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Age of Last Alcohol Use Disorder Relates to Processing Speed Among Older Adults Living with HIV

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Abstract

Aims: Older persons living with HIV (PLWH) and past alcohol use disorder (AUD) are at higher risk for neurocognitive deficits compared to those with either condition alone; however, factors underlying this relationship are unknown. Given that aging potentiates multi-system damage from alcohol misuse, the current study examined whether neurocognitive functioning among older adults relates to the age at which they last met criteria for AUD (i.e. 'age of last AUD'), and whether this relationship differed by HIV serostatus.

Methods: All participants (aged between 50 and 75 years) were grouped by HIV/AUD status: 345 HIV+/AUD+, 148 HIV-/AUD+, 273 HIV+/AUD-, and 206 HIV-/AUD-. Neurocognitive functioning was assessed globally and within seven domains. Among only the two AUD+ groups, multivariable linear regressions examined the interaction between age of last AUD and HIV status on neurocognitive functioning, controlling for demographics and clinical characteristics.

Results: Older age of last AUD related to worse processing speed among PLWH ($b = -0.03$; $P = 0.006$); however, this relationship was not significant among persons without HIV ($b = 0.01$; $P = 0.455$). The interaction between age of last AUD and HIV status did not predict neurocognitive functioning in other domains. Processing speed appeared clinically important, as slower speed related to worse everyday functioning, including more reported cognitive difficulties ($r = -0.26$, $P < 0.001$) and higher rates of functional dependence (OR = 0.87, 95%CI = 0.80–0.95, $P = 0.002$).

Conclusions: Our novel findings, demonstrating slower processing speed when a past AUD occurred at an older age in PLWH, highlight the value in assessing older PLWH for processing speed deficits, even if other cognitive domains appear to be intact.

INTRODUCTION

HIV is now considered a chronic disease rather than an acute, life-threatening illness (Deeks *et al.*, 2013). People living with HIV (PLWH) have near comparable life expectancies as those without HIV, and there is a rising rate of individuals living into the sixth decade and beyond. The Centers for Disease Control and Prevention

(2016) estimates that 42% of PLWH in the USA are over the age of 50 years. Between 2010 and 2014, there was a 59% increase in the prevalence of HIV in persons over age 65 years (84.3 per 100,000 in 2010 to 133.8 in 2014). The increased lifespan of PLWH presents unique medical risks over and above those associated with aging outside of the context of HIV, including more rapid disease

progression, immune downregulation, and greater rates of comorbid chronic health problems (e.g. hypertension, diabetes, chronic pain, hepatitis, arthritis; [Balderson et al., 2013](#)).

Aging is additionally associated with increased risk for HIV-associated neurocognitive impairment among PLWH. Although the use of combination antiretroviral therapy (cART) has decreased the prevalence of HIV-associated dementia ([Heaton et al., 2011](#)), milder HIV-associated neurocognitive impairment still affects up to 50% of PLWH and relates to functional disability ([Heaton et al., 2004a](#); [Kordovski et al., 2017](#)). Older PLWH exhibit higher rates of neurocognitive impairment compared to both younger PLWH and their HIV-seronegative counterparts ([Valcour et al., 2004a,b](#); [Heaton et al., 2010](#)). Proposed biological mechanisms for this observed age-related neurocognitive decline among PLWH include a combination of chronic inflammation, chronic immune dysfunction, long-term use of potentially neurotoxic cART regimens, and vascular and metabolic co-pathology ([Deeks, 2011](#); [McCutchan et al., 2012](#); [Decloedt and Maartens, 2013](#)). Behavioral and psychosocial risk factors, such as alcohol and substance use, also play a major role in cognitive outcomes with advancing age. Compared to biological mechanisms, alcohol and substance use behaviors may constitute a more feasible target for interventions aiming to reduce the risk of neurocognitive impairment among older PLWH. Specifically, understanding whether long-term neurocognitive outcomes are worse when alcohol/substance misuse occurs at older ages is critical in this aging population.

Comorbid alcohol use disorder (AUD) and HIV-infection are especially common, and the rate of heavy drinking among PLWH (ranging from 8–42%) is substantially higher than in the general population ([Galvan et al., 2002](#); [Samet et al., 2004](#)). PLWH who drink heavily also demonstrate worse medication adherence, greater viral load, and more rapid progression of disease ([Paolillo et al., 2017](#); [Rehm et al., 2017](#)). Heavy drinking and HIV are each associated with adverse effects on neurocognitive functioning, particularly in the domains of processing speed, visual attention and learning, and motor dexterity and speed ([Rothlind et al., 2005](#); [Sassoon et al., 2007](#); [Monnig et al., 2017](#)). When comorbid, the combination of heavy drinking and HIV puts individuals at much higher risk for neurocognitive impairment ([Fama et al., 2009](#); [Woods et al., 2016](#)). Less is known about the lasting effects of a past AUD on neurocognitive functioning among PLWH, and how the age at which an individual last misused alcohol may impact vulnerability to alcohol- and HIV-related neurocognitive impairment.

Previous studies have shown that even a past AUD has a negative impact on current cognitive function among older PLWH ([Green et al., 2004](#); [Gongvatana et al., 2014](#)), suggesting a potential combined detrimental effect of alcohol misuse, HIV, and age. These studies, however, do not account for the age at which individuals were most recently misusing alcohol, which may be an important factor to consider when trying to understand the impact of age on vulnerability to alcohol- and HIV-related neurocognitive impairment. For example, meeting criteria for an AUD at an older age may increase susceptibility to direct alcohol-induced brain damage and/or secondary brain injury due to alcohol-induced organ dysfunction ([Gongvatana et al., 2014](#)), potentially worsening the lasting neurocognitive effects after AUD recovery. Research has shown that aging potentiates the damaging effects of alcohol misuse ([Kennedy et al., 1999](#); [Dowling et al., 2008](#)), and this relationship is likely to be exacerbated by HIV-infection. Prior research suggests that the immunosuppressant properties of alcohol in combination with HIV may synergistically contribute to risk of neurocognitive impairment in older PLWH ([Ellis et al., 2011](#)).

Therefore, the current study examined whether neurocognitive functioning was associated with the age at which individuals last met criteria for an AUD (hereafter written as ‘age of last AUD’) among a sample of older (50–75 years) PLWH and HIV-uninfected individuals. We hypothesized that older age of last AUD would be related to worse neurocognitive functioning, and that this relationship would be stronger among PLWH. Additionally, we hypothesized that among PLWH, this relationship would be driven by the neurocognitive domains known to be affected in AUD and/or HIV-infection (i.e. processing speed, learning, executive functioning, and motor skills). Understanding how neurocognitive functioning among older PLWH may be influenced by the age at which they most recently met criteria for an AUD has potential to elucidate specific risk factors associated with neurocognitive impairment, and may guide development of targeted AUD prevention and treatment strategies for this population.

MATERIALS AND METHODS

Participants

Participants included 345 older PLWH and 138 older HIV-uninfected (HIV–) participants (50–75 years old) with a lifetime history of AUD, as well as 479 older adults without history of AUD (AUD–; 273 HIV+ and 206 HIV–) to serve as comparison groups. All participants were enrolled in various NIH-funded research studies at University of California, San Diego’s (UCSD) HIV Neurobehavioral Research Program (HNRP) from 2003 to 2016, and were provided written, informed consent. The current cross-sectional study represents a secondary analysis on existing alcohol use data from each participant’s baseline visit at the HNRP. Exclusion criteria were: (1) diagnosis of psychotic or mood disorder with psychotic features; (2) presence of a neurological condition (other than HIV) with potential to negatively influence cognitive functioning (e.g. traumatic brain injury, stroke, epilepsy); and (3) positive urine toxicology for illicit drugs (except marijuana) or Breathalyzer test for alcohol on the day of testing.

Measures

Neuromedical evaluation

All participants were tested for HIV infection using an HIV/HCV finger stick point of care test (Abbott RealTime HIV–1 test, Abbott Laboratories, Illinois, USA) and, if positive, confirmed with Western Blot. All participants completed comprehensive medical evaluations, including a thorough medical history and blood draw. For PLWH, levels of HIV viral load in plasma were measured using reverse transcriptase-polymerase chain reaction (RT-PCR; Amplicor, Roche Diagnostics, Indianapolis, IN, USA).

Psychiatric and alcohol use disorder evaluation

The Composite International Diagnostic Interview (CIDI, v2.1), a fully-structured, computer-based interview, was administered to determine DSM-IV diagnoses for current and past mood and alcohol and substance use disorders ([World Health Organization, 1998](#)). Of note, the DSM-IV was utilized in this study, as the parent grants from which subjects were drawn were funded before the DSM 5 was published. In accordance with DSM-IV criteria, alcohol abuse was met when participants endorsed drinking despite recurring problems (e.g. interpersonal, work-related, legal) that result from alcohol use, and alcohol dependence was met when participants endorsed experiencing symptoms of tolerance, withdrawal, and impaired control over drinking ([American Psychiatric](#)

Association, 1994). Alcohol abuse and dependence criteria were combined into one AUD variable, consistent with previous studies that attempt to capture more than one definition of alcohol/substance misuse (e.g. (Azar *et al.*, 2010; Heinz *et al.*, 2014) and to be more consistent with current DSM 5 criteria and terminology. When an individual's self-reported history of alcohol use met criteria for a past AUD, the individual was asked to report the age at which they first experienced those problems (i.e. age of first AUD) and the age at which they most recently experienced those problems (i.e. age of last AUD). Thus, age of last AUD captures the oldest age at which an individual met criteria for an AUD, and is the primary predictor variable of interest in the current study. Additionally, we calculated time in years since participants' last AUD (i.e. 'years since last AUD'), as well as estimated total years of AUD duration (calculated by subtracting age of first AUD from age of last AUD). Although our estimate of AUD duration does not capture possible periods of AUD remission, we explored estimated total years of AUD as a covariate that may relate to neurocognitive functioning. Last, a subset of 438 participants (i.e. 278 HIV+/AUD+, 83 HIV-/AUD+, and 77 HIV-/AUD-) underwent a modified timeline follow-back interview to estimate total lifetime alcohol use quantity (drinks) and frequency (drinking days).

Neuropsychological battery

Participants were administered a standardized, comprehensive neuropsychological battery, which was designed in agreement with international consensus conference recommendations for HIV-associated neurocognitive impairment (Antinori *et al.*, 2007). The battery covers seven neurocognitive domains: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor skills (Table 1). Raw scores for each test were converted to uncorrected scaled scores ($M = 10$, $SD = 3$). Scaled scores were used to measure neurocognitive functioning (as opposed to demographically-corrected T -scores) so that demographic covariates could be properly interpreted in planned regression models (see below). Scaled scores were averaged across all tests to create a global scaled score, and averaged within domains to create domain-specific scaled scores. Self-reported cognitive difficulties and dependence in instrumental activities of daily living (IADL) were also assessed via the Patient Assessment of Own Functioning Inventory (PAOFI) (Chelune *et al.*, 1986) and a modified version of the Lawton and Brody Activities of Daily Living questionnaire (Lawton and Brody, 1969; Heaton *et al.*, 2004a), respectively. Higher PAOFI score represents a higher number of self-reported cognitive difficulties (out of 31). Participants were categorized as IADL dependent if they reported a decline or need for assistance in ≥ 2 IADL domains.

Statistical analyses

To initially characterize comorbid HIV and lifetime AUD in relation to other relevant groups, demographic and clinical characteristics were compared between the four HIV/AUD status groups using analysis of variance (ANOVA) or Chi-square tests as appropriate. All following analyses included only the 483 participants with lifetime AUD. Consistent with our hypothesis that age of AUD will be related to neurocognitive functioning (regardless of HIV status), Pearson r correlations were used to examine bivariate relationships between neurocognition and age of last AUD. Consistent with our next hypothesis that age of last AUD will be more strongly related to neurocognitive functioning among PLWH compared to HIV-, we used multivariable linear regression models to examine an interaction effect between age of last AUD and HIV status for each

neurocognitive domain that showed a bivariate association with age of last AUD at $\alpha = 0.05$. Demographic variables (i.e. age, sex, education, race/ethnicity) were entered as covariates into each model to account for group differences as well as differences in neuropsychological performance (Heaton *et al.*, 2004b). Additional covariates included estimated total years of AUD and any clinical characteristics that significantly differed between the HIV+/AUD+ and HIV-/AUD+ groups. Years since last AUD was not considered for inclusion in the regression models because the convergence between age of last AUD, age, and years since last AUD would prevent model estimation.

Due to potential lack of power to detect an interaction effect, a follow-up analysis was conducted for any model with at least a trend-level interaction term ($P < 0.10$). This follow-up analysis examined the association between the neurocognitive outcome and age of last AUD within each HIV serostatus group, covarying for the same demographic and clinical variables in primary regression analyses. Given that we applied a liberal threshold for detecting an interaction effect, strict Bonferroni correction for multiple comparisons was applied for the follow-up analysis ($\alpha = 0.05/2 = 0.025$) to ensure that the effects modeled within HIV serostatus groups were statistically meaningful. As a secondary follow-up analysis for the subset of PLWH, HIV characteristics known to be related to neurocognitive functioning in the cART era (i.e. nadir CD4 < 200 [yes/no], current CD4 < 200 [yes/no], HIV plasma viral load detectability, and ARV status [on cART/other]; Heaton *et al.*, 2010, 2011) were added as additional covariates to examine potential attenuation of the effect of age of last AUD.

Two additional exploratory analyses were conducted to support any findings from the above stated analyses. First, additional linear regression models were examined for each neurocognitive outcome (regardless of its bivariate relationship with age of last AUD) to ensure that no interaction effects were missed due to possible opposing main effects of age of last AUD within HIV status groups. Next, in order to distinguish the age of last AUD from the amount of time that has elapsed since one's last reported AUD (i.e. a potential proxy for time in AUD recovery), all multivariable regression models that included a significant interaction effect between age of last AUD and HIV status were repeated using years since last AUD in place of age of last AUD.

Finally, relationships between significant neurocognitive outcomes and indices of everyday functioning (i.e. self-reported cognitive difficulties and dependence in IADLs) were examined. These relationships were examined with and without covariates (i.e. age). All analyses were performed using JMP Pro version 12.0.1 (JMP®, Version < 12.0.1 > . SAS Institute Inc., Cary, NC, USA, 1989–2007).

RESULTS

Demographic and clinical differences between HIV/AUD groups

Demographic and clinical characteristics for each HIV/AUD group are presented in Table 2. Groups differed on all demographic characteristics, major depressive disorder (MDD) diagnoses, and non-alcohol substance use disorder diagnoses. Among the subset of 658 individuals whose lifetime alcohol use was characterized, lifetime alcohol use estimates differed by group, such that the AUD+ groups had significantly more lifetime alcohol drinks and lifetime alcohol drinking days than the AUD- groups. Regarding neurocognition, participants with comorbid HIV and lifetime AUD displayed the

Table 1. Individual measures comprising each neurocognitive domain

Neurocognitive domain	Individual measures
Verbal fluency	Controlled Oral Word Association Test Category Fluency (Animals) Category Fluency (Actions)
Executive functioning	Wisconsin Card Sorting Test (64-item) Trail Making Test, Part B Stroop Color Word Trial
Processing speed	WAIS-III Digit Symbol WAIS-III Symbol Search Trail Making Test, Part A Stroop Color Trial
Learning	Learning Trials of: Hopkins Verbal Learning Test-Revised Brief Visuospatial Memory Test-Revised
Delayed recall	Delayed Recall Trials of: Hopkins Verbal Learning Test-Revised Brief Visuospatial Memory Test-Revised
Working memory	WAIS-III Letter-Number Sequencing PASAT (1 st channel only)
Motor skills	Grooved Pegboard test (dominant & non-dominant hands)

worst cognitive performance across all domains compared to the other three groups (P s < 0.001; Table 2). Notably, group differences in neurocognitive performance remain even when covarying for age, sex, education, and race/ethnicity.

Bivariate relationships between age of last AUD and neurocognitive outcomes

Although the bivariate association between age of last AUD and global neurocognitive performance only approached significance ($r = -0.082$; $P = 0.076$), age of last AUD was significantly associated with the domains of processing speed ($r = -0.095$; $P = 0.039$) and motor skills ($r = -0.097$, $P = 0.036$). Thus, multivariable regression analyses were only conducted for processing speed and motor skills outcomes. Covariates included in these regression models were the demographic and clinical characteristics that differed between HIV+/AUD+ and HIV-/AUD+ groups (i.e. sex, race/ethnicity, and current and lifetime MDD) as well as age, years of education, and total years of AUD. The inclusion of age as a covariate was included to parse apart the unique variance accounted for by age versus age of last AUD, as the two are inherently correlated ($r = 0.26$, $P < 0.001$).

Relationships among age of last AUD, HIV status and neurocognitive outcomes

Multivariable regression analyses revealed main effects of HIV status on both processing speed and motor skills, such that PLWH performed worse than HIV- participants (Table 3). There was also a main effect of age of last AUD on processing speed such that older age of last AUD was related to worse processing speed; this association was not significant for motor skills. The interaction term (age of last AUD $\times$ HIV status) approached significance for only processing speed ($P = 0.064$). Variance inflation factors (VIF) were < 1.5 for all predictors in each model, indicating very minimal multicollinearity. Follow-up analyses revealed that the negative relationship

between age of last AUD and processing speed performance was significant among PLWH ($P = 0.006$), but was not significant among HIV- participants ($P = 0.501$), covarying for demographics, total years of AUD, and current and lifetime MDD (Table 4; Fig. 1). Even after additionally covarying for HIV characteristics, older age of last AUD still significantly predicted lower processing speed scaled scores among PLWH ($P = 0.004$; Table 4). Notably, there were five participants who met criteria for current marijuana use disorder; sensitivity analyses removing these five participants from the sample revealed that results remained unchanged. There were no other participants who met criteria for any other current substance use disorders.

Additional exploratory linear regression analyses ensured that the interaction effect between age of last AUD and HIV status was not significant in any other neurocognitive outcome (i.e. global and all other domains; all P s > 0.10). Next, in order to distinguish the age of last AUD from the amount of time that has elapsed since one's last reported AUD (i.e. a potential proxy for time in AUD recovery), the multivariable regression model predicting processing speed among all participants with lifetime AUD was repeated using years since last AUD in place of age of last AUD. Although there were main effects of HIV status ($b = -0.76$; $P < 0.01$) and years since last AUD ($b = 0.03$; $P < 0.01$), the interaction term (HIV status $\times$ years since last AUD) was not significant ($b = -0.01$; $P > 0.10$).

Relationships between processing speed and everyday functioning

Last, in order to understand the clinical relevance of processing speed on everyday functioning, we examined its relationships with self-reported cognitive difficulties (PAOFI score) and IADL dependence among all participants with lifetime history of AUD ($n = 483$). Bivariate correlational analysis showed that processing speed was related to PAOFI score ($r = -0.26$, $P < 0.001$) such that participants with worse processing speed performance reported more cognitive difficulties. This relationship remained significant in a linear regression model while covarying for age ($b = -0.80$, $P < 0.001$). Bivariate logistic regression showed that participants with better processing speed were less likely to be IADL dependent ($OR = 0.87$ [per unit increase], 95%CI = 0.80–0.95, $P = 0.002$), and this relationship held after covarying for age ($OR = 0.87$ [per unit increase], 95%CI = 0.80–0.95, $P = 0.001$).

DISCUSSION

As the population of PLWH continues to age and live into late life, it is critical to monitor factors that put these individuals at greater risk for neurocognitive impairment, including treatable and potentially preventable factors such as AUD. In partial support of our hypothesis, we demonstrated that older age of last AUD was significantly associated with worse processing speed, only among PLWH. In fact, age of last AUD was not related to any other neurocognitive domain, suggesting that age of last AUD may be selectively related to processing speed among PLWH. Our findings are consistent with previous studies that have found an association between past AUD and worse processing speed performance among older PLWH (Gongvatana *et al.*, 2014), and importantly extends the literature by elucidating a novel association between processing speed and the age at which an individual last met criteria for an AUD. Notably, we also found that processing speed was clinically important, as

Table 2. Demographic and clinical characteristics for each HIV/AUD group

Variable	A HIV+/AUD+ (N = 345)	B HIV-/AUD+ (N = 138)	C HIV+/AUD- (N = 273)	D HIV-/AUD- (N = 206)	P-value	Pairwise comparisons ^a
<i>Demographics</i>						
Age (years)	54.8 (4.6)	56.2 (5.9)	55.8 (5.4)	57.7 (6.6)	<0.001	A,C < D
Education (years)	13.2 (2.8)	13.2 (2.8)	14.1 (2.9)	13.9 (2.7)	<0.001	A,B < C
Sex (male)	305 (88.4%)	104 (75.4%)	210 (76.9%)	119 (57.8%)	<0.001	A > B,C > D
Ethnicity (White)	182 (52.8%)	99 (71.7%)	153 (56.0%)	134 (65.1%)	0.001	A < B
<i>Comorbidities</i>						
Current MDD	58 (16.8%)	13 (9.4%)	38 (13.9%)	1 (0.9%)	<0.001	A,B,C > D
Lifetime MDD	185 (53.6%)	48 (34.8%)	121 (44.3%)	32 (27.8%)	<0.001	A > B,D
Lifetime non-alcohol SUD ^b	245 (71.8%)	102 (73.9%)	97 (35.5%)	24 (11.7%)	<0.001	A,B > C > D
Hepatitis C	127 (36.9%)	46 (33.6%)	56 (20.5%)	66 (33.5%)	0.001	A,B,D > C
<i>AUD characteristics</i>						
Age of first AUD (years)	28.9 (10.6)	27.8 (10.2)			0.288	
Age of last AUD (years)	39.6 (11.2)	40.4 (11.8)			0.505	
Total years of AUD	10.7 (11.5)	12.6 (12.5)			0.113	
Years since last AUD	15.1 (11.0)	15.7 (11.5)			0.614	
Lifetime alcohol drinks ^c	39,290 (58,470)	45,621 (71,546)	8797 (19,542)	6173 (16,582)	<0.001	A,B > C,D
Lifetime drinking days ^c	4892 (3818)	5430 (4424)	2387 (3158)	1661 (2558)	<0.001	A,B > C,D
<i>HIV characteristics</i>						
History of AIDS	231 (67.0%)		182 (66.7%)		0.939	
Detectable viral load ^d	121 (36.4%)		92 (35.5%)		0.816	
Current CD4 count	461 [294–638]		477 [325–656]		0.382	
Nadir CD4 count	141 [51–265]		160 [52–250]		0.927	
Estimated years of infection	13.8 (7.7)		13.3 (7.8)		0.443	
ARV status (on cART)	289 (84.5%)		218 (80.2%)		0.159	
<i>Neurocognitive Scaled Scores (SS)</i>						
Global SS	7.8 (1.9)	8.6 (1.9)	7.9 (1.9)	9.1 (1.9)	<0.001	A,C < B < D
Verbal fluency SS	9.2 (2.5)	9.6 (2.1)	9.3 (2.4)	10.1 (2.3)	0.001	A,C < D
Executive functioning SS	7.5 (2.6)	8.4 (2.7)	7.5 (2.4)	8.9 (2.5)	<0.001	A,C < D
Processing speed SS	8.5 (2.3)	9.4 (2.3)	8.8 (2.3)	9.8 (2.3)	<0.001	A < D
Learning SS	6.5 (2.2)	7.2 (2.3)	6.4 (2.3)	7.7 (2.6)	<0.001	A,C < D
Delayed recall SS	7.3 (2.5)	7.2 (2.3)	7.2 (2.7)	8.3 (2.7)	<0.001	A,B,C < D
Working memory SS	8.3 (2.6)	9.5 (2.7)	8.4 (2.6)	9.5 (2.5)	<0.001	A,C < B,D
Motor skills SS	6.7 (2.5)	7.8 (2.6)	7.1 (2.5)	8.2 (1.7)	<0.001	A < B,D

Note. Bolded P-values are significant at $P < 0.05$. Values are presented as mean (SD), median [IQR], or N (%). ARV = antiretrovirals; MDD = major depressive disorder; SUD = substance use disorder; AUD = alcohol use disorder; cART = combination antiretroviral therapy.

^aPairwise comparisons were examined using Tukey's H.S.D. ($\alpha = 0.05$) for continuous outcomes or Bonferroni-adjustments ($\alpha = 0.05/4 = 0.0125$) for dichotomous outcomes.

^bIncludes lifetime SUDs for marijuana, cocaine, hallucinogens, inhalants, methamphetamine, opioids, PCP, sedatives, and 'other'.

^cIncludes data on a subset of only 658 participants: 278 HIV+/AUD+, 83 HIV-/AUD+, 220 HIV+/AUD-, and 77 HIV-/AUD-.

^dDefined as >50 copies/ml in plasma.

slower speed related to more self-reported cognitive difficulties and greater likelihood of everyday functioning impairment.

Previous research has shown that long-term sustained sobriety after recovery from AUD is associated with at least some neural recovery and improvements in neurocognitive functioning among HIV seronegative adults (Stavro *et al.*, 2013; Pfefferbaum *et al.*, 2014). Thus, we additionally examined the interaction between HIV status and years since last AUD in order to understand whether the demonstrated age effect was simply a reflection of amount of time in potential 'recovery' from AUD. Although we found that greater time since last AUD was associated with better processing speed performance across the entire sample, this relationship did not differ by HIV status. This finding preliminarily supports that, in the context of HIV infection, age of last AUD may be an important predictor of neurocognitive outcomes beyond amount of time since last meeting criteria for an AUD.

Thus, the current findings are consistent with knowledge about the increasingly detrimental impact of alcohol misuse among individuals aging with HIV (Kennedy *et al.*, 1999; Dowling *et al.*, 2008). Our results support the hypothesis that experiencing an AUD at an older age may exacerbate alcohol-related neural injury among PLWH, leading to lasting effects on neurocognitive functioning even after AUD recovery. In particular, the influence of AUD on processing speed is consistent with what is known about increased white matter damage among individuals aging with HIV or AUD (Cloak *et al.*, 2004; Wu *et al.*, 2006; Sorg *et al.*, 2015; Underwood *et al.*, 2017). We are unaware of any neuroimaging studies that focus particularly on older individuals with comorbid HIV and AUD, however, studies of the combined neural effects of HIV and AUD across adulthood demonstrate white matter damage particularly in frontal regions and the corpus callosum (Pfefferbaum *et al.*, 2007; Rosenbloom *et al.*, 2010), which are consistently associated with

Table 3. Regression coefficients for each predictor variable in multivariable regression models for each neurocognitive domain

Predictor variables	Processing speed		Motor skills	
	Regression coefficient (SE)	P-value	Regression coefficient (SE)	p-Value
Age of last AUD	-0.03 (0.01)	0.021	-0.01 (0.01)	0.435
HIV status ^a	-0.74 (0.23)	0.002	-1.09 (0.26)	<0.001
Age of last AUD × HIV status interaction	0.04 (0.02)	<i>0.064</i>	0.02 (0.02)	0.416
Total years of AUD	-0.002 (0.01)	0.856	-0.001 (0.01)	0.935
Age	-0.06 (0.02)	0.009	-0.14 (0.02)	<0.001
Sex ^b	-0.48 (0.29)	0.099	-0.60 (0.32)	0.061
Education	0.23 (0.04)	<0.001	0.16 (0.04)	<0.001
Race/ethnicity ^c	0.91 (0.21)	<0.001	0.31 (0.24)	0.197
Current MDD ^d	-0.15 (0.31)	0.618	-0.57 (0.35)	0.105
LT MDD ^e	-0.23 (0.23)	0.304	-0.31 (0.25)	0.221

Note. Bolded P-values are significant at $P < 0.05$. Italicized p-values indicate trending significance levels. SE = standard error; AUD = alcohol use disorder; LT = lifetime; MDD = major depressive disorder.

^aHIV seropositive compared to HIV seronegative status.

^bMale compared to female sex.

^cWhite compared to non-White race/ethnicity.

^dCompared to no current MDD.

^eCompared to no lifetime history of MDD.

Table 4. Primary and secondary follow-up regression analyses predicting processing speed within each HIV status group

Follow-up analysis 1	HIV+/AUD+		HIV-/AUD+	
	Regression coefficient (SE)	P-value	Regression coefficient (SE)	P-value
Age at last AUD	-0.03 (0.01)	0.006	0.01 (0.02)	0.501
Total years of AUD	-0.002 (0.01)	0.889	-0.002 (0.02)	0.905
Age	-0.04 (0.03)	0.180	-0.09 (0.03)	0.010
Sex ^a	-0.46 (0.38)	0.222	-0.70 (0.45)	0.120
Education	0.20 (0.05)	<0.001	0.33 (0.07)	<0.001
Race/ethnicity ^b	1.17 (0.25)	<0.001	0.18 (0.42)	0.668
Current MDD ^c	0.03 (0.35)	0.940	-0.74 (0.70)	0.295
LT MDD ^d	0.18 (0.26)	0.490	-0.46 (0.44)	0.299
Follow-up analysis 2 (covarying for HIV characteristics)				
Age at last AUD	-0.04 (0.01)	0.004		
Total years of AUD	0.004 (0.01)	0.743		
Age	-0.03 (0.03)	0.335		
Sex ^a	-0.34 (0.38)	0.371		
Education	0.19 (0.05)	<0.001		
Race/ethnicity ^b	1.28 (0.27)	<0.001		
Current MDD ^c	0.01 (0.36)	0.973		
LT MDD ^d	0.20 (0.28)	0.475		
Nadir CD4 <200	-0.39 (0.28)	0.168		
Current CD4 <200	-0.19 (0.38)	0.611		
HIV viral load detectability ^e	-0.51 (0.29)	0.085		
ART Status ^f	0.03 (0.38)	0.946		

Note. Bolded P-values for follow-up analysis 1 are significant at the Bonferroni corrected level ($\alpha = 0.05/2 = 0.025$). SE = standard error; AUD = alcohol use disorder; LT = lifetime; MDD = major depressive disorder; ART = antiretroviral therapy.

^aMale compared to female sex.

^bWhite compared to non-White race/ethnicity.

^cCompared to no current MDD.

^dCompared to no lifetime history of MDD.

^eDetectable compared to undetectable.

^fOn cART compared to other ART.

processing speed. It is important to note that white matter hyperintensities and declines in processing speed also occur in normal aging among individuals not living with HIV (Salthouse, 2000; Nilsson et al., 2014; Papp et al., 2014); however, our results indicated that

age of last AUD uniquely accounted for variance in processing speed performance above and beyond that of current age among our HIV + participants. Furthermore, the white matter damage and associated processing speed deficits reported in previous studies of

Fig. 1. Processing speed scaled scores by age of last AUD, with predicted slopes for each HIV status group controlling for age, sex, total years of AUD, education, race and current and lifetime major depressive disorder.

individuals with HIV and/or AUD are greater than that of expected age-related changes (McMurray *et al.*, 2008; Rosenbloom *et al.*, 2010; Sorg *et al.*, 2015).

Several possible neurological and/or physiological mechanisms may explain the interactive effect of age of last AUD and HIV status on processing speed in our sample. In the context of HIV-infection, alcohol misuse is associated with decreased adherence to cART (Hendershot *et al.*, 2009; Paolillo *et al.*, 2017) and greater immunosuppression in older PLWH, leading to higher plasma HIV viral load and increased risk for HIV-associated neuronal damage in selectively vulnerable areas (e.g. frontostriatal circuits; Woods *et al.*, 2009; Rosenbloom *et al.*, 2010). Furthermore, the detrimental neurocognitive and physical effects of alcohol misuse are typically more severe among older individuals regardless of HIV status (Downing *et al.*, 2008; Sorg *et al.*, 2015). Research suggests that certain changes that occur with normal aging (e.g. reduced alcohol dehydrogenase activity, lower total body water and interstitial fluid volume) increase sensitivity to alcohol and the brain's vulnerability to toxic substances (Oscar-Berman and Marinkovic, 2007; Ferreira and Weems, 2008). Heavy alcohol use in later life may also intensify multi-organ system damage, leading to downstream effects on the brain. For example, research suggests that liver damage acquired from a past episode of heavy alcohol use (which is more likely when heavy use occurs at an older age; Meier and Seitz, 2008) may increase risk of neuronal damage via minimal hepatic encephalopathy (Schiff *et al.*, 2014), hyperammonemia and increased inflammation (Felipo *et al.*, 2012), and reduced ability to metabolize cART (after acquiring and getting treatment for HIV) and other medications, thus increasing neurotoxicity (Moore *et al.*, 2007). These alcohol-induced changes, even if remote from HIV-infection, are likely to make individuals more vulnerable to HIV-associated neurocognitive impairment after becoming infected. Still, future research is needed to elucidate specific mechanisms affecting cognitive outcome in the context of age, alcohol use, and HIV infection.

Interestingly, HIV characteristics were not significant predictors of processing speed among PLWH in multivariable analyses. This finding may reflect a possible survival bias in our older sample of PLWH, such that older adults who have been living with HIV for an extended period of time may be more resilient to adverse HIV-related events (i.e. low current and nadir CD4 counts, being virally

detectable, and not being on cART) that normally contribute to worse outcomes and mortality. In depth examinations of stable and healthy older PLWH (i.e. those who are 'aging successfully'; Moore *et al.*, 2014; Moore *et al.*, 2018; Escota *et al.*, 2018; Moore *et al.*, 2018) is warranted to further understand protective factors in this aging population.

The current study has several limitations. First, our data were limited in their ability to fully characterize the lifetime frequency and quantity of all past AUDs, including periods of AUD remission. We also used DSM-IV criteria for alcohol abuse and dependence to define AUD, which may limit generalizability to studies and clinics that currently utilize DSM-5 criteria. Additionally, history of AUD was self-reported by participants, which, like all self-report data, may be biased or inaccurate. Objectively measured use of alcohol (e.g. breathalyzer) over time would have been ideal; however, we believe that our data, collected via structured interviews, are still clinically relevant. Next, although we had a subset of participants with lifetime alcohol quantity and frequency data, we did not have data on other AUD-specific factors (e.g. recency of any alcohol use, quantity and frequency of alcohol consumption during self-identified periods of misuse). Relatedly, our 'years since last AUD' variable does not take into account whether participants have maintained sobriety (i.e. an important predictor of neurocognitive recovery during AUD remission); rather, it simply captures time since last experiencing problems related to alcohol misuse. Our study was also limited in its cross-sectional nature; longitudinal work may build upon current findings to examine whether individuals who misuse alcohol at older ages are more likely to demonstrate cognitive decline over time. Furthermore, we did not assess anxiety, which may be an important factor as it is often comorbid with AUD and relates to neuropsychological performance. Lastly, we were restricted in our ability to interpret results in the context of biological mechanisms. More research is needed to elucidate specific biomarkers in the context of age, alcohol use, and HIV infection (e.g. liver enzymes, fluid biomarkers of inflammation) that may identify individuals most vulnerable to developing neurocognitive impairment.

In conclusion, our results demonstrate lasting neurocognitive effects of a past AUD when acquired at older ages, specifically on processing speed. Results also emphasize the clinical importance of processing speed among older PLWH who have a recent history of AUD given that processing speed was related to indices of everyday functioning. These findings suggest that assessment of processing speed may be particularly important for characterizing neurocognitive functioning in this population, as functioning in other neurocognitive domains may be intact. This presents a challenge to primary care settings because commonly used cognitive screening measures (e.g. Mini Mental State Examination, Montreal Cognitive Assessment) do not assess processing speed. Thus, we highlight the importance of full neuropsychological evaluations for guiding treatment recommendations in this population.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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