et al*, 2012; Hinkin *et al*, 2008; Jernigan *et al*, 2011).

For the current analysis, participants were stratified based on age (50–59 and 60–69 years) and the presence of a lifetime diagnosis of alcohol dependence. Table 1 summarizes participant characteristics within the groups. The participant groups had comparable gender and ethnicity compositions, estimated VIQ, and the rates of lifetime diagnosis of affective disorders ($p > .10$). The groups also had comparable HIV disease and ART characteristics ($p > .10$). Significant group differences were found in education ($p = .0109$) and HCV serostatus ($p = .0248$), while a marginal group difference was found in lifetime diagnosis of non-alcohol substance use disorders ($p = .0816$). Participants with lifetime history of alcohol dependence in the two age groups did not differ in their age of first alcohol dependence diagnosis, lifetime duration of diagnosis, or duration since the diagnosis was most recently met ($p > .10$).

Medical and Psychiatric Evaluations

Each participant completed a comprehensive medical evaluation including phlebotomy and laboratory assessment of HIV disease. Common comorbidities of HIV disease were evaluated, including HCV serostatus (MedMira Multiplo rapid test; MedMira Inc., Nova Scotia, Canada). Clinical laboratory markers of liver function and injury were also measured, including albumin, total/direct bilirubin, AST/ALT ratio, and alkaline phosphatase.

Lifetime history of alcohol dependence, was established using the Composite International Diagnostic Interview (CIDI version 2.1) (World Health Organization, 1998), which is a computer-assisted, lay-administered psychiatric instrument that yields diagnoses consistent with DSM-IV criteria. Each diagnosis is accompanied by age of onset and how recently the diagnostic criteria were met (Table 1). The research criterion for current disorder was defined as meeting diagnostic criteria within 30 days prior to the assessment. Lifetime history of non-alcohol substance use disorders and affective disorders (i.e., major depressive disorder, dysthymia, anxiety disorders) was also established using the CIDI (Table 1).

Neuropsychological Evaluation

All participants received a comprehensive neuropsychological battery consisting of tests previously demonstrated to be sensitive to HIV-associated neurocognitive disorders (HAND), including those assessing the domains of executive functions, attention/working memory, episodic learning and memory, verbal fluency, processing speed, and fine motor skills (Antinori *et al*, 2007; Heaton *et al*, 2010). Given the emphasis of the current study on older adults, additional tests of the semantic knowledge domain were administered, including the Boston Naming Test (BNT) and the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test (KAIT) (Fama *et al*, 2011; Goodglass *et al*, 2001; Kaufman and Kaufman, 1993). WTAR Verbal IQ (VIQ) (Psychological Corporation, 2001) was used as a measure of estimated premorbid verbal intellectual function.

Raw test scores were converted to demographically adjusted T-scores that corrected for age, education, sex, and ethnicity as appropriate (Heaton *et al*, 2004; Norman *et al*, 2011). T-scores for measures within each domain were averaged to derive a domain T-score, reflecting neurocognitive function within each domain. Similarly, T-scores across all

measures in the battery were averaged to derive the global T-score, with higher score reflecting better function.

Statistical Analysis

Statistical analyses were conducted in R version 3.0.1 (<http://www.r-project.org>). Between-group comparisons of participant characteristics were conducted using analysis of variance or Chi-squared tests as appropriate. CD4+ T-cell variables were square root-transformed prior to group comparison due to skewed distributions. A series of linear multiple regression models were used to examine the independent contributions of a set of predictors on each neurocognitive variable. Primary predictors in each regression model consisted of age group (50–59 and 60–69 years), presence of lifetime diagnosis of alcohol dependence, and an interaction term of these variables. All models also included years of education, HCV serostatus, and the presence of lifetime diagnosis of any non-alcohol substance use disorder to account for group differences in these covariates. We employed a two-tiered analytic approach to examine the neurocognitive variables. First, the effects of clinical variables on global neurocognitive function (global T-score) were examined. Second, the clinical effects on the T-scores for individual neurocognitive domains were examined. Significant interaction effects were followed-up by simple effects analyses examining the effects of lifetime alcohol dependence within each age group, covarying for the same variables as above. In addition, the distributions of T-scores within participant groups were graphically represented to visualize the directions of these simple effects.

RESULTS

The global and relevant domain neurocognitive T-scores, stratified by age group and lifetime diagnosis of alcohol dependence, are graphically represented in Figure 1. Table 2 shows the parameter estimates indicating effect sizes and directions, and associated p-values from the primary regression analyses.

Global Neurocognitive T-score

A regression analysis of the global T-score showed a significant age*alcohol interaction ($\beta = -6.50$, $p = .0147$). Follow-up simple effect analyses indicated a significant negative effect of lifetime alcohol dependence in the older participant group ($\beta = -7.00$, $p = .0109$), which was absent in the younger group ($p = .2458$).

Another regression analysis was conducted to examine the effects of age as a continuous variable and its interaction with alcohol dependence history, with the same covariates included in the model. Results from this analysis also indicated a significant age*alcohol interaction ($\beta = -0.51$, $p = .0323$), corroborating the results from the age-group analysis above.

Domain Neurocognitive T-scores

A series of regression analyses examining individual domain T-scores showed significant age*alcohol interactions in the executive function ($\beta = -7.99$, $p = .0319$), processing speed ($\beta = -10.33$, $p = .0090$), and semantic memory ($\beta = -11.11$, $p = .0078$) domains. Follow-up

simple effect analyses of the interaction terms indicated significant negative effects of lifetime alcohol dependence on executive function ($\beta = -7.07$, $p = .0194$) and processing speed ($\beta = -7.63$, $p = .0217$) in the older participant group, while these effects were absent in the younger group ($p = .6740$ and $.6470$, respectively). A trend was found indicating a beneficial effect of an absence of lifetime alcohol dependence on semantic memory ($\beta = -6.87$, $p = .1044$) in the older participant group, but not in the younger group ($p = .3010$). Finally, a significant main effect of age was found in the learning domain ($p = .0094$).

DISCUSSION

Excessive alcohol use is common among HIV-infected persons. Given the growing prevalence of older adults living with HIV, and observations that older adults with either HIV disease or alcoholism are at higher risk for neurocognitive impairment, a better understanding of the combined impact of HIV disease and alcohol use in the context of this increasingly aged population is crucial. In this preliminary study, we examined a cohort of 112 older HIV-infected individuals ranging in age from 50 to 69 who differed by lifetime history of alcohol dependence. A notable strength of the current analysis is the inclusion of HIV+ individuals over the age of 60, which permitted an examination of the impact of HIV disease and alcohol use history in an increasingly prevalent population that remains underrepresented in the neuroAIDS literature. Consistent with our expectations, significant interactions between age and alcohol dependence were found regardless of whether age was included in the statistical models as a grouping or continuous variable. Follow-up analyses within age groups indicated an adverse impact of alcohol use history on neurocognitive function that was evident only in HIV+ participants 60 years and older. These findings were apparent in global neurocognitive function, as well as performances in the executive function, processing speed, and semantic memory domains (Figure 1).

While the current findings indicate a moderating role of alcohol use history on the expression of HAND that is specific to older individuals, the mechanisms underlying the importance of this lifetime alcohol use variable are unclear. An intriguing aspect of the current study is that none of our alcohol dependent participants met criteria for a current diagnosis at the time of the neuropsychological assessment. In fact, participants had not met alcohol dependence criteria for an average of 13 years. Several putative mechanisms may explain the observed residual neurocognitive impact of alcohol use history in older adults. First, the impact of alcohol use on HIV RNA levels and immune deficiency earlier in the course of the disease could increase the risk of HAND later in life, similar to a recent report in the context of methamphetamine use (Ellis *et al*, 2011; Iudicello *et al*, 2014; Seigniny *et al*, 2004). Second, the impact of alcohol use in the past on the liver could worsen age-associated declines in hepatic functioning (Floreani, 2007). This could then lead to brain injury by predisposing individuals to subclinical hepatic encephalopathy (Schiff *et al*, 2013), toxicity by reduced metabolism of ART and other prescribed drugs, or vascular disease due to coagulation imbalances (Deeks *et al*, 2013). Third, past alcohol use could injure the brain and reduce cognitive reserve, which may make individuals more vulnerable to additional insults to the brain, such as those related to HIV disease and aging. Finally, the combination of HIV disease and older age may results in a diminished capability to recover from brain injury related to alcohol abuse despite prolonged abstinence. While many possibilities exist,

the specific neuropathophysiological pathways for such mechanisms remain to be determined. Further investigations of the roles of more recent alcohol use and the quantity and chronicity of alcohol exposure during the lifetime are needed to examine specific contributions of recent and distant alcohol use history.

We also considered the possibility that these findings may have been influenced by liver dysfunction. Even though HCV serostatus was included as a covariate in the regression models, we could not rule out the possible role of liver disease on poorer neurocognitive functioning observed in the older remote alcohol users. To examine this issue further, the participant groups were compared on biomarkers of hepatic function and injury described above. The study groups were statistically similar on these laboratory markers ($p > .10$), with the exception of the AST/ALT ratio, which was marginally higher in older participants with alcohol dependence history relative to the younger groups ($p < .10$). Addition of this variable as a covariate to the regression models did not alter the significance of the age and alcohol results, indicating that our conclusions were not confounded by group differences in liver status. Nevertheless, further investigations in individuals with a wider range of liver disease status, including those related to HCV disease, are necessary to examine the roles of liver abnormalities on neurocognitive function in the context of HIV disease, alcohol use, and aging.

The findings related to executive function and processing speed expand on an extensive existing literature implicating these neurocognitive domains separately in the contexts of aging, HIV disease, and alcoholism (Buckner, 2004; Heaton *et al*, 2010; Oscar-Berman and Marinkovic, 2007). Impairment in these domains may be of particular clinical concern, as they are thought to play an important supportive role in a variety of real-world functions for persons living with HIV, such as ART adherence (Hinkin *et al*, 2002). In addition, alcohol use disorders have been related to worse everyday functioning among immunocompetent HIV+ individuals (Blackstone *et al*, 2013). It should be noted that the subtests within the executive function domain in our assessment battery (e.g., Tower of London - Total Moves index, and Trail Making Test B) prominently involve visually mediated planning, complex attention, and sequencing abilities, which are of particular relevance to the right-hemisphere hypothesis of alcoholism (Oscar-Berman and Marinkovic, 2007), and may contribute to the sensitivity of this domain. Future studies examining other aspects of executive function, including those involving abstraction, cognitive flexibility, and ecologically relevant constructs such as multitasking, are needed to further explore the effects of these clinical factors. Further investigations are needed to delineate the nature of the combined and likely synergistic impact of these clinical factors on neurocognitive function and their neuroanatomical correlates.

We also observed an interaction between older age and alcohol use history on semantic memory, which describes one's memory for general information (e.g., facts, concepts) and in this case was measured by tests of confrontational naming of objects and famous faces. Prior studies show that in younger and middle-aged HIV-infected persons, alcohol dependence is associated with deficits in the sequencing and free recall of remote semantic information (Fama *et al*, 2011). In the present study, the semantic memory interaction was driven by marginally *better* performance in the non-alcohol 60+ participants relative to the

other three study groups. This pattern, which runs in contrast to those in the executive and processing speed domains, suggests the possibility that the older participants without alcohol history may have higher levels of cognitive reserve which prior studies indicate may serve a protective role against HAND (Morgan *et al*, 2012). Alternatively, prior alcohol use history in older HIV+ participants may inhibit the relative stability and enhancement of semantic memory commonly observed with normal aging (Nilsson, 2003). These possibilities remain to be explored in future studies examining additional aspects of semantic memory.

While the relatively small number of participants age 60 and above with alcohol dependence history is a limitation of the study, it should be noted that our findings reached significance despite the associated modest statistical power, indicating robust effect sizes. To our knowledge, the inclusion of these elderly HIV+ individuals is a unique contribution of our study to the literature. Moreover, the proportion of this participant group in our cohort likely reflects the actual prevalence of HIV+ individuals with these characteristics in the community, which while remaining relatively low will likely increase together with the rising prevalence of older HIV+ people. While our clinical comorbidity ratings indicate that this participant group exhibited a relatively high prevalence of co-occurring conditions possibly contributing to worse neurocognitive function (Antinori *et al*, 2007), the addition of this regressor to the statistical models did not alter our findings. Nevertheless, future studies are needed that further examine the effects of individual comorbid factors in the context of HIV infection, alcohol use, and aging.

Mounting evidence indicates that HIV and alcohol synergistically worsen neurocognitive function and brain integrity (Fama *et al*, 2009; Green *et al*, 2004; Pfefferbaum *et al*, 2005; Pfefferbaum *et al*, 2007; Pfefferbaum *et al*, 2006; Pfefferbaum *et al*, 2012). Our novel preliminary findings specific to elderly HIV+ individuals provide important information for clinicians when considering the potential long-term neurocognitive impact of heavy alcohol use, which may not become apparent until much later in life, despite refraining from alcohol abuse for many years. Such information is especially relevant when considered together with recent findings linking neurocognitive compromise, quality of life, and mood symptoms in the context of HIV and alcohol (Sassoon *et al*, 2012), which may be exacerbated in older age. Although future studies are needed to further identify specific neurocognitive aspects that are especially relevant to HIV and alcohol, the available findings provide preliminary information for identifying targets for cognitive rehabilitation and other behavioral interventions.

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References

- Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69:1789–99. [PubMed: 17914061]
- Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008; 372:293–9. [PubMed: 18657708]
- Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, Porter K, Collaboration C. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008; 300:51–9. [PubMed: 18594040]
- Blackstone K, Iudicello JE, Morgan EE, Weber E, Moore DJ, Franklin DR, Ellis RJ, Grant I, Woods SP. Translational Methamphetamine ARCG. Human immunodeficiency virus infection heightens concurrent risk of functional dependence in persons with long-term methamphetamine use. *J Addict Med*. 2013; 7:255–63. [PubMed: 23648641]
- Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006; 20:2165–74. [PubMed: 17086056]
- Bryant KJ. Expanding research on the role of alcohol consumption and related risks in the prevention and treatment of HIV/AIDS. *Subst Use Misuse*. 2006; 41:1465–507. [PubMed: 17002990]
- Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*. 2004; 44:195–208. [PubMed: 15450170]
- Byrd DA, Fellows RP, Morgello S, Franklin D, Heaton RK, Deutsch R, Atkinson JH, Clifford DB, Collier AC, Marra CM, Gelman B, McCutchan JA, Duarte NA, Simpson DM, McArthur J, Grant I, Group C. Neurocognitive impact of substance use in HIV infection. *J Acquir Immune Defic Syndr*. 2011; 58:154–62. [PubMed: 21725250]
- Centers for Disease Control and Prevention. HIV Surveillance Report, 2011. 2013.
- Cook RT, Stapleton JT, Ballas ZK, Klinzman D. Effect of a single ethanol exposure on HIV replication in human lymphocytes. *J Investig Med*. 1997; 45:265–71.
- Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, Schouten JT, Smieja M, Working G. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation*. 2008; 118:e29–35. [PubMed: 18566319]
- Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med*. 2011; 62:141–55. [PubMed: 21090961]
- Deeks SG, Tracy R, Douek DC. Systemic Effects of Inflammation on Health during Chronic HIV Infection. *Immunity*. 2013; 39:633–45. [PubMed: 24138880]
- Department of Health and Human Services. Multidisciplinary Studies of HIV/AIDS and Aging (R01) PAR-12-175. 2012.
- Devlin KN, Gongvatana A, Clark US, Chasman JD, Westbrook ML, Tashima KT, Navia B, Cohen RA. Neurocognitive effects of HIV, hepatitis C, and substance use history. *J Int Neuropsychol Soc*. 2012; 18:68–78. [PubMed: 22132928]
- Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, Collier AC, Gelman B, McArthur J, Morgello S, McCutchan JA, Grant I, Group C. CD4 nadir is a predictor of HIV neurocognitive

- impairment in the era of combination antiretroviral therapy. *AIDS*. 2011; 25:1747–51. [PubMed: 21750419]
- Fama R, Rosenbloom MJ, Nichols BN, Pfefferbaum A, Sullivan EV. Working and episodic memory in HIV infection, alcoholism, and their comorbidity: baseline and 1-year follow-up examinations. *Alcohol Clin Exp Res*. 2009; 33:1815–24. [PubMed: 19656122]
- Fama R, Rosenbloom MJ, Sassoon SA, Thompson MA, Pfefferbaum A, Sullivan EV. Remote semantic memory for public figures in HIV infection, alcoholism, and their comorbidity. *Alcohol Clin Exp Res*. 2011; 35:265–76. [PubMed: 21121935]
- Floreani A. Liver diseases in the elderly: an update. *Dig Dis*. 2007; 25:138–43. [PubMed: 17468549]
- Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, Longshore D, Morton SC, Orlando M, Shapiro M. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. *J Stud Alcohol*. 2002; 63:179–86. [PubMed: 12033694]
- Goodglass, H.; Kaplan, E.; Barresi, B. *Boston Diagnostic Aphasia Examination*. 3. Lippincott Williams & Wilkins; Philadelphia: 2001.
- Grant I. Alcohol and the brain: neuropsychological correlates. *J Consult Clin Psychol*. 1987; 55:310–24. [PubMed: 3597943]
- Green JE, Saveanu RV, Bornstein RA. The effect of previous alcohol abuse on cognitive function in HIV infection. *Am J Psychiatry*. 2004; 161:249–54. [PubMed: 14754773]
- Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010; 75:2087–96. [PubMed: 21135382]
- Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, et al. The HNRC 500--neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. *J Int Neuropsychol Soc*. 1995; 1:231–51. [PubMed: 9375218]
- Heaton, RK.; Miller, SW.; Taylor, MJ.; Grant, I. *Revised Comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults*. Psychological Assessment Resources, Inc; Lutz, FL: 2004.
- Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci*. 2004; 5:87–96. [PubMed: 14735112]
- Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. *J Acquir Immune Defic Syndr*. 2009; 52:180–202. [PubMed: 19668086]
- Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, Thrasher D, Goetz MB, Stefaniak M. Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology*. 2002; 59:1944–50. [PubMed: 12499488]
- Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ. Neurocognition in individuals co-infected with HIV and hepatitis C. *J Addict Dis*. 2008; 27:11–7. [PubMed: 18681187]
- Iudicello JE, Morgan EE, Gongvatana A, Letendre SL, Grant I, Woods SP. Translational Methamphetamine ARCG. Detrimental impact of remote methamphetamine dependence on neurocognitive and everyday functioning in older but not younger HIV+ adults: evidence for a legacy effect? *J Neurovirol*. 2014; 20:85–98. [PubMed: 24470237]
- Jernigan TL, Archibald SL, Fennema-Notestine C, Taylor MJ, Theilmann RJ, Julaton MD, Notestine RJ, Wolfson T, Letendre SL, Ellis RJ, Heaton RK, Gamst AC, Franklin DR Jr, Clifford DB, Collier AC, Gelman BB, Marra C, McArthur JC, McCutchan JA, Morgello S, Simpson DM, Grant I. Clinical factors related to brain structure in HIV: the CHARTER study. *J Neurovirol*. 2011; 17:248–57. [PubMed: 21544705]
- Justice AC. HIV and aging: time for a new paradigm. *Curr HIV/AIDS Rep*. 2010; 7:69–76. [PubMed: 20425560]
- Kaufman, AS.; Kaufman, NL. *Kaufman adolescent and adult intelligence test*. Manual. American Guidance Service; Circle Pines, MN: 1993.

- Kirk GD, Merlo C, POD, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis*. 2007; 45:103–10. [PubMed: 17554710]
- Meyerhoff DJ. Effects of alcohol and HIV infection on the central nervous system. *Alcohol Res Health*. 2001; 25:288–98. [PubMed: 11910707]
- Moore RC, Fazeli PL, Jeste DV, Moore DJ, Grant I, Woods SP. Group HIVNRP. Successful cognitive aging and health-related quality of life in younger and older adults infected with HIV. *AIDS Behav*. 2014; 18:1186–97. [PubMed: 24633788]
- Morgan EE, Woods SP, Smith C, Weber E, Scott JC, Grant I. Group HIVNRP. Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). *AIDS Behav*. 2012; 16:2279–85. [PubMed: 22677976]
- Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La Rosa A, Kuller LH, Pett SL, Ristola M, Ross MJ, Shlipak MG, Tracy R, Neaton JD. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis*. 2010; 201:1788–95. [PubMed: 20446848]
- Nilsson LG. Memory function in normal aging. *Acta Neurol Scand Suppl*. 2003; 179:7–13. [PubMed: 12603244]
- Norman MA, Moore DJ, Taylor M, Franklin D Jr, Cysique L, Ake C, Lazarretto D, Vaida F, Heaton RK, Group H. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. *J Clin Exp Neuropsychol*. 2011; 33:793–804. [PubMed: 21547817]
- Oscar-Berman M, Marinkovic K. Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychol Rev*. 2007; 17:239–57. [PubMed: 17874302]
- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Cortical NAA deficits in HIV infection without dementia: influence of alcoholism comorbidity. *Neuropsychopharmacology*. 2005; 30:1392–9. [PubMed: 15812566]
- Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV. Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. *Brain*. 2007; 130:48–64. [PubMed: 16959813]
- Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Adalsteinsson E, Kemper CA, Deresinski S, Sullivan EV. Contribution of alcoholism to brain dysmorphology in HIV infection: effects on the ventricles and corpus callosum. *Neuroimage*. 2006; 33:239–51. [PubMed: 16877010]
- Pfefferbaum A, Rosenbloom MJ, Sassoon SA, Kemper CA, Deresinski S, Rohlfing T, Sullivan EV. Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. *Biol Psychiatry*. 2012; 72:361–70. [PubMed: 22458948]
- Psychological Corporation. Wechsler Test of Adult Reading. Psychological Corporation; San Antonio, TX: 2001.
- Purcell DW, Parsons JT, Halkitis PN, Mizuno Y, Woods WJ. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse*. 2001; 13:185–200. [PubMed: 11547619]
- Samet JH, Cheng DM, Libman H, Nunes DP, Alperen JK, Saitz R. Alcohol consumption and HIV disease progression. *J Acquir Immune Defic Syndr*. 2007; 46:194–9. [PubMed: 17667330]
- Sassoon SA, Rosenbloom MJ, Fama R, Sullivan EV, Pfefferbaum A. Selective neurocognitive deficits and poor life functioning are associated with significant depressive symptoms in alcoholism-HIV infection comorbidity. *Psychiatry Res*. 2012; 199:102–10. [PubMed: 22648011]
- Schiff S, D'Avanzo C, Cona G, Goljahani A, Montagnese S, Volpato C, Gatta A, Sparacino G, Amodio P, Bisiacchi P. Insight into the relationship between brain/behavioral speed and variability in patients with minimal hepatic encephalopathy. *Clin Neurophysiol*. 2013
- Sevigny JJ, Albert SM, McDermott MP, McArthur JC, Sacktor N, Conant K, Schifitto G, Selnes OA, Stern Y, McClernon DR, Palumbo D, Kieburtz K, Riggs G, Cohen B, Epstein LG, Marder K. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. *Neurology*. 2004; 63:2084–90. [PubMed: 15596754]

- Shiu C, Barbier E, Di Cello F, Choi HJ, Stins M. HIV-1 gp120 as well as alcohol affect blood-brain barrier permeability and stress fiber formation: involvement of reactive oxygen species. *Alcohol Clin Exp Res*. 2007; 31:130–7. [PubMed: 17207111]
- Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, Holck P, Grove J, Sacktor N. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology*. 2004; 63:822–7. [PubMed: 15365130]
- Weber E, Morgan EE, Iudicello JE, Blackstone K, Grant I, Ellis RJ, Letendre SL, Little S, Morris S, Smith DM, Moore DJ, Woods SP, Group T. Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection. *J Neurovirol*. 2013; 19:65–74. [PubMed: 23250704]
- Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Akerlund B, Calvo G, Monforte A, Rickenbach M, Ledergerber B, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006; 166:1632–41. [PubMed: 16908797]
- World Health Organization. Composite International Diagnostic Interview (CIDI, version 2.1). Author; Geneva, Switzerland: 1998.

Figure 1.

Boxplots and scatterplots showing global and domain T-scores for the executive function, processing speed, and semantic domains, stratified by age group and lifetime diagnosis of alcohol dependence. Normal neurocognitive performance ($T = 50$) is represented by dotted horizontal lines.

Table 1

Relevant demographic and clinical information of study participants stratified by age group and lifetime diagnosis of alcohol dependence.

Age	50–59		60–69		p
Lifetime Alcohol Dependence	No (n = 60)	Yes (n = 23)	No (n = 20)	Yes (n = 9)	
<u>Demographic Characteristics</u>					
Age (years)	53.60 (2.92)	53.74 (3.03)	63.70 (3.01)	62.44 (3.32)	0.0001 *
Education (years)	14.68 (2.52)	12.65 (2.60)	14.85 (2.11)	13.89 (2.26)	0.0109 *
Gender (% male)	83%	83%	85%	89%	0.9732
Ethnicity (% Caucasian)	70%	57%	85%	56%	0.1845
Estimated Verbal IQ (WTAR)	102.23 (10.79)	98.87 (11.01)	106.6 (10.04)	99.78 (14.10)	0.2840
<u>HIV Disease Characteristics</u>					
Nadir CD4+ T-cells (cells/mm ³)	124 (55, 231)	164 (76, 275)	166 (32, 312)	120 (63, 200)	0.2810
Current CD4+ T-cells (cells/mm ³)	526 (383, 767)	500 (387, 707)	594 (360, 806)	459 (400, 506)	0.2790
Detectable plasma HIV RNA (%)	20%	13%	15%	0%	0.7362
Duration of HIV disease (years)	16.49 (8.44)	16.23 (7.76)	18.28 (5.38)	17.57 (8.86)	0.8100
AIDS (%)	67%	74%	55%	56%	0.5495
ART (% reporting)	88%	96%	90%	89%	0.7949
<u>Medical/Psychiatric Characteristics</u>					
Hepatitis C seropositive (%)	28%	57%	15%	33%	0.0248 *
Lifetime affective disorder (%)	65%	78%	65%	78%	0.6077
Lifetime non-alcohol SUD (%)	60%	78%	40%	67%	0.0816
Cannabis	37%	65%	30%	44%	0.0720
Methamphetamine	33%	57%	0%	22%	0.0009 *
Cocaine	27%	57%	5%	44%	0.0020 *
Opioid	5%	26%	0%	22%	0.0068 *
Others	18%	43%	20%	22%	0.1110
<u>Lifetime Alcohol Dependence</u>					
Age at first diagnosis	-	29.36 (9.94)	-	38.12 (16.30)	0.1874

Age	50-59		60-69		p
	No (n = 60)	Yes (n = 23)	No (n = 20)	Yes (n = 9)	
Lifetime Alcohol Dependence					
Age at most recent diagnosis	-	41.00 (11.03)	-	50.50 (13.33)	0.0995
Years of diagnosis	-	11.64 (10.02)	-	12.38 (13.72)	0.8920
Years since most recent diagnosis	-	12.64 (10.01)	-	13.97 (12.86)	0.7853

Note. Continuous variables are reported as mean (SD), except for CD4 variables as median (Q1, Q3) due to skewed distributions. Proportions are reported as %. WTAR = Wechsler Test of Adult Reading; SUD = substance use disorder; ART = antiretroviral therapy.

* p < .05.

Table 2

Regression coefficients and associated p-values (in parentheses) of clinical covariates comprising each multiple regression model predicting a neurocognitive variable.

	Age	Lifetime Alcohol Dependence	Age * Alcohol Interaction	Education	HCV Status	Lifetime Substance Use
Global T-score	3.5471 (0.0165) *	-1.3443 (0.3562)	-6.4954 (0.0147) *	0.5197 (0.0255) *	0.9566 (0.4298)	1.3492 (0.2359)
Domain T-scores						
Attention	3.0388 (0.1841)	-4.1017 (0.0731)	-1.3069 (0.7500)	0.9239 (0.0113) *	1.1373 (0.5477)	2.7473 (0.1232)
Executive Function	3.0027 (0.1442)	-0.2344 (0.9085)	-7.9881 (0.0319) *	0.1248 (0.6988)	0.4544 (0.7889)	2.2589 (0.1577)
Learning	5.8175 (0.0094) **	-3.8280 (0.0837)	-6.6659 (0.0951)	1.1300 (0.0015) **	2.6497 (0.1493)	0.5128 (0.7649)
Memory	3.0190 (0.1758)	-4.2133 (0.0591)	-4.4933 (0.2623)	0.9803 (0.0060) **	3.0119 (0.1041)	1.0570 (0.5409)
Motor	-1.5171 (0.5265)	-1.9324 (0.4186)	-3.6668 (0.3953)	-0.0594 (0.8750)	0.5465 (0.7831)	-0.6241 (0.7375)
Processing Speed	1.7908 (0.4086)	1.5869 (0.4625)	-10.3335 (0.0090) **	0.1743 (0.6095)	-0.7217 (0.6877)	2.1499 (0.2032)
Semantic	9.2433 (<.0001) ***	2.8458 (0.2121)	-11.1068 (0.0078) **	0.5613 (0.1204)	-0.7653 (0.6857)	0.8890 (0.6163)

Note:

* p < .05,

** p < .01,

*** p < .001.

HCV = hepatitis C infection; TOL = Tower of London; KAIT = Kaufman Adolescent and Adult Intelligence Test. Lifetime substance use indicates the presence of a lifetime diagnosis of any non-alcohol substance use disorder.