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The Effects of Low-Risk Drinking ON Neurocognition Among Older Persons Living with HIV as Compared to Those Without HIV

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ABSTRACT

Background: Heavy alcohol use negatively impacts neurocognition, but some studies report neurocognitive benefits associated with light drinking among HIV-seronegative (HIV-) older persons, suggesting a non-linear or an inverted “J-shaped” association of alcohol consumption on neurocognition. Alcohol use is common among people with HIV (PWH), however, the association between recent “low-risk” alcohol consumption and neurocognition among PWH is poorly understood.

Methods: Participants included 310 PWH and 89 HIV- older (≥ 50 years) adults who reported alcohol abstinence or “low-risk” drinking, defined per the National Institute on Alcohol Abuse and Alcoholism criteria (i.e., ≥ 15 drinks/week or ≥ 5 drinks/day for men; ≥ 8 drinks/week or ≥ 4 drinks/day for women). Neurocognition was measured using global and domain-specific demographically-corrected T-scores. Multiple linear regressions examined the interaction between total drinks in the last 30 days (linear and quadratic terms) and HIV serostatus on neurocognition, covarying for age, sex, lifetime Major Depressive Disorder, lifetime non-alcohol substance use disorders, and lifetime alcohol use disorder.

Results: Total drinks consumed in the last 30 days did not differ by HIV serostatus ($p=.202$). Among HIV- older adults, quadratic effects of total drinks on neurocognition occurred such that optimal neurocognition (i.e., global function, executive function, learning, delayed recall, and motor skills) was detected at intermediate levels of “low-risk” drinking (~ 20 to 40 drinks), with poorer performance at the lower and higher ranges of “low-risk” consumption. In PWH, total drinks did not exhibit linear or quadratic associations with neurocognition.

Conclusions: In HIV- “low-risk” drinkers, intermediate levels of recent alcohol use were associated with better neurocognition, consistent with the inverted J-shaped association. The same non-linear effect of recent alcohol consumption on neurocognition was absent in PWH indicating there may be no beneficial or deleterious effects of low-risk alcohol consumption on neurocognition among PWH. Future research is warranted to examine associations between alcohol consumption and HIV-related biopsychosocial disadvantages that may supersede the neurocognitive benefits of alcohol.

Keywords: alcohol drinking; aging; cognition; neuropsychology; cognitive aging

Introduction

Alcohol consumption, particularly heavy use, is prevalent among PWH with rising rates of consumption in older PWH (Edelman et al., 2018, Deren et al., 2019). To date, most studies in older PWH have focused on the combined presence of heavy alcohol use and HIV disease as risk factors for mortality and the development of age-related, multi-system comorbidities (e.g., metabolic disorders, frailty, renal disease) (Molina et al., 2018). With respect to neurobehavioral health, there is evidence that heavy alcohol use compounds HIV-related neurotoxicity (Pfefferbaum et al., 2012, Rosenbloom et al., 2010), thereby impairing higher-order neurocognitive abilities critical for daily functioning (e.g., medication management) (Paolillo et al., 2019, Paolillo et al., 2017, Heinz et al., 2014, Fama et al., 2009). Despite the known adverse neurocognitive effects of heavy alcohol use among older PWH, it is poorly understood whether lower levels of alcohol use similarly increase risk for neurocognitive impairment or, conversely, confer a degree of neuroprotection as has been proposed in prior studies of HIV-seronegative (HIV-) adults (Lang et al., 2007, Kim et al., 2012, Neafsey and Collins, 2011).

[Note: Definitions of light, moderate and heavy drinking have been arbitrarily characterized across the literature; therefore, we are using “low-risk” henceforth to represent less than heavy alcohol consumption] (Kim et al., 2012, Abuse and Alcoholism, 2004, Health and Services, 2007, Dawson, 2011).

The evidence supporting protective effects of alcohol, suggests an inverted J-shaped association between levels of alcohol consumed and risk for a multitude of diseases (e.g., coronary heart disease, myocardial infarction, peripheral arterial disease), such that there is a higher risk among heavy drinkers and abstainers compared to those with low-risk alcohol consumption (Fernández-Solà, 2015, Mostofsky et al., 2016, Klatsky, 2015). The existing literature examining the association between alcohol consumption and neurocognition among HIV- adults also suggests an inverted J-shaped association, such that low-risk alcohol consumption is associated with better neurocognition than alcohol abstinence, and heavy consumption is associated with the worst neurocognition compared to both no consumption and low-risk consumption (Reas et al., 2016, Zuccalà et al., 2001, Lang et al., 2007). A longitudinal study using the UK Biobank found, among middle and older aged adults, a significant curvilinear association between alcohol consumption and neurocognition. Specifically, neurocognitive performance improved with increased alcohol use, up to one standard

drink (i.e., roughly 14 grams of pure alcohol) per day, at which point performance worsened (Piumatti et al., 2018).

Results of studies examining this curvilinear association, however, have been inconsistent. Conflicting evidence suggests a positive linear association between neurocognition and alcohol consumption, rather than a curvilinear association (Parsons and Nixon, 1998). Previous literature suggests that neurocognitive deficits increase with heavier alcohol consumption among older adults (Panza et al., 2012, Cooper et al., 2009, Chan et al., 2010, Parsons and Nixon, 1998). Furthermore, Parsons and Nixon suggest a potential threshold-effect, such that the deleterious effects of alcohol only occur after a specific threshold of consumption (i.e., more than five or six standard drinks per day over an extended period of time for men); with heightened effects occurring at heavier levels of alcohol consumption (Parsons and Nixon, 1998). These inconsistent findings between a curvilinear, linear, and threshold association between alcohol consumption and neurocognition could result from confounding effects of other medical comorbidities, socioeconomic factors, and past alcohol use among current alcohol abstainers, that could contribute more strongly to neurocognitive deficits (Panza et al., 2012, Anstey, 2008).

The putative multisystem benefits of low-risk alcohol consumption in HIV- individuals have not been systematically investigated among PWH. Results of earlier studies suggest elevated rates of alcohol use among PWH while more recent reports show similar rates compared to the general population (Blair et al., 2014, Grant et al., 2017). The majority of alcohol-focused research among PWH has focused on the detrimental effects of heavy drinking or alcohol use disorders (AUD) (Galvan et al., 2002). For example, research has consistently shown combined detrimental effects of heavy drinking and HIV disease on neurocognitive function as well as gray and white matter integrity, with the worst outcomes among the heaviest drinkers (e.g., >100 drinks per month and >6 drinks per occasion) (Rosenbloom et al., 2010, Rothlind et al., 2005). Considering that majority of PWH do not report heavier drinking compared to the general population (Galvan et al., 2002, Blair et al., 2014), there is a need for a more comprehensive understanding of the impact of low-risk alcohol consumption among PWH. Examination of whether low-risk drinking exerts differential neurocognitive effects based on HIV serostatus is particularly salient given the increasingly popular recommendations for older adults to follow certain nutritional guidelines (e.g., Mediterranean diet)

(Morris et al., 2015). Given that HIV disease can enhance vulnerability to physiological damage from environmental stressors (e.g., alcohol) (Desquilbet et al., 2007), there may be no level of alcohol associated with better neurocognitive functioning among PWH.

Advancing age is independently associated with a higher risk of neurocognitive and neurodegenerative diseases including Alzheimer's Disease and its precursor mild cognitive impairment (Wing, 2016). Despite use of combination antiretroviral therapy, older PWH remain particularly vulnerable to HIV-associated neurocognitive impairment and neurodegenerative diseases associated with aging (Heaton et al., 2011, Salthouse, 2009). Considering alcohol consumption is common among PWH, and with advancing age these persons are at a heightened risk for neurocognitive impairment, the present study examined associations between the non-linear effect of recent low-risk alcohol consumption and HIV status on global and domain-specific neurocognitive outcomes. Within the range of low-risk drinking, we hypothesize a curvilinear association between recent alcohol consumption and neurocognition among HIV- individuals, such that intermediate levels of low-risk drinking will be associated with better neurocognitive function compared to non-drinkers and heavier levels; however, we do not expect this curvilinear association among PWH.

Materials and Methods

Participants

Participants included 310 PWH and 89 HIV- older (aged 50 and older) adults enrolled in NIH-funded research studies at the University of California, San Diego (UCSD) HIV Neurobehavioral Research Program (HNRP) from 2003-2016. Participants were recruited from the greater San Diego area by the HNRP. Regulatory approval was obtained from the University of California San Diego Institutional Review Board prior to the start of protocol implementation. We have previously published several papers using other aspects of these data including medication adherence, age of first alcohol use, and neurocognitive function (Paolillo et al., 2017, Paolillo et al., 2019, Saloner et al., 2020, Saloner et al., 2019b). The current study represents a secondary analysis of baseline alcohol use and neurobehavioral data from the HNRP. Exclusion criteria for the current analysis included 1) self-reported current or past diagnosis of a psychotic or mood disorder with psychotic features; 2) presence of a neurological condition that could impair neurocognitive function (e.g., traumatic brain injury with loss of consciousness > 30min, stroke, epilepsy); 3) positive urine toxicology for illicit

drugs (except marijuana) or evidence of alcohol intoxication by Breathalyzer test on the day of testing; 4) current diagnosis of AUD; 5) current diagnosis of non-alcohol substance use disorders (i.e., cannabis, cocaine, hallucinogen, inhalant, opioid, sedative, and methamphetamine); 6) recent (i.e., within the last 30 days) “at risk” alcohol consumption as defined per the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria for “at risk” drinking (i.e., ≥ 15 drinks/week or ≥ 5 drinks/day for men; ≥ 8 drinks/week or ≥ 4 drinks/day for women) (Abuse and Alcoholism, 2005); and 7) aged 49 years and younger. The UCSD Institutional Review Board approved this study, and all participants provided written informed consent to participate.

Neuromedical Evaluation

All participants completed comprehensive medical evaluations and were tested for HIV by enzyme-linked immunosorbent assay (ELISA). A Western Blot confirmed positive results. Reverse transcriptase-polymerase chain reaction (RT-PCR; Amplicor, Roche Diagnostics, Indianapolis, IN) tested levels of HIV viral load in plasma (undetectable < 50 copies/mL).

Psychiatric, Alcohol, and Substance Use Evaluation

Current (i.e., past 12 months) and lifetime mood and substance use disorders were assessed via The Composite International Diagnostic Interview (CIDI, v2.1), a fully-structured, computer-based interview (World Health Organization, 1998). Diagnoses were made in accordance with DSM-IV criteria, as the parent grants from which baseline data were collected were funded before the DSM 5 was published. DSM-IV criteria for alcohol abuse are met when participants report continued alcohol use despite recurring problems (e.g., interpersonal, work-related, legal). DSM-IV criteria for alcohol dependence are met when participants endorse symptoms of tolerance, withdrawal, and impaired control over drinking (American Psychiatric Association, 2000). AUD was assigned when DSM-IV criteria for alcohol abuse or dependence was met in order to maintain consistency with DSM 5 criteria and nomenclature.

Recent alcohol use was assessed via the HNRP Substance Use History form. This form is a modified timeline follow-back measure that assesses alcohol use metrics including the quantity and frequency of alcohol use in the last 30 days (Paolillo et al., 2017). The variable capturing the total number of drinks consumed in the last 30 days was calculated by multiplying the daily rate of alcohol consumption (number of drinks/drinking day) by the number of consumption days in the last 30 days

(number of drinking days/30 days). Total number of drinks consumed in the last 30 days will be hereafter referred to as total drinks. Participants who reported no recent alcohol consumption were included in analyses as alcohol abstainers, with total drinks coded as 0.

Neuropsychological Battery

Participants were administered a well-validated, comprehensive battery of neuropsychological tests designed in accordance with the international consensus conference recommendations (i.e., Frascati criteria) for HIV-associated Neurocognitive Disorders (Heaton et al., 2010, Antinori et al., 2007). The battery assesses seven neurocognitive domains: verbal fluency, executive function, processing speed, learning, delayed recall, working memory, and motor skills. Individual test raw scores were converted into demographically-adjusted (i.e., age, sex, education, race/ethnicity) T-scores ($M = 50$, $SD = 10$ in healthy subjects), which were then averaged across the entire battery and within each domain to derive mean global and domain-specific T-scores, respectively (Heaton et al., 2003, Heaton et al., 2004, Antinori et al., 2007).

Statistical Analyses

HIV group differences on demographic, psychiatric, neurocognitive, and alcohol use characteristics were compared using independent t-tests, Wilcoxon tests, and Chi-square statistics as appropriate. Separate multiple linear regressions examined the interaction between the quadratic effects of total drinks and HIV status on global and domain-specific T-scores. Demographic variables that significantly differed by HIV status at a $p < .05$ threshold (i.e., age, sex, and lifetime Major Depressive Disorder (MDD)) were included as covariates. Considering the high prevalence of lifetime AUD in both persons with and without HIV, lifetime AUD was included as a covariate. Additionally, diagnosis of a lifetime non-alcohol substance use disorder was included as a covariate to account for potential confounding effects of non-alcohol substance use on neurocognitive outcomes. A follow-up analysis was conducted for any model that did not reveal a significant or trend-level interaction term between the quadratic effect of total drinks ($p > .06$) and HIV status. The follow-up analysis examined the interaction between the linear effect of total drinks and HIV status on domain-specific T-scores, covarying for demographic variables included in primary regression analyses. As a secondary follow-up analysis, the independent effects of total drinks and HIV status were examined for any model that did not show a significant interaction term ($p > .05$), covarying for the same demographic variables in

primary regression analyses. Regression analyses were performed using JMP Pro version 14.0.0 (JMP®, Version <14.0.0>. SAS Institute Inc., Cary, NC, 1989-2007).

Exploratory analyses, stratified by HIV status, employed the Johnson-Neyman (J-N) technique to identify specific regions along the quadratic curve of total drinks at which total drinks had a statistically significant effect on neurocognition (Preacher et al., 2006, Johnson and Neyman, 1936, Saloner et al., 2019a). Compared to simple slope analyses that describe quadratic effects based on how the effect of a predictor (i.e., total drinks) changes at different levels (e.g., -1 SD, mean, +1 SD) of that predictor, the J-N technique computes the full range of values for which the predictor slope is statistically significant. These boundaries are referred to as regions of significance. Region of significance analyses were computed using the jtools package in R statistical software (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria)(Long, 2018). Considering long-term heavy alcohol use may have ongoing neurocognitive effects, an additional exploratory analysis examined the association between lifetime history of AUD and alcohol abstinence using a Chi-squared statistic. Finally, we explored the associations between HIV disease characteristics (described in Table 1) and global neurocognitive function using independent t-tests. We have included any significant variables as covariates in the linear regression analysis by HIV-serostatus. These analyses were performed using JMP Pro version 14.0.0 (JMP®, Version <14.0.0>. SAS Institute Inc., Cary, NC, 1989-2007).

Results

Demographic and Clinical Differences by HIV serostatus

Demographic, psychiatric, substance use, alcohol use, HIV disease, and neurocognitive characteristics by HIV group are presented in Table 1. The PWH group was significantly younger, had a higher proportion of males, and had higher rates of current MDD and lifetime MDD than the HIV- group. With respect to recent alcohol consumption, PWH on average reported more drinks per drinking day and more drinking days within the last 30 days than HIV- individuals, yet groups were comparable on all other alcohol use characteristics. In regards to neurocognition, univariably PWH had significantly lower (worse) global function, verbal fluency, executive function, processing speed, working memory, and motor skills T scores ($ps<.05$) than the HIV- group.

Recent Alcohol Consumption, HIV Status, and Neurocognitive Outcomes

Results of linear regressions examining the interaction between the quadratic effect of total drinks and HIV status (i.e., $[\text{total drinks}]^2 \times \text{HIV}$) on neurocognitive outcomes are presented in Table 2. In these adjusted models, the interaction between the quadratic effect of total drinks and HIV status was significant for global function ($p=.030$), executive function ($p=.049$), learning ($p=.003$), delayed recall ($p=.037$), and motor skills ($p=.021$). With respect to covariates, older age, a lifetime history of MDD, and a lifetime history of a non-alcohol substance use disorder were associated with worse neurocognitive performance across multiple domains. Follow-up analyses were conducted to examine the interaction between the linear effect of total drinks and HIV status (i.e., $\text{total drinks} \times \text{HIV}$) on neurocognitive outcomes that showed no significant or trend-level interaction term ($p > .05$) (i.e., verbal fluency, processing speed, and working memory) (Table 3). Similar adjusted linear regression models revealed no significant interaction effects between total drinks and HIV status on domain-specific neurocognition ($ps>.05$). To further examine the independent effects of total drinks and HIV status on neurocognition, linear regression models examined the effects of HIV status, total drinks, and covariates from previous models on neurocognitive outcomes (see Table 4). In these adjusted models, HIV status was significantly associated with verbal fluency ($p=.012$), processing speed ($p=.004$), and working memory ($p<.001$), such that PWH performed significantly worse than their HIV- counterparts. There were no detected effects of total drinks on domain specific neurocognitive outcomes.

Additional follow-up analyses on domains that revealed significant quadratic associations (i.e., global function, executive function, learning, delayed recall, motor skills) were stratified by HIV serostatus (Table 5). Results exploring the associations between HIV disease characteristic and global neurocognitive function suggest a significant negative association between estimated duration of HIV disease and global neurocognitive function ($p=.010$). Therefore, estimated duration of disease was included as a covariate in the linear regression model for PWH. The number of total drinks was not associated with neurocognition in PWH. Estimated duration of disease approached significance for global function ($p=.086$). In the HIV- group, results indicated significant quadratic effects of total drinks on global function ($p=.017$; see Figure 1), executive function ($p=.011$), learning ($p=.011$), delayed recall ($p=.024$), and motor skills ($p=.013$). We applied the J-N technique to inspect these significant changes in the slope of total drinks on neurocognition as a function of total drinks within

the HIV- group (see Figure 2). Total drinks demonstrated positive, statistically significant associations with neurocognition (i.e., lower bound of total drinks slope > 0) at the lower end of “low-risk” drinking (regions of significance: global [0 – 18]; executive function [0 – 14.5]; learning [0 – 23.5]; motor [0 – 22]; delayed recall [0-19]). Conversely, total drinks demonstrated negative, statistically significant associations with neurocognition (i.e., upper bound of total drinks slope < 0) at the higher end of “low-risk” drinking (regions of significance: global [52 – 60]; executive function [45 – 60]; learning [39 – 60]; motor [40 – 60]). Although there was a significant quadratic association between total drinks and delayed recall, the negative slope did not reach statistical significance. Finally, to examine potential ongoing neurocognitive effects of lifetime AUD among alcohol abstainers, a Chi-square statistic was calculated. Results indicate no significant association between having a lifetime history of AUD and currently abstaining from alcohol, $\chi^2(1, N = 421) = 1.11, p = .292$.

Discussion

Our study is among the first to examine the curvilinear association between recent “low-risk” alcohol consumption and neurocognition among persons with and without HIV. Among HIV- individuals, the association between low-risk drinking and neurocognition expectedly followed an inverted-J shaped pattern, with better neurocognition occurring at intermediate levels of “low-risk” drinking compared to alcohol abstinence and heavier consumption. Specifically, region of significance analyses indicated a positive slope of alcohol consumption on global neurocognitive function when the range of total drinks was zero to 18 drinks, whereas a negative slope emerged when the range of total drinks was 52 to 60 drinks; suggesting a potentially innocuous range between 18 to 52 drinks per month for HIV- individuals. This global effect was driven by abilities supported by frontal brain regions (i.e., executive function, learning and motor skills) where alcohol metabolism is thought to be particularly active (Gilman et al., 1990). Additionally, consistent with our hypotheses, there was no quadratic (or linear) association between level of low-risk alcohol consumption and neurocognition among PWH. This suggests the presence of other factors that may supersede the potentially beneficial neurocognitive effects of low-risk alcohol consumption in the context of HIV. For example, age was significantly associated with global function, executive function, learning, and delayed recall in PWH, despite using age-adjusted T-scores in analyses.

Extant literature suggests that the inverted-J shaped association is not unique to neurocognition, which may point towards possible mechanisms underlying the neuroprotective effect of low-risk alcohol consumption. For example, evidence supports a cardioprotective effect of low-risk alcohol consumption including a reduced risk of coronary heart disease, myocardial infarction, ischemic stroke, peripheral arterial disease, and all-cause mortality (Agarwal, 2002, Augusto Di Castelnuovo, 2017, Steven Bell and Martin Bobak, Bell et al., 2017). There is a higher risk among alcohol abstainers and when alcohol consumption is high, and lower risk when alcohol consumption is low (Fernández-Solà, 2015, Mostofsky et al., 2016, Klatsky, 2015). Although our data does not directly measure pathways underlying a potential neuroprotective effect of low-risk alcohol consumption, including its specificity to HIV- adults, several plausible biopsychosocial mechanisms can be drawn from the extant literature. From a biological perspective, low-risk alcohol use has been linked to increased high-density lipoprotein levels (Mukamal et al., 2005) and may carry antithrombotic, antioxidative, and anti-inflammatory effects that benefit the neurovascular unit (Renaud and Ruf, 1996, Nova et al., 2012, Richard et al., 2017). Additionally, alcohol may directly enhance learning and executive function via stimulation of acetylcholine in the prefrontal cortex and hippocampus (Stancampiano et al., 2004, Letenneur et al., 2004). Considering that alcohol consumption increases HDL cholesterol levels, it has been proposed that the association between HDL cholesterol and lowered risk of coronary heart disease is mediated in part by alcohol-induced increases in HDL cholesterol (Suh et al., 1992, De Oliveira e Silva et al., 2000, Gordon et al., 1977).

Other possible mechanisms underlying the observed beneficial effect of low-risk drinking on neurocognition among HIV- individuals in our sample may involve lifestyle factors and/or indicators of socioeconomic status not measured in the current study. For example, previous research exploring beneficial effects of drinking have suggested that low-risk alcohol consumption may be an indicator of higher socioeconomic status and engagement in a healthier lifestyle that includes better nutrition and physical activity (Huckle et al., 2010, Green and Polen, 2001, Piazza-Gardner and Barry, 2012). Moreover, persons of lower socioeconomic status may not have the means to afford alcohol and be more medically compromised which could lead to voluntary or medically recommended abstinence (Collins, 2016). In addition, it is also well known that individuals of higher socioeconomic status are less likely to experience negative consequences from alcohol use compared to those of lower

socioeconomic status who drink the same amount (Katikireddi et al., 2017, Collins, 2016). It is possible that our sample of HIV- participants were of relatively high socioeconomic status, especially compared to our sample of PWH, as HIV disproportionately affects individuals from lower income areas with fewer resources (Oldenburg et al., 2014).

Although we examined associations between certain HIV disease characteristics, alcohol use, and neurocognition, PWH face additional biopsychosocial disadvantages that may explain the lack of beneficial effects of low-risk drinking among this group. Even in the context of low-risk use, the immunosuppressant properties of alcohol may counteract the cardioprotective effects on downstream neurocognitive health among PWH, as immunosuppression leads to greater viral infectivity, replication, and subsequently poorer neuronal integrity (Samet et al., 2007). Furthermore, our HIV groups had different proportions of individuals with current and lifetime depression, with significantly higher rates among PWH. Depression is known to have adverse effects on neurocognitive performance in HIV (Rubin and Maki, 2019), possibly limiting the expression of potentially beneficial effects of low-risk drinking among our PWH sample.

The current study has several limitations. Although we detected effects that remained statistically significant after adjusting for relevant covariates, there could be potential unmeasured health and lifestyle confounders such as disability, social status, and reason for drinking, that may mediate the association between alcohol consumption and neurocognition. Next, our sample of low-risk drinkers, especially among the HIV- group, had fewer drinkers on the high end of the low-risk drinking range, more alcohol abstainers, and more drinkers on the lower end of the low-risk drinking range. Furthermore, we did not have any method to verify self-reported alcohol abstinence. Despite our skewed sample in terms of levels of alcohol consumption, we still detected robust effects even after adjusting for relevant covariates. Objectively measured recent alcohol consumption would have reduced the possibility of misreporting alcohol abstinence, drinking quantities, and frequency; however, we believe structured interviews are still clinically relevant given that our timeline follow-back was only 30 days prior. Future alcohol consumption research should employ methodologies to capture real time and ecologically valid data, rather than relying on retrospective recall. While the full range of “low-risk” drinking does not have discretely defined cut-points for minimal, light, and moderate alcohol use, our inclusion of the J-N technique allowed us to identify specific boundaries of

recent alcohol consumption in which alcohol confers neurocognitive benefits or risks among HIV- individuals. Although these analyses may help clinical efforts at identifying intervals of safe drinking for certain populations, interpretations must caution against the differences in low-risk drinking criteria for men and women. According to the NIAAA criteria for low-risk drinking, we included women who self-report 0-30 drinks in the last 30 days, and men who self-report 0-60 drinks. Therefore, the results of the J-N technique for lower regions of significance are applicable to both men and women, whereas the results in the upper regions of significance are applicable only to men. Future work with equal sample sizes by sex should investigate the associations between recent drinking and neurocognitive function to further adjust for sex differences.

In conclusion, our results are consistent with the hypothesis of a curvilinear association between recent alcohol consumption and neurocognition within the range of low-risk drinking and only among HIV- older adults, such that intermediate levels (~20 to 40 drinks) of recent alcohol use were associated with better neurocognition compared to alcohol abstinence as well as lower and higher ranges of low-risk consumption. Among PWH, there were no detected beneficial or deleterious effects of low-risk alcohol consumption on neurocognition, suggesting that other factors that may supersede the neurocognitive effects of low-risk alcohol consumption in the context of HIV.

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References

- Abuse, N. I. o. A. & Alcoholism 2004. Helping Patients with Alcohol Problems: A Health Practitioner's Guide.
- Abuse, N. I. o. A. & Alcoholism 2005. A pocket guide for alcohol screening and brief intervention. NIAAA Rockville, MD.
- Agarwal, D. P. 2002. Cardioprotective effects of light-moderate consumption of alcohol: A review of putative mechanisms. *Alcohol & Alcoholism*, 37, 409-415.
- American Psychiatric Association 2000. *Diagnostic and statistical manual of mental disorders*, Washington, DC.
- Anstey, K. J. 2008. Alcohol exposure and cognitive development: An example of why we need a contextualized, dynamic life course approach to cognitive ageing—A mini-review. *Gerontology*, 54, 283-291.
- Antinori, A., Arendt, G., Becker, J., Brew, B., Byrd, D., Cherner, M., Clifford, D., Cinque, P., Epstein, L. G. & Goodkin, K. 2007. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, 69, 1789-1799.
- Augusto Di Castelnuovo, S. C., Marialaura Bonaccio, Livia Rago, Amalia De Curtis, Mariarosaria Persichillo, Francesca Bracone, Marco Olivieri, Chiara Cerletti, Maria Benedetta Donati, Giovanni de Gaetano, Licia Iacoviello, on behalf of the Moli-sani Investigators 2017. Moderate alcohol consumption is associated with lower risk for heart failure but not atrial fibrillation. *JACC: Heart Failure*, 5.
- Bell, S., Daskalopoulou, M., Rapsomaniki, E., George, J., Britton, A., Bobak, M., Casas, J. P., Dale, C. E., Denaxas, S. & Shah, A. D. 2017. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *bmj*, 356, j909.
- Blair, J. M., Fagan, J. L., Frazier, E. L., Do, A., Bradley, H., Valverde, E. E., McNaghten, A., Beer, L., Zhang, S. & Huang, P. 2014. Behavioral and clinical characteristics of persons receiving medical care for HIV infection—Medical Monitoring Project, United States, 2009. *Morbidity and Mortality Weekly Report: Surveillance Summaries*, 63, 1-28.

- Chan, K. K. K., Chiu, K. C. & Chu, L. W. 2010. Association between alcohol consumption and cognitive impairment in Southern Chinese older adults. *International journal of geriatric psychiatry*, 25, 1272-1279.
- Collins, S. E. 2016. Associations between socioeconomic factors and alcohol outcomes. *Alcohol research: current reviews*, 38, 83.
- Cooper, C., Bebbington, P., Meltzer, H., Jenkins, R., Brugha, T., Lindesay, J. E. & Livingston, G. 2009. Alcohol in moderation, premorbid intelligence and cognition in older adults: results from the Psychiatric Morbidity Survey. *J Neurol Neurosurg Psychiatry*, 80, 1236-9.
- Dawson, D. A. 2011. Defining risk drinking. *Alcohol Research: Current Reviews*.
- De Oliveira e Silva, E. R., Foster, D., McGee Harper, M., Seidman, C. E., Smith, J. D., Breslow, J. L. & Brinton, E. A. 2000. Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins AI and A-II. *Circulation*, 102, 2347-2352.
- Deren, S., Cortes, T., Dickson, V. V., Guilamo-Ramos, V., Han, B. H., Karpiak, S., Naegle, M., Ompad, D. C. & Wu, B. 2019. Substance Use Among Older People Living With HIV: Challenges for Health Care Providers. *Front Public Health*, 7, 94.
- Desquilbet, L., Jacobson, L. P., Fried, L. P., Phair, J. P., Jamieson, B. D., Holloway, M., Margolick, J. B. & Multicenter, A. C. S. 2007. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. *J Gerontol A Biol Sci Med Sci*, 62, 1279-86.
- Edelman, E. J., Williams, E. C. & Marshall, B. D. L. 2018. Addressing unhealthy alcohol use among people living with HIV: recent advances and research directions. *Curr Opin Infect Dis*, 31, 1-7.
- Fama, R., Rosenbloom, M. J., Nichols, B. N., Pfefferbaum, A. & Sullivan, E. V. 2009. Working and episodic memory in HIV infection, alcoholism, and their comorbidity: baseline and 1-year follow-up examinations. *Alcohol Clin Exp Res*, 33, 1815-24.
- Fernández-Solà, J. 2015. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. *Nature Reviews Cardiology*, 12, 576-587.
- Galvan, F. H., Bing, E. G., Fleishman, J. A., London, A. S., Caetano, R., Burnam, M. A., Longshore, D., Morton, S. C., Orlando, M. & Shapiro, M. 2002. 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*, 63, 179-86.

Gilman, S., Adams, K., Koeppe, R. A., Berent, S., Klun, K. J., Modell, J. G., Kroll, P. & Brunberg, J. A. 1990. Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with positron emission tomography. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, 28, 775-785.

Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B. & Dawber, T. R. 1977. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *The American journal of medicine*, 62, 707-714.

Grant, B. F., Chou, S. P., Saha, T. D., Pickering, R. P., Kerridge, B. T., Ruan, W. J., Huang, B., Jung, J., Zhang, H. & Fan, A. 2017. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA psychiatry*, 74, 911-923.

Green, C. A. & Polen, M. R. 2001. The health and health behaviors of people who do not drink alcohol. *Am J Prev Med*, 21, 298-305.

Health, U. D. o. & Services, a. H. 2007. Helping patients who drink too much: a clinician's guide. *Bethesda, Md: National Institute on Alcohol Abuse and Alcoholism*.

Heaton, R., Clifford, D., Franklin, D., Woods, S., Ake, C., Vaida, F., Ellis, R., Letendre, S., Marcotte, T., Atkinson, J., Rivera-Mindt, M., Vigil, O., Taylor, M., Collier, A., Marra, C., Gelman, B., McArthur, J., Morgello, S., Simpson, D., McCutchan, J., Abramson, I., Gamst, A., Fennema-Notestine, C., Jernigan, T., Wong, J., Grant, I. & Group, C. 2010. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, 75, 2087-96.

Heaton, R., Miller, S., Taylor, M. J. & Grant, I. 2004. Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. *Lutz, FL: Psychological Assessment Resources*.

- Heaton, R., Taylor, M. & Manly, J. 2003. Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III. *Clinical interpretation of the WAIS-III and WMS-III*. Elsevier.
- Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., Leblanc, S., Corkran, S. H., Duarte, N. A., Clifford, D. B., Woods, S. P., Collier, A. C., Marra, C. M., Morgello, S., Mindt, M. R., Taylor, M. J., Marcotte, T. D., Atkinson, J. H., Wolfson, T., Gelman, B. B., McArthur, J. C., Simpson, D. M., Abramson, I., Gamst, A., Fennema-Notestine, C., Jernigan, T. L., Wong, J., Grant, I., Group, C. & Group, H. 2011. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*, 17, 3-16.
- Heinz, A. J., Fogler, K. A., Newcomb, M. E., Trafton, J. A. & Bonn-Miller, M. O. 2014. Problematic alcohol use among individuals with HIV: relations with everyday memory functioning and HIV symptom severity. *AIDS Behav*, 18, 1302-14.
- Huckle, T., You, R. Q. & Casswell, S. 2010. Socio-economic status predicts drinking patterns but not alcohol-related consequences independently. *Addiction*, 105, 1192-202.
- Johnson, P. O. & Neyman, J. 1936. Tests of certain linear hypotheses and their application to some educational problems. *Statistical research memoirs*.
- Katikireddi, S. V., Whitley, E., Lewsey, J., Gray, L. & Leyland, A. H. 2017. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *Lancet Public Health*, 2, e267-e276.
- Kim, J. W., Lee, D. Y., Lee, B. C., Jung, M. H., Kim, H., Choi, Y. S. & Choi, I. G. 2012. Alcohol and cognition in the elderly: a review. *Psychiatry Investig*, 9, 8-16.
- Klatzky, A. 2015. Alcohol and cardiovascular diseases: where do we stand today? *Journal of internal medicine*, 278, 238-250.
- Lang, I., Wallace, R. B., Huppert, F. A. & Melzer, D. 2007. Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. *Age and ageing*, 36, 256-261.
- Letenneur, L., Larrieu, S. & Barberger-Gateau, P. 2004. Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. *Biomed Pharmacother*, 58, 95-9.

- Long, J. A. 2018. jtools: Analysis and presentation of social scientific data. *R package version*, 1.
- Molina, P. E., Simon, L., Amedee, A. M., Welsh, D. A. & Ferguson, T. F. 2018. Impact of Alcohol on HIV Disease Pathogenesis, Comorbidities and Aging: Integrating Preclinical and Clinical Findings. *Alcohol Alcohol*, 53, 439-447.
- Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Bennett, D. A. & Aggarwal, N. T. 2015. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement*, 11, 1007-14.
- Mostofsky, E., Mukamal, K. J., Giovannucci, E. L., Stampfer, M. J. & Rimm, E. B. 2016. Key findings on alcohol consumption and a variety of health outcomes from the Nurses' Health Study. *American journal of public health*, 106, 1586-1591.
- Mukamal, K. J., Jensen, M. K., Gronbaek, M., Stampfer, M. J., Manson, J. E., Pischon, T. & Rimm, E. B. 2005. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation*, 112, 1406-13.
- Neafsey, E. J. & Collins, M. A. 2011. Moderate alcohol consumption and cognitive risk. *Neuropsychiatr Dis Treat*, 7, 465-84.
- Nova, E., Baccan, G., Veses, A., Zapatera, B. & Marcos, A. 2012. Potential health benefits of moderate alcohol consumption: current perspectives in research. *Proceedings of the Nutrition Society*, 71, 307-315.
- Oldenburg, C. E., Perez-Brumer, A. G. & Reisner, S. L. 2014. Poverty matters: contextualizing the syndemic condition of psychological factors and newly diagnosed HIV infection in the United States. *Aids*, 28, 2763-9.
- Panza, F., Frisardi, V., Seripa, D., Logroscino, G., Santamato, A., Imbimbo, B. P., Scafato, E., Pilotto, A. & Solfrizzi, V. 2012. Alcohol consumption in mild cognitive impairment and dementia: harmful or neuroprotective? *Int J Geriatr Psychiatry*, 27, 1218-38.
- Paolillo, E. W., Gongvatana, A., Umlauf, A., Letendre, S. L. & Moore, D. J. 2017. At-Risk Alcohol Use is Associated with Antiretroviral Treatment Nonadherence Among Adults Living with HIV/AIDS. *Alcohol Clin Exp Res*, 41, 1518-1525.

- Paolillo, E. W., Inkelis, S. M., Heaton, A., Saloner, R., Moore, R. C. & Moore, D. J. 2019. Age of Last Alcohol Use Disorder Relates to Processing Speed Among Older Adults Living with HIV. *Alcohol Alcohol*, 54, 139-147.
- Parsons, O. A. & Nixon, S. J. 1998. Cognitive functioning in sober social drinkers: a review of the research since 1986. *Journal of studies on alcohol*, 59, 180-190.
- Pfefferbaum, A., Rosenbloom, M. J., Sasso, S. A., Kemper, C. A., Deresinski, S., Rohlfing, T. & Sullivan, E. V. 2012. Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. *Biol Psychiatry*, 72, 361-70.
- Piazza-Gardner, A. K. & Barry, A. E. 2012. Examining physical activity levels and alcohol consumption: are people who drink more active? *Am J Health Promot*, 26, e95-104.
- Piumatti, G., Moore, S. C., Berridge, D. M., Sarkar, C. & Gallacher, J. 2018. The relationship between alcohol use and long-term cognitive decline in middle and late life: a longitudinal analysis using UK Biobank. *Journal of Public Health*, 40, 304-311.
- Preacher, K. J., Curran, P. J. & Bauer, D. J. 2006. Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *Journal of educational and behavioral statistics*, 31, 437-448.
- Reas, E. T., Laughlin, G. A., Kritz-Silverstein, D., Barrett-Connor, E. & McEvoy, L. K. 2016. Moderate, regular alcohol consumption is associated with higher cognitive function in older community-dwelling adults. *The journal of prevention of Alzheimer's disease*, 3, 105.
- Renaud, S. C. & Ruf, J. C. 1996. Effects of alcohol on platelet functions. *Clin Chim Acta*, 246, 77-89.
- Richard, E. L., Kritz-Silverstein, D., Laughlin, G. A., Fung, T. T., Barrett-Connor, E. & McEvoy, L. K. 2017. Alcohol intake and cognitively healthy longevity in community-dwelling adults: the Rancho Bernardo Study. *Journal of Alzheimer's disease*, 59, 803-814.
- Rosenbloom, M. J., Sullivan, E. V. & Pfefferbaum, A. 2010. Focus on the brain: HIV infection and alcoholism: comorbidity effects on brain structure and function. *Alcohol Res Health*, 33, 247-57.

- Rothlind, J. C., Greenfield, T. M., Bruce, A. V., Meyerhoff, D. J., Flenniken, D. L., Lindgren, J. A. & Weiner, M. W. 2005. Heavy alcohol consumption in individuals with HIV infection: effects on neuropsychological performance. *J Int Neuropsychol Soc*, 11, 70-83.
- Rubin, L. H. & Maki, P. M. 2019. HIV, Depression, and Cognitive Impairment in the Era of Effective Antiretroviral Therapy. *Curr HIV/AIDS Rep*, 16, 82-95.
- Saloner, R., Marquine, M. J., Sundermann, E. E., Hong, S., McCutchan, J. A., Ellis, R. J., Heaton, R. K., Grant, I. & Cherner, M. 2019a. COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for Neurocognitive Impairment in Men Living with HIV. *J Acquir Immune Defic Syndr*.
- Saloner, R., Paolillo, E. W., Kohli, M., Murray, S. S., Moore, D. J., Grant, I. & Cherner, M. 2020. Genetic variation in alcohol dehydrogenase is associated with neurocognition in men with HIV and history of alcohol use disorder: preliminary findings. *J Neurovirol*.
- Saloner, R., Paolillo, E. W., Umlauf, A., Moore, D. J., Heaton, R. K., Grant, I., Cherner, M. & Group, T. 2019b. Conditional Effects of Lifetime Alcohol Consumption on Methamphetamine-Associated Neurocognitive Performance. *J Int Neuropsychol Soc*, 25, 787-799.
- Salthouse, T. A. 2009. When does age-related cognitive decline begin? *Neurobiology of aging*, 30, 507-514.
- Samet, J. H., Cheng, D. M., Libman, H., Nunes, D. P., Alperen, J. K. & Saitz, R. 2007. Alcohol consumption and HIV disease progression. *J Acquir Immune Defic Syndr*, 46, 194-9.
- Stancampiano, R., Carta, M., Cocco, S., Curreli, R., Rossetti, Z. L. & Fadda, F. 2004. Biphasic effects of ethanol on acetylcholine release in the rat prefrontal cortex. *Brain Res*, 997, 128-32.
- Steven Bell, M. D., Eleni Rapsomaniki, Julie George, Annie Britton, & Martin Bobak, J. P. C., Caroline E Dale, Spiros Denaxas, Anoop D Shah, Harry Hemingway Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ*, 356, j909.
- Suh, I., Shaten, B. J., Cutler, J. A. & Kuller, L. H. 1992. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. *Annals of Internal Medicine*, 116, 881-887.
- Wing, E. J. 2016. HIV and aging. *Int J Infect Dis*, 53, 61-68.

World Health Organization 1998. *Composite Diagnostic International Interview (CIDI, version 2.1)*, Geneva, Switzerland, World Health Organization.

Zuccalà, G., Onder, G., Pedone, C., Cesari, M., Landi, F., Bernabei, R. & Cocchi, A. 2001.

Dose-related impact of alcohol consumption on cognitive function in advanced age: results of a multicenter survey. *Alcoholism: Clinical and Experimental Research*, 25, 1743-1748.

Figure Legends.

Figure 1. Total drinks and global neurocognitive performance by HIV serostatus

Figure 2. Regions of significance (i.e., ranges at which the association between total drinks and neurocognition are significant) among HIV- only. Displayed are the neurocognitive outcomes for which linear regression models showed a significant interaction between alcohol consumption and HIV serostatus. The region of significance to the left of each dashed line indicates the association between total drinks and neurocognition is significantly positive. The region to the right of the right dashed line indicates the association between total drinks and neurocognition is significantly negative. For example, the association between total drinks and global neurocognition (Panel A) is significantly positive below 18 drinks, and is significantly negative above 52 drinks. Note. sig = significant; ns = not significant

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	PWH N=310	HIV- N=89	
	Mean (SD), n (%), or	median [IQR]	p-value
<i>Demographics</i>			
Age (years)	56.2 (5.7)	59.2 (7.9)	<.001
Education (years)	14.2 (3.0)	14.0 (2.5)	.458
Sex (male)	268 (86.5%)	59 (66.3%)	<.001
Ethnicity (Non-Hispanic White)	184 (59.4%)	62 (69.7%)	.084
WRAT4 Reading	102.0 (15.8)	104.3 (13.8)	.933
<i>Psychiatric and Substance Use Diagnosis</i>			
Current MDD	44 (14.2%)	3 (3.3%)	.004
Lifetime MDD	177 (57.1%)	22 (24.7%)	<.001
Lifetime Non-Alcohol SUD	134 (43.2%)	36 (40.5%)	.716
Current Cannabis Use Disorder	0 (0%)	0 (0%)	–
Lifetime Cannabis Use Disorder	69 (22.3%)	25 (28.1%)	.259
<i>AUD Characteristics</i>			
Current AUD	0 (0%)	0 (0%)	–
Lifetime AUD	147 (47.4%)	43 (48.3%)	.905
Years of AUD	10.0 (11.2)	12.4 (15.2)	.584
Years Since AUD	14.2 (10.6)	16.8 (12.6)	.411
Drinks/Drinking Day	1.7 (0.8)	2.0 (0.9)	.017
Drinking Days/30 days	8.0 (10.0)	6.1 (9.1)	.022
Total Drinks/30 days	10.3 (16.0)	9.9 (16.1)	.674
Alcohol Abstainer (yes)	79 (25.5%)	16 (18.0%)	.160
<i>HIV Characteristics</i>			
History of AIDS	222 (71.6%)	–	–
Detectable plasma viral load ^a	97 (31.3%)	–	–
Current CD4 count	471 [306, 665]	–	–
Nadir CD4 count	133.5 [50, 245.3]	–	–
Estimated years of HIV disease	14.4 [8.8, 20.5]	–	–
ARV Status (on cART)	256 (82.6%)	–	–
<i>Neurocognitive Function</i>			

GDS Impairment (impaired)	147 (47.4%)	33 (37.1%)	.092
Global Mean T-score	44.4 (6.8)	47.5 (6.1)	<.001
Verbal Fluency Mean T-score	46.9 (9.2)	49.8 (8.1)	.005
Executive Function Mean T-score	43.8 (9.5)	48.0 (8.2)	<.001
Processing Speed Mean T-score	46.1 (8.8)	49.5 (8.0)	.003
Learning Mean T-score	40.4 (9.1)	42.3 (8.9)	.086
Delayed Recall Mean T-score	41.1 (10.1)	42.6 (9.2)	.206
Working Memory Mean T-score	45.1 (8.7)	49.1 (8.2)	<.001
Motor Skills Mean T-score	45.5 (10.2)	48.3 (10.0)	.023

Note. PWH = people with HIV; WRAT4 Reading = Wide-Range Achievement Test 4 reading subtest; GDS = global deficit score; MDD = Major Depressive Disorder; SUD = Substance Use Disorder; AUD = Alcohol Use Disorder; ART = antiretroviral therapy
p-values were calculated using Wilcoxon Signed-Rank Tests for non-normally distributed continuous outcomes or t-test for normally distributed continuous outcomes. Chi-squared statistics were used for dichotomous outcomes

^aDefined as >50 copies/mL in plasma

Predictor Variables	Global Function		Verbal Fluency		Executive Function		Processing Speed	
	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
HIV Status ^a	-5.03 (1.17)	<.001	-4.21 (1.59)	.009	-6.74 (1.66)	<.001	-3.46 (1.54)	.026
Total Drinks	0.24 (0.09)	.017	0.14 (0.13)	.289	0.32 (0.14)	.024	0.02 (0.13)	.849
(Total Drinks) ²	-0.007 (0.003)	.020	-0.004 (0.004)	.324	-0.009 (0.004)	.021	-0.002 (0.004)	.598
Total Drinks x HIV	-0.26 (0.11)	.017	-0.23 (0.15)	.116	-0.30 (0.15)	.053	-0.01 (0.14)	.942
(Total Drinks) ² x HIV	0.007 (0.003)	.030	0.005 (0.004)	.246	0.009 (0.004)	.049	0.001 (0.004)	.764
Age	-0.21 (0.05)	<.001	-0.18 (0.07)	.017	-0.18 (0.08)	.017	-0.21 (0.07)	.003
Sex ^b	-0.29 (0.91)	.752	0.88 (1.23)	.475	-1.56 (1.29)	.226	-0.01 (1.19)	.995
Lifetime MDD ^c	-1.89 (0.68)	.006	-1.33 (0.92)	.149	-1.96 (0.96)	.041	-2.76 (0.89)	.002
Lifetime SUD ^d	1.58 (0.71)	.027	2.90 (0.97)	.003	0.65 (1.01)	.518	1.11 (0.94)	.238
Lifetime AUD ^e	-0.53 (0.70)	.444	-1.54 (0.95)	.105	-1.02 (0.99)	.301	0.28 (0.92)	.759

Predictor Variables	Learning		Delayed Recall		Working Memory		Motor	
	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
HIV Status ^a	-5.37 (1.59)	<.001	-4.37 (1.74)	.012	-5.72 (1.56)	<.001	-6.00 (1.83)	.001
Total Drinks	0.45 (0.13)	<.001	0.36 (0.15)	.014	0.21 (0.13)	.109	0.44 (0.15)	.005
(Total Drinks) ²	-0.01 (0.004)	.002	-0.009 (0.004)	.029	-0.005 (0.004)	.182	-0.01 (0.004)	.012
Total Drinks x HIV	-0.51 (0.15)	<.001	-0.38 (0.16)	.018	-0.23 (0.14)	.109	-0.46 (0.17)	.007
(Total Drinks) ² x HIV	0.01 (0.004)	.003	0.01 (0.005)	.037	0.006 (0.004)	.157	0.01 (0.005)	.021
Age	-0.30 (0.07)	<.001	-0.36 (0.08)	<.001	-0.11 (0.07)	.126	-0.15 (0.08)	.084
Sex ^b	0.77 (1.23)	.529	1.03 (1.35)	.446	-1.51 (1.21)	.212	-0.83 (1.42)	.561
Lifetime MDD ^c	-1.99 (0.92)	.030	-1.92 (1.00)	.056	-1.47 (0.90)	.104	-1.49 (1.06)	.161
Lifetime SUD ^d	1.23(0.96)	.203	1.96 (1.06)	.065	1.33 (0.95)	.162	2.28 (1.11)	.042
Lifetime AUD ^e	0.18 (0.94)	.846	0.46 (1.03)	.653	-0.15 (0.93)	.873	-1.72 (1.09)	.115

Note. Bolded p -values are significant at $p < .05$. SE = standard error; MDD = major depressive disorder; SUD = substance use disorder; AUD = alcohol use disorder

^aHIV seropositive compared to HIV seronegative status

^bFemale compared to male sex

^cLifetime history of MDD compared to no lifetime MDD

^dLifetime history of SUD compared to no lifetime SUD

^eLifetime history of AUD compared to no lifetime AUD

Predictor Variables	Verbal Fluency		Processing Speed		Working Memory	
	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
HIV Status ^a	-2.92 (1.15)	.011	-3.16 (1.11)	.005	-4.19 (1.12)	<.001
Total Drinks	0.02 (0.06)	.680	-0.04 (0.06)	.522	0.05 (0.06)	.354
Total Drinks x HIV	-0.08 (0.07)	.234	0.03 (0.06)	.662	-0.05 (0.07)	.453
Age	-0.17 (0.07)	.017	-0.22 (0.07)	.002	-0.11 (0.07)	.126
Sex ^b	0.87 (1.22)	.475	-0.11 (1.18)	.926	-1.57 (1.20)	.190
Lifetime MDD ^c	-1.35 (0.92)	.142	-2.74 (0.89)	.002	-1.48 (0.90)	.101
Lifetime SUD ^d	2.91 (0.97)	.004	1.07 (0.93)	.253	1.32 (0.95)	.165
Lifetime AUD ^e	-1.59 (0.94)	.093	0.29 (0.91)	.749	-0.20 (0.93)	.829

Note. Bolded *p*-values are significant at $p < .05$. SE = standard error; PWH = people with HIV; MDD = major depressive disorder

^aHIV seropositive compared to HIV seronegative status

^bFemale compared to male sex

^cLifetime history of MDD compared to no lifetime MDD

^dLifetime history of SUD compared to no lifetime SUD

^eLifetime history of AUD compared to no lifetime AUD

Predictor Variables	Verbal Fluency		Processing Speed		Working Memory	
	β (SE)	p -value	β (SE)	p -value	β (SE)	p -value
HIV Status ^a	-2.88 (1.15)	.012	-3.17 (1.11)	.004	-4.17 (1.12)	<.001
Total Drinks	-0.04 (0.03)	.192	-0.01 (0.03)	.594	0.02 (0.03)	.574
Age	-0.17 (0.07)	.022	-0.22 (0.07)	.002	-0.11 (0.07)	.141
Sex ^b	0.78 (1.22)	.524	-0.08 (1.18)	.949	-1.63 (1.20)	.173
Lifetime MDD ^c	-1.40 (0.92)	.129	-2.72 (0.89)	.002	-1.51 (0.90)	.094
Lifetime SUD ^d	1.92 (0.97)	.003	1.06 (0.93)	.255	1.32 (0.95)	.163
Lifetime AUD ^e	-1.55 (0.94)	.101	0.28 (0.91)	.760	-0.18 (0.92)	.849

Note. Bolded p -values are significant at $p < .05$. SE = standard error; PWH = people with HIV; MDD = major depressive disorder

^aHIV seropositive compared to HIV seronegative status

^bFemale compared to male sex

^cLifetime history of MDD compared to no lifetime MDD

^dLifetime history of SUD compared to no lifetime SUD

^eLifetime history of AUD compared to no lifetime AUD

	HIV-		PWH	
Outcome: Global Function	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
Total Drinks	0.22 (0.09)	.020	-0.02 (0.05)	.706
(Total Drinks) ²	-0.006 (0.003)	.017	0.00008 (0.001)	.948
Age	-0.18 (0.08)	.029	-0.22 (0.07)	.002
Sex ^a	-1.28 (1.38)	.357	-0.17 (1.17)	.886
Lifetime MDD ^b	-3.21 (1.46)	.030	-1.35 (0.77)	.082
Lifetime SUD ^c	1.04 (1.42)	.466	1.72 (0.82)	.037
Lifetime AUD ^d	-1.72 (1.43)	.232	-0.02 (0.80)	.843
Estimated duration of HIV disease ^e	–	–	-0.09 (0.05)	.086
Outcome: Executive Function	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
Total Drinks	0.27 (0.12)	.029	0.03 (0.07)	.715
(Total Drinks) ²	-0.009 (0.003)	.011	-0.0007 (0.002)	.713
Age	-0.14 (0.11)	.185	-0.20 (0.10)	.047
Sex ^a	-3.36 (1.83)	.071	-0.80 (1.68)	.636
Lifetime MDD ^b	-5.14 (1.93)	.009	-1.11 (1.11)	.317
Lifetime SUD ^c	-0.72 (1.88)	.703	0.89 (1.18)	.451
Lifetime AUD ^d	-0.95 (1.89)	.618	-0.82 (1.15)	.474
Estimated duration of HIV disease ^e	–	–	-0.06 (0.07)	.431
Outcome: Learning	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
Total Drinks	0.47 (0.13)	<.001	-0.06 (0.07)	.345
(Total Drinks) ²	-0.01 (0.004)	.011	0.0006 (0.002)	.760
Age	-0.28 (0.12)	.019	-0.32 (0.09)	<.001
Sex ^a	1.08 (2.02)	.594	0.32 (1.57)	.837
Lifetime MDD ^b	-1.82 (2.12)	.395	-1.85 (1.04)	.075
Lifetime SUD ^c	2.03 (2.07)	.331	1.11 (1.10)	.315
Lifetime AUD ^d	-1.99 (2.09)	.342	0.69 (1.07)	.523
Estimated duration of HIV disease ^e	–	–	-0.05 (0.07)	.465
Outcome: Delayed Recall	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
Total Drinks	0.37 (0.14)	.014	-0.03 (0.07)	.649
(Total Drinks) ²	-0.009 (0.004)	.024	0.0006 (0.002)	.750
Age	-0.21 (0.13)	.112	-0.44 (0.10)	<.001
Sex ^a	1.48 (2.19)	.499	0.35 (1.72)	.841
Lifetime MDD ^b	-3.04 (2.30)	.191	-0.71 (0.57)	.211

Lifetime SUD ^c	2.26 (2.25)	.317	0.92 (0.60)	.127
Lifetime AUD ^d	-1.21 (2.26)	.593	0.50 (0.59)	.399
Estimated duration of HIV disease ^e	–	–	-0.07 (0.07)	.348
Outcome: Motor Skills	β (SE)	<i>p</i> -value	β (SE)	<i>p</i> -value
Total Drinks	0.39 (0.15)	.011	-0.02 (0.08)	.798
(Total Drinks) ²	-0.01 (0.004)	.013	0.00005 (0.002)	.981
Age	-0.05 (0.14)	.697	-0.20 (0.11)	.063
Sex ^a	-1.83 (2.30)	.428	-0.54 (1.80)	.763
Lifetime MDD ^b	-5.75 (2.42)	.020	-0.37 (1.19)	.753
Lifetime SUD ^c	0.45 (2.36)	.849	2.62 (1.27)	.040
Lifetime AUD ^d	-1.99 (2.38)	.406	-1.34 (1.23)	.276
Estimated duration of HIV disease ^e	–	–	-0.06 (0.07)	.434

Note. Bolded *p*-values are significant at $p < .05$. SE = standard error; PWH = people with HIV; MDD = major depressive disorder

^aFemale compared to male sex

^bLifetime history of MDD compared to no lifetime MDD

^cLifetime history of SUD compared to no lifetime SUD

^dLifetime history of AUD compared to no lifetime AUD

^eCovariate included for PWH only

Table Legends.

Table 1. Demographic and clinical characteristics by HIV serostatus

Table 2. Results of linear regressions examining the interaction between the quadratic effect of total drinks and HIV status on neurocognitive outcomes

Table 3. Results of follow-up regression analysis examining the interaction between the linear effect of total drinks and HIV status (i.e., total drinks x HIV) on neurocognitive outcomes that showed no significant interaction term

Table 4. Results of follow-up regression analysis examining the independent effects of total drinks and HIV status on neurocognition

Table 5. Results of follow-up regression analyses examining the quadratic effect of total drinks on significant neurocognitive outcomes by HIV serostatus

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