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Age-Accelerated Increase of White Matter Hyperintensity Volumes is Exacerbated by Heavy Alcohol Use in People Living with HIV

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Abstract

Background.—Antiretroviral treatment has enabled people living with HIV infection to have a near-normal lifespan. With longevity come opportunities for engaging in risky behavior, including initiation of excessive drinking. Given that both HIV infection and alcohol use disorder (AUD) can disrupt brain white matter integrity, we questioned whether HIV infection, even if successfully treated, or AUD alone results in signs of accelerated white matter aging and whether HIV+AUD comorbidity further accelerates brain aging.

Methods.—Longitudinal MRI-FLAIR data were acquired over 15 years in 179 controls, 204 AUD participants, 70 with HIV, and 75 comorbid for HIV+AUD. White matter hyperintensity (WMH) volumes were quantified and localized and their functional relevance was examined with cognitive and motor testing.

Results.—The three diagnostic groups each had larger WMH volumes than controls. Although all four groups exhibited accelerating volume increases with aging, only the HIV groups showed faster WMH enlargement than controls; the comorbid group showed faster acceleration than the HIV-only group. Sex and HIV infection length, but not viral suppression status, moderated acceleration. Correlations emerged between WMH volumes and Attention/Working Memory and Executive Function scores of the AUD and HIV groups, and between WMH volumes and Motor Skills in the three diagnostic groups.

Conclusions.—Even treated HIV can show accelerated aging, possibly from treatment sequelae or legacy effects, and notably from AUD comorbidity. WMH volumes may be especially relevant

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for tracking HIV and AUD brain health because each condition is associated with liability for hypertensive processes, for which WMHs are considered a marker.

Keywords

HIV infection; alcohol; brain; white matter hyperintensity; aging; cognition

INTRODUCTION

Currently, an estimated 38.4 million people worldwide are aging with the human immunodeficiency virus (HIV)(1), and 51% of people living with HIV (PLWH) in the U.S. are 50 years and older(2). Antiretroviral therapy (ART) has reduced the risk for opportunistic infections(3) and has considerably improved prognosis and life expectancy in PLWH(4–6). Brain white matter injuries such as progressive multifocal leukoencephalopathy(7–9), HIV-related encephalopathy(10), and ART-triggered immune responses (i.e., immune reconstitution inflammatory syndrome, IRIS)(11–13) have all declined. Yet, quantitative neuroimaging studies provide initial cross-sectional(14) and longitudinal(15) (but see16) evidence for greater age-related declines in cortical volume of largely treated HIV groups than in uninfected control groups. Thus, even in ART-treated, virally-suppressed HIV, infection or pharmacotreatment legacy effects may contribute to accelerated aging(17–19).

Accompanying expanded longevity are opportunities to develop comorbidities, thereby complicating an understanding of aging in PLWH. Indeed, a large-scale longitudinal study reported more comorbidities in PLWH than in uninfected participants who were followed biennially for about 6 years. At their initial examination, participants, who were ages 50–55 years old, had nearly all been treated successfully indexed by low viral loads. Greater numbers of comorbidities unrelated to HIV infection in PLWH increased their risk of death and number of disability-adjusted life-years(20) and highlight the need to consider common comorbidities in studies of aging with HIV.

Evidence for quadratic or even exponential increases in brain structural features, such as lateral ventricular volumes(21) or presence of white matter hyperintensities (WMH),(22, 23) occurs with advancing age in neurologically healthy men and women. The possibility of acceleration of normal aging in PLWH is consistent with the hypothesis that early disease or insult, even when overcome, can re-emerge as a factor to accelerate normal aging(24). Accelerated aging in HIV alone and in combination with common comorbidities, notably alcohol use disorder (AUD)(25, 26), may also herald signs of premature cognitive and motor decline(15, 27–29) and HIV Associated Neurocognitive Disorder(30, 31), especially as PLWH reach ages at risk for dementia. For brain structure, factors accelerating gray matter and white matter degradation are HIV+AUD comorbidity and aging(15, 32). Several studies noted a compounded adverse effect of HIV+AUD comorbidity on white matter diffusivity metrics(33, 34). Additionally, WMH, visible in periventricular (PVWMH) and deep (DWMH) white matter regions, occur in HIV, AUD, and normal aging(18, 35–37), and tracking the trajectories of these neuroradiological signs may serve to identify modifiable risk factors and comorbidity targets for prevention.

WMH is a neuroimaging feature of cerebral small vessel disease commonly found in normal aging(38–43), HIV infection(44, 45) (46–48), and AUD(49, 50). As in the general population, age, hypertension, and diabetes(36, 51–55) are major risk factors(35) contributing to WMH burden, which is also associated with worse cognitive performance [general population(56–58); PLWH on ART(35, 52, 54, 59, 60)]. Relations between WMH and cognitive and motor performance may be mediated by hypertension(61, 62) or other factors(63, 64), including education(14, 65), ART(52, 66, 67), hepatitis C virus (HCV) comorbidity(68), and WMH location(69–72).

Quantitative measurement of the size and location of WMH(73) in AUD, HIV, and HIV+AUD comorbidity has the potential of leading to a mechanistic understanding of this anomalous tissue as people age with these conditions(41). Accordingly, we focused on WMH volumetry to test the following hypotheses in people with AUD, HIV, and HIV+AUD and in an unaffected comparison group examined contemporaneously: 1) MRI data acquired longitudinally would reveal significantly larger WMH volumes and faster enlargement in the three diagnostic groups than in control participants; 2) high viral load, high blood pressure, and heavy alcohol use would be associated with faster acceleration of WMH volumes; and 3) greater WMH volumes would be predictive of poorer cognitive and motor performance regardless of diagnosis. Exploratory analysis examined potential sex differences in presence and progression of WMH volume enlargement.

METHOD

Participants

Data collection proceeded from 12 October 2006 to 25 October 2021 of our four study groups: 179 control, 204 AUD, 70 HIV, 75 HIV+AUD (Supplemental Figure 1; Table 1). Participants were recruited from local alcohol and drug recovery centers, HIV clinics, post card mailings, recruitment flyers, and word of mouth. Most of these participants were also represented in our earlier longitudinal studies(15, 74). The current study focus was on the detection and quantification of WMHs quantified from 1,056 FLAIR images; participants were aged 18.5 to 86.1 years old at study entry.

After obtaining written informed consent for study participation, approved by the SRI International and Stanford University School of Medicine Institutional Review Boards, all participants underwent Structured Clinical Interviews for DSM-IV revised (75) to determine diagnosis for alcohol dependence and DSM-5 diagnosis for AUD.(76) Interviews included structured health questionnaires, a semi-structured timeline follow-back interview to quantify lifetime alcohol consumption.(77, 78) Principal exclusion criteria at study entry were history of schizophrenia, bipolar disorder, and neurological disorders other than AUD. Substance use dependence (current or in remission) for illicit drugs was common and involved cocaine, amphetamines, opiates, and cannabis (although now legal in California). Hematological evaluation determined HIV and hepatitis C presence and load. All participants also completed screening to ensure MRI safety. Starting each study day, participants underwent a breathalyzer to test for recent alcohol consumption.

Neuroimaging acquisition and analysis

Protocols and specific parameters are presented in supplemental material. Briefly, scanning was conducted at SRI International on a GE Discovery MR750 system. Detection and localization of WMHs used three MRI acquisition protocols: T1-weighted (T1-w) MRI for anatomical localization, T2-weighted MRI for skull stripping, and FLAIR (FLuid-Attenuated Inversion Recovery) imaging for estimates of WMH volumes.

WMH analysis was accomplished with the "UBO Detector," a cluster-based, fully automated pipeline for extracting and calculating WMH on a voxel basis(79, 80); see Supplemental Material. This procedure yielded voxel maps of total, periventricular (PVWMH), and deep (DWMH) WMHs (Figure 1) and WMH locations by four lobar regions. Analysis required that FLAIR and T1-w data be transformed into MNI space prior to non-rigid transformation into standard SRI atlas space. This was necessary for accurate placement of anatomical locations to enable comparisons across individuals and across imaging modalities on a voxel-wise basis without the need for further correction for intracranial volume.

Functional measures

The neuropsychological test battery used cognitive and motor tests (Supplemental Table 1) to calculate neuropsychological composite scores(30, 31) representing five functional domains: Executive Functioning, Attention/Working Memory, Verbal and Visual Learning, Verbal and Visual Memory, and Motor Skills. To create a composite, scores of each test were transformed into age, education, and sex corrected Z-scores based on scores from 102 cognitively-intact, volunteers (47 women; 47.9±14.9 years; 50 White, 25 Black, 27 other race; 15.8±2.4 years educated; 27.1±12.9 SES; 90 right handed)(81). Composite scores for each domain equaled the average, demographically-adjusted Z-scores comprising that domain. A summary composite score was the mean of the five domain composite scores(82).

Sitting blood pressure was collected twice. The mean of each of the two diastolic and systolic measures was used as a correlate of WMH metrics.

Statistical analysis

Statistical analysis was performed using R 3.5.1 (R Core Team, 2019) on WMH volumes obtained with the UBO analysis procedure. The primary statistic was a linear mixed effects model (*lmer*) separately predicting each WMH volume as a function of group (control, AUD, HIV, and HIV+AUD)+age. Because of the heteroscedasticity of WMH volumes across individuals, their values were square-root transformed before statistical analysis. Interactions with age tested potential group differences in rates of change over the exam range. To account for differences in demographic characteristics, statistical models included diagnosis, age (and age^2), sex, race, socioeconomic status (SES), years of education, BMI, systolic and diastolic blood pressure, and depressive symptoms (Beck Depression Inventory score) in multiple regression to test whether any of these variables could account for group differences observed in WMH volumes or their interactions with age. Secondary analyses examined the influence on the WMH volumes of HIV-related factors in the HIV groups and four principal drugs of abuse—cocaine, amphetamine, opiates, and cannabis—within

each patient group. The model outputs produced t and p values for each diagnostic group relative to the controls. To compare HIV to HIV+AUD, the model was rerun on the two HIV groups with HIV as the index level. Further *lmer* calculations included sex in the model. Correlations examined relations between regional WMH volumes and cognitive and motor, hematological, and blood pressure scores within each diagnostic group. Bonferroni correction was applied to correct for multiple comparisons in each primary analysis.

RESULTS

The mainstay of the statistical test results is presented in the tables and figures.

Tests of diagnostic differences in WMH volumes and evidence for accelerated aging

For all four study groups, age-squared regression rather than linear age models best fit the relations between regional WMH volumes and age (Figure 2). Thus, WMH volumes were larger in older than younger participants in all four study groups, including those in the control group screened to meet health criteria. Tests of group differences were based on multiple regression using *lmer* accounting for sex, race, SES, education, BMI, BDI, and systolic and diastolic blood pressure. The results indicated that the three diagnostic groups—AUD, HIV, and HIV+AUD—had significantly larger total, PVWMH, and DWMH volumes than the control group, with one exception: the DWMH volume difference was not significant between the control and comorbid group (Table 2, left).

The next analyses sought accelerated aging differences by testing for interactions between diagnostic group and the age-squared functions. The age-related accelerations in the AUD group were not statistically greater than those in the control group. By contrast, significant group by age interactions were identified in both HIV groups relative to controls in PVWMH and total WMH volumes (Table 2, right). A further comparison of aging interactions focused on the two HIV groups and yielded a significantly greater accelerated aging of PVWMH volumes in the HIV+AUD group relative to the HIV only group (Figure 3).

Of the factors intended to adjust for demographic differences among the groups, sex, SES, race, and blood pressure emerged as significant contributors in a few instances but did not remove the primary group or interaction effects noted above. Specifically, for the comparisons between AUD and controls, the significant effects were for age and diagnosis for all three WMH measures but not accelerated age effects greater than those in the controls. For the HIV comparisons, age and diagnosis effects were significant as were the effects of sex (larger relative WMH volumes in women than men) and SES (larger volumes in people with poorer SES); interactions endured for total and PVWM but not DWMH volumes. For the HIV+AUD comparisons, significant age and diagnosis effects endured for total and PVWMH volume despite additional significant effects of sex (larger relative WMH volumes in women than men), race (greater burden in Black and Asian participants), and systolic blood pressure; interactions endured for total and PVWM but not DWMH volumes. Finally, for the HIV only vs. HIV+AUD comparisons, the age-by diagnosis interaction remained significant for PVWMH, where the volumes accelerated faster over age in the comorbid group than in HIV-only group.

Disease and drug variables potentially influencing WMH volumes

Factors relevant to AUD were age of AUD onset and to HIV infection were estimated age of infection, ART history with reference to history of efavirenz, CD4 nadir and count, CD8 count, CD4/CD8, viral suppression, and HCV infection. Specifically, more years with an HIV infection diagnosis in the HIV+AUD group (total r=.378, p=0013; PVWMH r=.270, p=.024; DWMH r=.392, p=8e-04) and older age at initial AUD diagnosis in the AUD group correlated significantly with larger WMH volumes (total r=.282, p=.0001; PVWMH r=.265, p=.0003; DWMH r=.278, all p's=.0001). Individuals with versus without an HIV-related disease conditions—CD4 cell count nadir, CD4 cell count, history of an AIDS-defining event, HCV, and nicotine diagnosis—did not differ in regional WMH volumes (p-values=.0899 to .9377, data not shown). We also examined the potential effect of ART type, focusing on treatments that included efavirenz, which are considered especially neurotoxic(83), but found that history of efavirenz use did not remove evidence for age acceleration of the PVWMH volumes of the PLWH with versus without AUD (t=−0.229, p=.819).

Regarding the role of viral suppression on WMH volumes, the HIV groups were divided according to individuals with viral loads < 50 counts/mL (47 HIV and 46 HIV+AUD, considered virally suppressed) and those with viral loads ≥ 50 counts/mL (15 HIV and 21 HIV+AUD). In both HIV groups, those considered virally suppressed had significantly higher CD4 cell counts (HIV t=3.411, p=.0014; HIV+AUD t=4.29, p=.0001) and CD4/CD8 ratios (HIV t=5.10, p<.0001; HIV+AUD t=3.82, p=.0003). Despite these differences, virally suppressed versus non-suppressed HIV groups did not differ in the expected direction for any regional WMH volume. Although PVWMH volumes of the comorbid group were larger than those of the HIV-only group, the difference was not significant (t=1.744, p=.0852); unexpectedly, the non-suppressed HIV group had a lesser DWMH burden than the virally-suppressed group (t=2.92, p=.0051).

We also sought differences within each diagnostic group based on presence vs. absence of HCV infection. None was significant: HIV: total WMH t=0.947, p=.351; PVWMH t=1.162, p=.253; DWMH t=.435, p=.666. HIV+AUD: total WMH t=1.205, p=.233; PVWMH t=1.727, p=.090; DWMH t=−.113, p=.910.

Finally, the influence on the WMH volumes of recent use (that is, over the past month) of any of four principal drugs of abuse—cocaine, amphetamine, opiates, and cannabis—was tested within each patient group. In no case were our findings of group differences or age-accelerated changes in WMH burden accounted for by such use of any of these drugs. This result held whether the *lmer* was conducted for each drug alone (p=.163 to .944) or whether all drugs were entered into a single analysis for each diagnostic comparison (p=.083 to .948).

Group differences on test composite scores and correlations with WMH volumes

Each diagnostic group achieved five neuropsychological test composite scores and a composite mean score that were significantly lower than those of the control group (p≤.001, Figure 4). Performance on multiple composites across the four study groups correlated

with larger WMH volumes, and most correlations noted next met correction for multiple comparisons with directional testing ($p \leq .017$, Table 3; Figure 5). Specifically, in the AUD group, Attention/Working Memory, Executive Function, Motor Skills, and mean domain scores correlated with larger total, PVWMH, and DWMH volumes. In the HIV group, the strongest relations were between lower scores on the Attention/Working Memory and the Motor Skills composites and larger total and DWMH volumes. In the HIV+AUD group, Motor Skills and mean composite scores correlated with larger total and PVWMH volumes. The relations endured despite controlling for age and blood pressure.

The virally-suppressed HIV+AUD group achieved significantly better composite scores than the non-suppressed group on Attention/Memory ($t=2.92$, $p=.005$), Verbal/Visual Learning ($t=1.991$, $p=.0498$), Verbal/Visual Memory ($t=2.52$, $p=.0135$), and the mean of the five composite scores ($t=2.44$, $p=.0167$). None of the performance scores of the HIV-only subgroups differed significantly by viral suppression.

Group differences in lobar WMH volumes

The regression analysis results, adjusted for sex, race, SES, education, BMI, BDI, and systolic and diastolic blood pressure, on group and group-by-age^2 effects of the four lobar volumes, appear in Table 4 (Supplemental Figure 2). In general, the three diagnostic groups had larger regional WMH volumes than controls. Relative to the control group, the AUD group had significantly larger volume in frontal, temporal, and parietal regions; the volume difference was significant in the occipital region in the HIV only group; and the frontal volume difference from controls was marginal for the HIV+AUD group. Both HIV groups exhibited accelerated aging of the frontal WMH volumes relative to controls (Table 4).

Correlations between cognitive test composite scores and lobar WMH volumes

These exploratory analyses identified the most consistent set of correlations in the AUD group occurred between each composite score and frontal WMH volumes. In the HIV only group, Attention/Working Memory correlated with frontal, temporal, and parietal WMH volumes. The HIV+AUD group had its strongest correlations between Motor Skills and temporal and parietal WMH volumes (Table 5).

DISCUSSION

Quantitative analysis of the 1,056 FLAIR datapoints acquired longitudinally in 528 participants from four study groups supported the mainstay of our hypotheses regarding presence and progression of WMH volumes, their moderating factors, and functional outcomes: 1) the HIV, AUD, and HIV+AUD groups each had larger WMH volumes in both periventricular and deep white matter regions than the control group. All groups including controls exhibited accelerated volume increases with aging. Volume acceleration was greater in the two HIV groups than in controls, whereas the AUD acceleration did not differ from that of controls in any region despite larger WMH volumes in the AUD than control groups in periventricular and deep white matter regions. 2) Sex, length of HIV status, and blood pressure were moderating factors of WMH volumes and differed by diagnosis. 3) Functional

correlates of WMH volumes occurred most consistently with the composite measure of upper limb Motor Skills.

Acceleration of WMH volumes with normal aging and disease

WMH volumes were larger and expanded faster in older than younger control participants screened to meet health criteria. Extending the pattern of squared fits of WMH volume over age relative to controls, longitudinal examination revealed faster acceleration of WMH progression in the two HIV groups despite successful ART treatment. Although several participants in both HIV groups had unsuppressed viral counts (that is, their counts exceed the 50 copies/mL cut-off), their WMH burden was not greater statistically than their virally-suppressed counterparts. This lack of viral suppression difference comports with other attempts seeking such differences in brain age gaps for WMH(19). Insensitivity to a viral-suppression effect may reflect the variable measured, in this case edematous brain tissue, because in the current study splitting the HIV group by viral load suppression was successful in identifying viral load effect on cognitive performance in the HIV groups. By contrast, a previous study found that viral load did not differentiate the HIV groups in cognitive function but did so in cerebral blood flow, notably in older, treated HIV participants with unsuppressed viral load(but see47, 84), suggesting a role for small vessel disease even in treated HIV infection.

Our study had adequate power to detect an aging effect and age-HIV interactions, not forthcoming in earlier studies. One reported a 2-year follow-up of HIV and control participants age 60 years and older(35); another followed participants for 3 years using Fazekas ratings for WMH quantification(72). A direct comparison of DTI measures of white matter tissue integrity and WMH volume quantification revealed an interaction with age in the WMH volumes but not the DTI metrics(36).

The HIV groups showed a graded effect for WMH volume acceleration in the periventricular area, where the HIV-only participants significantly exceeded the aging effect of the controls, and the HIV+AUD group acceleration was faster than that of the HIV-only group. Despite the compounded HIV+AUD effect, AUD by itself did not show an age acceleration beyond control levels. Nonetheless, the AUD group had greater presence of WMH as noted in some earlier reports(85–87) but not others(88, 89). Further, age acceleration occurred in the AUD group in both deep and periventricular measures, which had been assessed but never before identified(85).

Moderating factors of WMH volume acceleration with aging

Older age of AUD onset, systolic and diastolic blood pressure, and more depressive symptoms were each at least modest predictors of larger WMH volumes in the AUD group. Although the role of hypertension as a correlate of WMH is well established(37, 40, 72, 90), high blood pressure metrics have been found to correlate with WMH volume in HIV in some studies(52) but not others(72). In the current study, only in the HIV group comorbid for AUD were high values of either blood pressure measure modestly related to WMH volumes. The commonality of AUD suggests a salient role for alcohol as a relevant moderator of WMH volume in the HIV group.

Location and shape of WMHs have been proposed to be caused by different pathological mechanisms(91). Multimodal imaging of regional WMH was interpreted to indicate that PVWMHs were attributable to ischemic damage to veins caused by glymphatic dysfunction, whereas DWMH arose from both ischemic-related hypoperfusion and glymphatic dysfunction(41). Such dysfunction would attenutate reabsorption of paraventricular interstitial fluid and result in edematous tissue imaged as hyperintense image signal. Significant volume increases at both WMH sites were detected in our control and diagnostic cohorts, and both sites showed accelerated aging, possibly reflecting cerebral small vessel disease or ischemia, which may spontaneously reverse, measured as WMH volume shrinkage(92), or be amenable to treatment.

Even though female participants in the diagnostic groups had larger total and PVWMH volumes for their head size than the male affected or control groups, the AUD men showed faster acceleration of these volumes than the AUD women and control men and women. By contrast, the comorbid group showed the opposite sex-age interaction in the DWMH, where women with HIV+AUD showed accelerated aging relative to controls. Further, the Black and Asian comorbid participants had a greater WMH burden than controls. Recent studies report that postmenopausal women(93) and middle-age Black individuals(94) in general are at heightened risk of cerebral small vessel disease evidenced by WMH burden.

Functional correlates of WMH volumes

Cerebrovascular risk factors of silent brain infarcts, intracranial large artery stenosis, and compromised white matter tissue integrity are risk factors for poor cognitive performance in populations in general(95). In PLWH, poorer cognitive scores correlated with greater WMH burden despite well-controlled HIV infection(26, 52). Herein, larger WMH volumes consistently predicted upper limb motor skills regardless of diagnosis, also observed by others(35, 55). Further, virally-suppressed PLWH comorbid for AUD achieved higher cognitive and motor scores than their non-suppressed counterparts; this difference did not hold for the HIV only group. Significant correlations between test scores and WMH volumes in any of our three diagnostic groups endured correction for age and blood pressure. Consistent with known functional localization, Attention/Working Memory and Executive Function scores of the AUD group were most strongly correlated with frontal and parietal WMH volumes as were the Attention/Working Memory scores of the HIV only group.

Limitations

Despite successful ART and viral suppression in longitudinal assessment, precise tracking when ART was initiated in the course of the infection and whether individuals suffered rebound effects with intermittent treatment(20, 96) are unknown. These factors have the potential to linger as legacy effects or to trigger inflammatory immune responses(11–13, 26). Although we attempted to account for comorbidities statistically, such concomitants, including tobacco use, high blood pressure, and diabetes, occur with high prevalence in both the HIV and the AUD populations(20) and may have contributed beyond statistical accounting to accelerate WMH volume expansion. Further, low vitamin D may be a risk factor for greater WMH burden(97), whereas physical exercise may enhance CNS

health(98); these measures were not available in our cohorts. Despite efforts to maintain contact with all study participants for longitudinal assessment, follow-up was voluntary and yielded an average return of 53% per group and potential attrition biases despite used of mixed cross-sectional/longitudinal modeling (*lmer*) designed to overcome problems of missing data. These limitations notwithstanding, we note that selection of fully rarified, comorbid-free groups of PLWH or AUD participants re-examined at precise target follow-up times would be unlikely to represent the reality of clinical study or these diseases.

Conclusion

Determination of the composition and constituents of neuroradiologically detectable abnormal tissue may provide insight into mechanisms causing the disruption, which would be an essential step for therapeutic targeting. WMH detection as a noninvasive measure of cerebral small vessel disease is commonly taken as evidence for microvascular rarefaction that occurs with aging and disease(99). Tracking WMH volumes may be especially relevant in treating HIV and AUD given that each is associated with liabilities for inflammatory or hypertensive processes and may display WMH volume reduction in response to treatment (cf., 20). Accelerated aging in HIV hastened by AUD comorbidity highlights a role for alcohol in increasing risk for premature cognitive and motor decline(15, 27–29) and HIV-related dementia. Although aging by time is linear, modifiable factors—such as good nutrition, exercise, and reduction alcohol in consumption—might mitigate its acceleration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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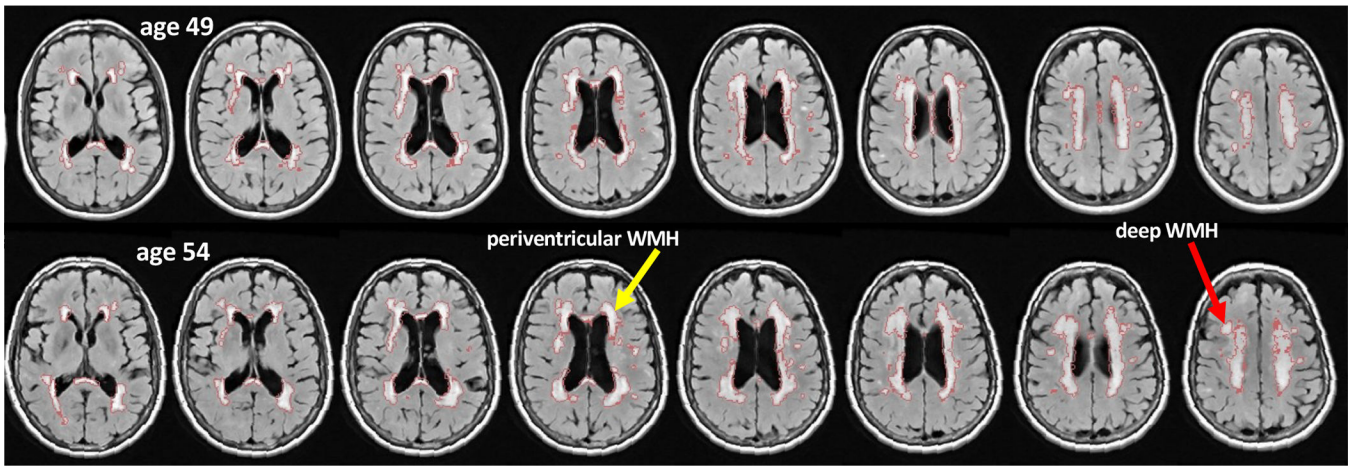

Figure 1.

Axial images from FLAIR images acquired in an HIV infected woman examined when she was age 49 and then 54 years old. Note the enlargement of the WMHs delineated in red outlining. Examples of periventricular WMH (yellow arrows) and deep WMH tissue (red arrows) are indicated.

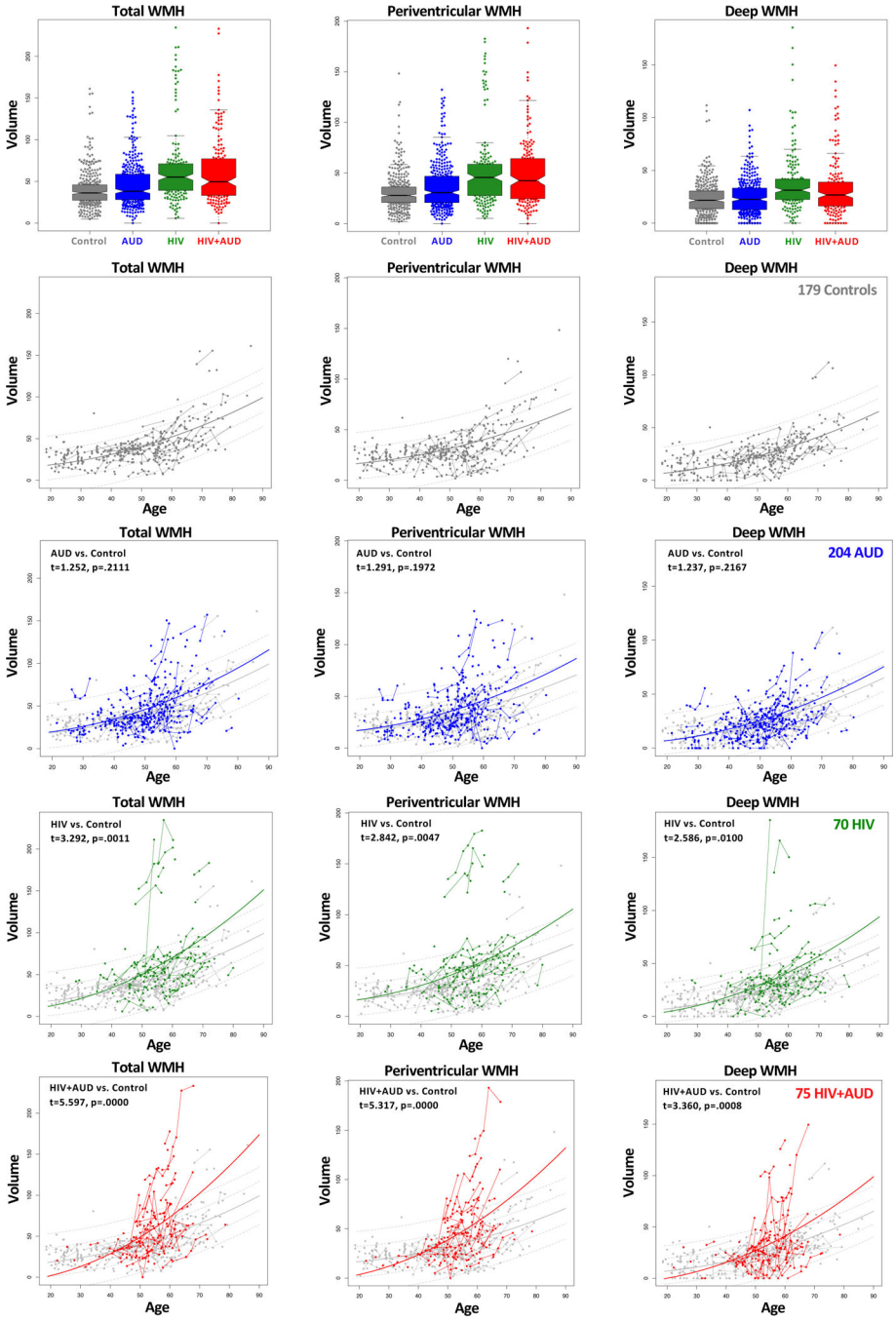

Figure 2.

Top row: Box plots and data points of volumes of the Total (left column), PVWMH (middle column), and DWMH (right column) volumes for each participant's data for all visits. Controls (gray), AUD (blue), HIV (green), and HIV+AUD (red). Bottom 12 spaghetti plots: Total, PVWMH, and DWMH volumes for individual from each study group. Data and regression lines of the three diagnostic groups are plotted on the control regression lines for comparison. The diagnostic group-by-control interaction results are provided in the upper left corner of the plots. Although all three diagnostic groups had larger WMH volumes in

each region, only the two HIV groups showed significant interactions with controls over age, indicating age accelerations.

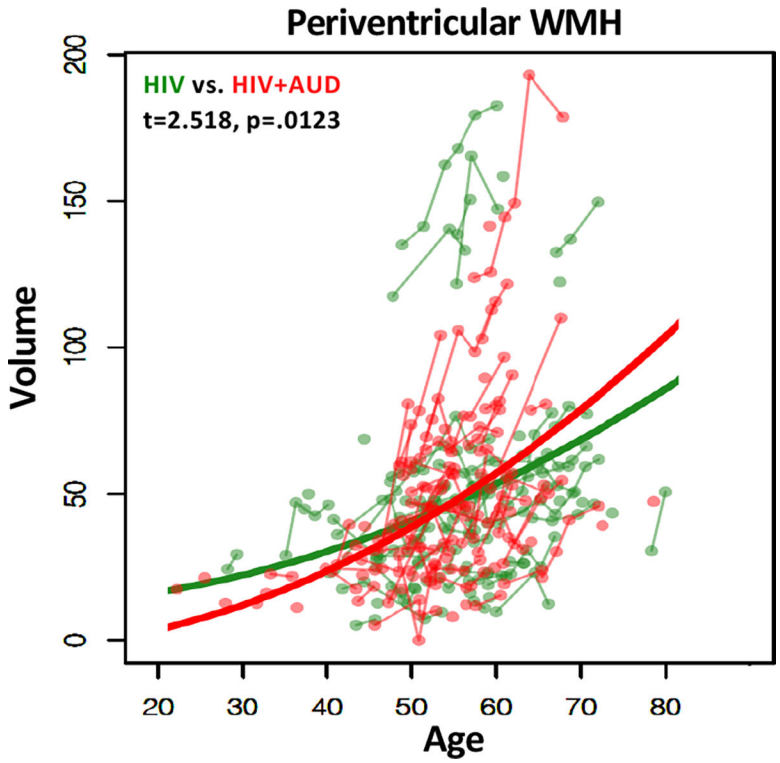

Figure 3.

Longitudinal data and regression lines for PVWMH volumes of individuals with HIV (green) and HIV+AUD (red). The HIV+AUD group shows a faster volume acceleration over age than the HIV group.

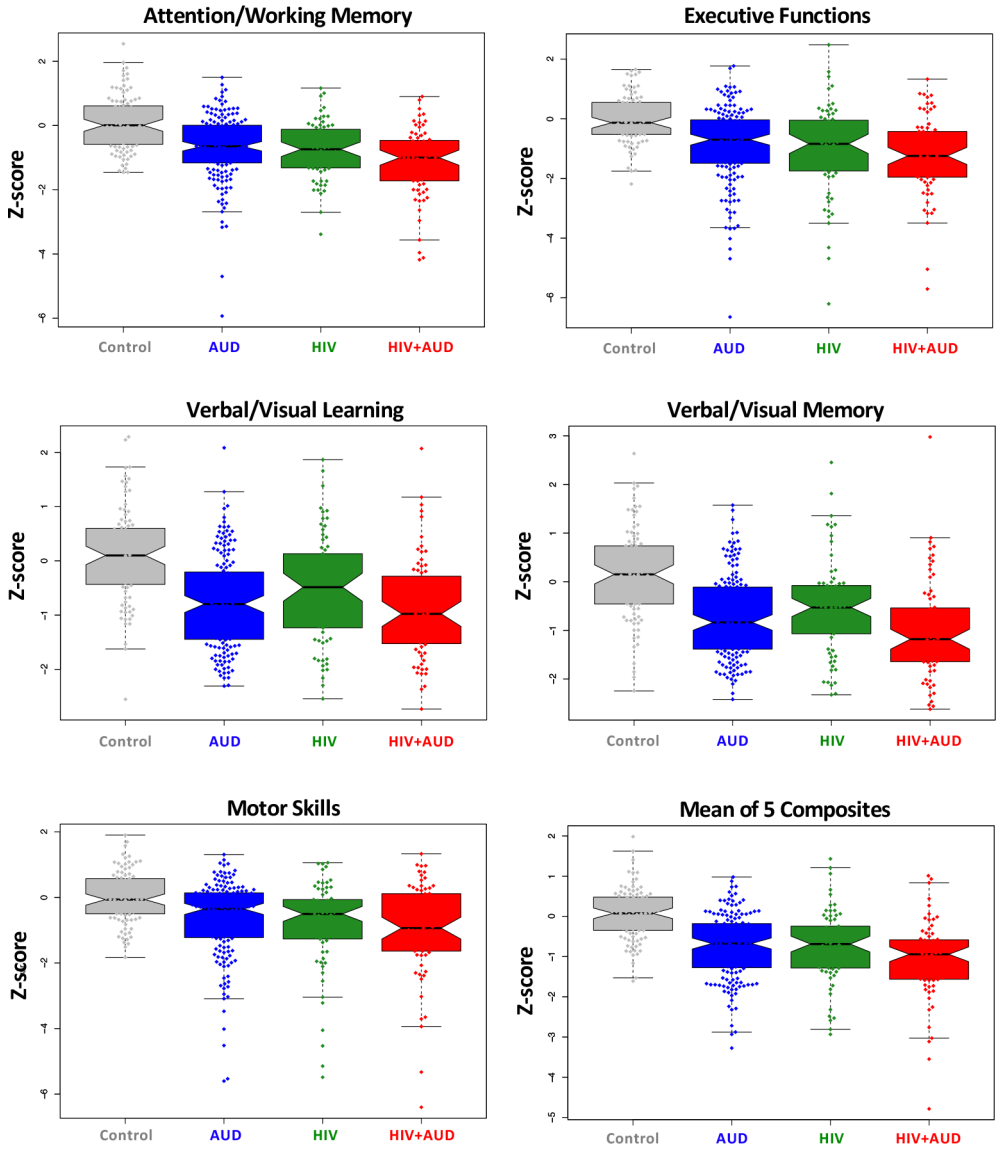

Figure 4.

Box plots overlaid on the scatterplots of Z-scores for the five domain composite scores and the mean domain scores, each of which was age, sex, and education adjusted on the controls and acquired at initial study time. The four study groups are color coded.

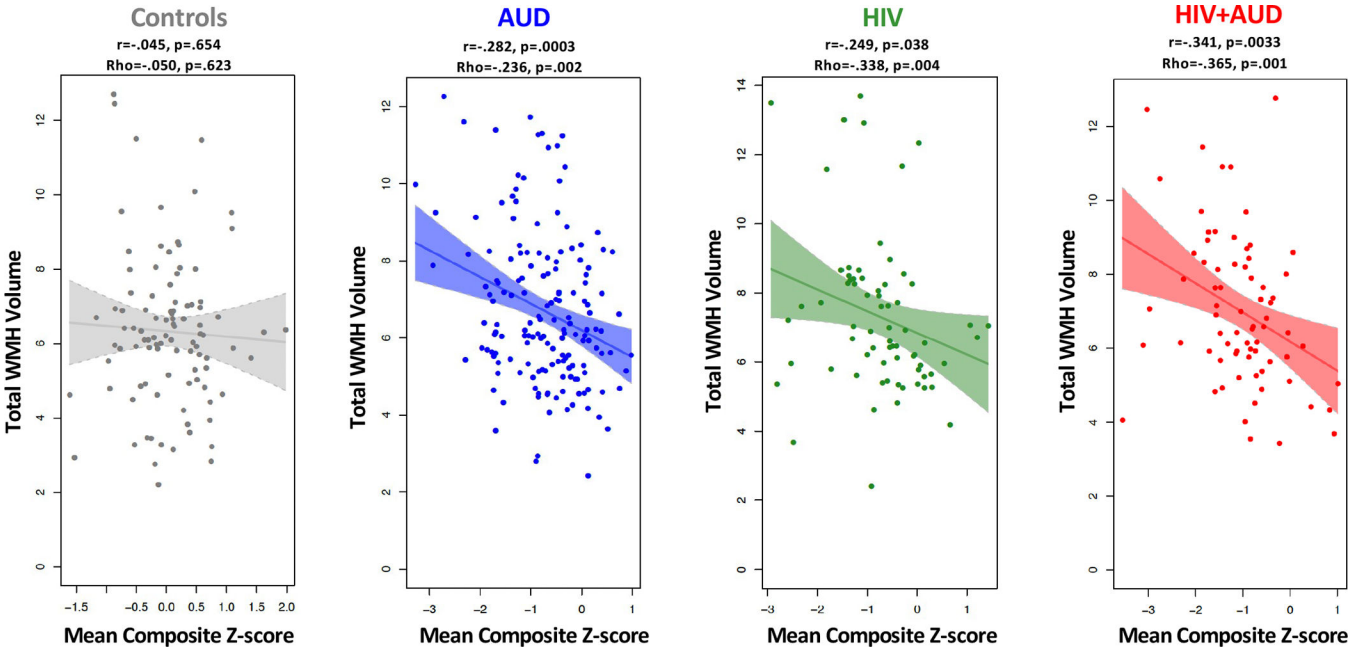

Figure 5.

Linear regressions and 95% confidence intervals for significant correlations between mean composite Z-scores and Total WMH volumes at initial study time, indicating that larger WMH volumes correlated with poorer performance in each group. Additional functional-WMH volume correlations appear in Tables 3 and 4.

Table 1.

Study entry demographics of the study groups at baseline: mean (SD) or frequency count.

	Control	AUD	HIV†	HIV+AUD	*lm* for Control vs. each diagnostic group
Age (yrs)	47.77	49.74	53.75	51.63	C<H, H+A
	(16.41)	(10.86)	(9.13)	(9.32)	
male/female n=	99/80	151/53	49/21	50/25	
Education (yrs)	16.25	13.27	13.49	13.11	C>A, H, H+A
	(2.29)	(2.46)	(2.76)	(2.00)	
n=	165	196	70	75	
Socioeconomic status (lower score=higher status)	24.67	41.47	38.97	43.57	C<A, H, H+A
	(11.75)	(15.01)	(15.15)	(12.52)	
n=	177	203	70	75	
Body Mass Index (BMI)	25.54	27.01	26.03	26.23	C<A
	(4.20)	(4.36)	(4.28)	(4.18)	
n=	143	186	70	74	
Diastolic blood pressure (dBP)	75.39	78.72	76.23	78.52	C<A
	(10.03)	(11.30)	(10.99)	(9.09)	
n=	87	161	60	56	
Systolic blood pressure (sBP)	126.91	129.33	125.80	128.88	n.s.
	(17.57)	(17.00)	(15.44)	(14.92)	
n=	87	161	60	56	
Mean test composite Z-score†† (lower scores=worse performance)	0.05	−0.75	−0.75	−1.06	C>A, H, H+A
	(0.63)	(0.81)	(0.89)	(0.89)	
n=	100	160	70	72	
Global Assessment of Functioning (GAF)	85.21	66.54	70.99	65.11	C>A, H, H+A
	(6.55)	(10.35)	(10.86)	(9.25)	
n=	147	196	70	73	
Falls in past year	1.00	1.49	0.97	1.09	n.s.
	(1.16)	(1.92)	(1.13)	(1.44)	
n=	35	63	30	32	
Beck Depression Inventory II (BDI)	2.20	8.64	9.88	10.52	C<A, H, H+A
	(3.45)	(8.20)	(8.02)	(8.92)	
n=	140	175	69	73	
Age at AUD diagnosis	—	25.67	—	—	—
		(9.56)			
n=		187			
Length of HIV diagnosis	—	—	18.44	17.09	HIV length: n.s.
			(8.97)	(8.09)	
n=			64	70	
Viral load (count/mL) **Median=**	—	—	48	47	n.s.
SD=			(20079.57)	(44418.00)	

		Control	AUD	HIV†	HIV+AUD	*lm* for Control vs. each diagnostic group
	n=			62	67	
10 Viral load log^{-10} (count/mL)	**Mean=**	—	—	2.03	2.23	n.s.
	Median=			(1.67)	(1.67)	
	n=			62	67	
CD4 (count/mL)	**Mean=**	—	—	597.34	552.80	n.s.
	SD=			(252.95)	(331.19)	
	n=			67	70	
CD8 (count/mL)	**Mean=**	—	—	1016.21	952.76	n.s.
	SD=			(487.26)	(461.11)	
	n=			67	70	
CD4/CD8 (count/mL)	**Mean=**	—	—	0.67	0.70	n.s.
	SD=			(0.30)	(0.50)	
	n=			67	70	
CD4 nadir		—	—	173.00	195.32	n.s.
				(142.53)	(163.50)	
	n=			54	53	
AIDS yes/no		—	—	35/29	41/31	chi^2=.07, p=.79
HCV yes/no		1/92	33/124	20/46	33/40	chi^2=48.77, p=.00001
Age at nicotine diagnosis		19.19	19.40	17.22	17.04	n.s.
		(3.61)	(8.39)	(6.52)	(5.12)	
	n=	21	125	27	42	
Smoker: never/past or current		121/21	64/132	39/27	24/44	chi^2=101.12, p=.00001
Race: Black/White/Asian/other		26/106/37/9	69/94/7/34	25/34/0/11	46/13/0/16	chi^2=117.96, p=.00001

Table 2.

Diagnostic and sex differences in volume and interaction with aging.

	Group difference		Group × age^2 interaction	
	t	p	t	p
AUD vs. control				
Total WMH	3.291	**0.001**	0.091	0.928
Periventricular WMH	3.130	**0.002**	0.308	0.758
Deep WMH	2.606	**0.010**	0.339	0.735
HIV vs. control				
Total WMH	3.054	**0.003**	2.124	**0.034**
Periventricular WMH	3.492	**0.001**	2.138	**0.033**
Deep WMH	2.235	**0.027**	1.667	0.097
HIV+AUD vs. control				
Total WMH	2.132	**0.034**	2.887	**0.004**
Periventricular WMH	2.426	**0.016**	2.729	**0.007**
Deep WMH	1.125	0.262	1.602	0.110
HIV+AUD vs. HIV				
Total WMH	−0.100	0.921	1.503	0.134
Periventricular WMH	−0.419	0.676	2.518	**0.012**
Deep WMH	−0.311	0.756	0.688	0.492

Group differences resulting from multiple regression using lmer accounting for sex, race (Asian, Black, other), SES, education, BMI, BDI, systolic and diastolic blood pressure

Bold font indicates p≤.05 without correction for multiple comparisons.

Table 3.

Results of *lm* analyses testing relations between diagnostic and other study variables and regional WMH volumes.

	Total WMH		PVWMH		DWMH	
AUD	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−3.641	**0.000**	−3.928	**0.000**	−2.088	0.038
Executive Functions	−3.619	**0.000**	−3.687	**0.000**	−2.781	**0.006**
Verbal/Visual Learning	−1.035	0.302	−0.961	0.338	−0.808	0.420
Verbal/Visual Memory	−1.909	0.058	−1.693	0.092	−1.580	0.116
Motor Skills	−3.279	**0.001**	−3.224	**0.002**	−2.490	**0.014**
Mean	−3.747	**0.000**	−3.769	**0.000**	−2.683	**0.008**
HIV	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−2.996	**0.004**	−2.423	0.018	−3.704	**0.000**
Executive Functions	−1.533	0.130	−1.572	0.121	−1.408	0.164
Verbal/Visual Learning	−1.042	0.301	−0.694	0.490	−1.491	0.140
Verbal/Visual Memory	−0.954	0.343	−0.671	0.504	−1.272	0.208
Motor Skills	−2.489	**0.015**	−2.108	0.039	−2.859	**0.006**
Mean	−2.240	0.028	−1.883	0.064	−2.620	**0.011**
HIV+AUD	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−1.738	0.087	−1.943	0.056	−1.112	0.270
Executive Functions	−0.902	0.370	−0.993	0.324	−0.403	0.688
Verbal/Visual Learning	−2.517	**0.014**	−2.363	0.021	−2.103	0.039
Verbal/Visual Memory	−2.228	0.029	−2.150	0.035	−1.844	0.069
Motor Skills	−3.657	**0.001**	−4.119	**0.000**	−1.889	0.063
Mean	−2.897	**0.005**	−3.055	**0.003**	−1.852	0.068
Control	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−1.826	0.071	−2.155	0.034	−0.772	0.442
Executive Functions	−2.117	0.037	−2.343	0.022	−0.968	0.336
Verbal/Visual Learning	1.190	0.237	1.328	0.188	0.954	0.343
Verbal/Visual Memory	0.634	0.527	0.815	0.417	0.467	0.642
Motor Skills	−1.728	0.087	−1.714	0.090	−1.182	0.240
Mean	−0.804	0.423	−0.799	0.426	−0.297	0.767

[†]The neuropsychological test scores were adjusted for age, education, and SES of a control sample.

Bold font indicates Bonferroni correction for 6 comparisons with α=.05, directional hypothesis requires p=.017.

Table 4.

Diagnostic difference in lobar WMH volume and interaction with aging.

	Group difference		Group × age^2 interaction	
	t	p	t	p
AUD vs. control				
Frontal	2.450	**0.015**	1.212	0.226
Temporal	2.390	**0.018**	0.499	0.618
Parietal	2.501	**0.013**	0.066	0.947
Occipital	0.864	0.388	−0.613	0.541
HIV vs. control				
Frontal	1.254	0.212	2.185	**0.030**
Temporal	1.495	0.138	0.163	0.871
Parietal	1.783	0.076	1.145	0.253
Occipital	2.024	**0.045**	1.596	0.112
HIV+AUD vs. control				
Frontal	1.963	0.051	2.377	**0.018**
Temporal	1.443	0.151	−1.074	0.284
Parietal	0.524	0.601	0.786	0.432
Occipital	−0.943	0.347	−0.430	0.667
HIV+AUD vs. HIV				
Frontal	0.731	0.466	1.819	0.070
Temporal	−0.192	0.848	−0.390	0.697
Parietal	−0.494	0.622	0.784	0.434
Occipital	−1.912	0.058	−1.531	0.127

Group differences resulting from multiple regression using lmer accounting for sex, race (Asian, Black, other), SES, education, BMI, BDI, systolic and diastolic blood pressure

Bold font indicates p≤.05 without correction for multiple comparisons.

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Table 5.

Results of *lm* analyses testing relations between diagnostic and other study variables and bilateral lobar WMH.

AUD	**Frontal WMH**		**Temporal WMH**		**Parietal WMH**		**Occipital WMH**	
lm(variable~WMH)	**t**	**p**	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−2.402	**0.017**	−1.612	0.109	−2.231	**0.027**	−1.029	0.305
Executive Functions	−3.057	**0.003**	−1.129	0.261	−2.856	**0.005**	−1.443	0.151
Verbal/Visual Learning	−1.609	0.110	−0.390	0.697	−0.031	0.976	−0.931	0.353
Verbal/Visual Memory	−2.164	**0.032**	−0.303	0.762	−0.838	0.404	−1.462	0.146
Motor Skills	−2.884	**0.004**	−2.491	**0.014**	−2.830	**0.005**	−0.970	0.333
Mean	−3.316	**0.001**	−1.675	0.096	−2.510	**0.013**	−1.502	0.135
HIV	**Frontal WMH**		**Temporal WMH**		**Parietal WMH**		**Occipital WMH**	
lm(variable~WMH)	**t**	**p**	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−2.875	**0.005**	−2.207	**0.031**	−3.846	**0.000**	−1.841	0.070
Executive Functions	−2.152	**0.035**	−1.790	0.078	−1.242	0.219	0.100	0.920
Verbal/Visual Learning	−1.361	0.178	−0.160	0.874	−1.499	0.138	−0.967	0.337
Verbal/Visual Memory	−1.330	0.188	−0.347	0.729	−1.357	0.179	−0.448	0.655
Motor Skills	−2.131	**0.037**	−0.721	0.473	−3.067	**0.003**	−0.958	0.341
Mean	−2.532	**0.014**	−1.337	0.186	−2.663	**0.010**	−0.881	0.381
HIV+AUD	**Frontal WMH**		**Temporal WMH**		**Parietal WMH**		**Occipital WMH**	
lm(variable~WMH)	**t**	**p**	**t**	**p**	**t**	**p**	**t**	**p**
Attention/Working Memory	−0.515	0.608	−1.017	0.313	−1.085	0.282	−1.899	0.062
Executive Functions	−0.595	0.554	−0.336	0.738	−1.085	0.282	−0.823	0.413
Verbal/Visual Learning	−1.927	0.058	−1.805	0.075	−1.581	0.118	−1.635	0.107
Verbal/Visual Memory	−1.586	0.117	−1.667	0.100	−1.714	0.091	−1.354	0.180
Motor Skills	−0.866	0.389	−3.304	**0.002**	−2.383	**0.020**	−1.937	0.057
Mean	−1.334	0.186	−2.097	**0.040**	−1.706	0.092	−2.004	**0.049**

Group differences resulting from multiple regression using lm accounting for age and systolic and diastolic blood pressure.

Neuropsychological test composite scores were standardized Z-scores adjusted for age, sex, and education of controls.

Bold font indicates p≤.05 without correction for multiple comparisons; corrected p≤.017.

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Antibody	NA	NA	NA	NA
Bacterial or Viral Strain	NA	NA	NA	NA
Biological Sample	NA	NA	NA	NA
Cell Line	NA	NA	NA	NA
Chemical Compound or Drug	NA	NA	NA	NA
Commercial Assay Or Kit	NA	NA	NA	NA
Deposited Data; Public Database	Pending upload of data to NIH/NIAAA NDAr	Pending upload of data to NIH/NIAAA NDAr	Pending upload of data to NIH/NIAAA NDAr	Pending upload of data to NIH/NIAAA NDAr
Genetic Reagent	NA	NA	NA	NA
Organism/Strain	NA	NA	NA	NA
Peptide, Recombinant Protein	NA	NA	NA	NA
Recombinant DNA	NA	NA	NA	NA
Sequence-Based Reagent	NA	NA	NA	NA
Software; Algorithm	UBO and other imaging software are open source	UBO and other imaging software are open source	UBO and other imaging software are open source	UBO and other imaging software are open source
Transfected Construct	NA	NA	NA	NA
Other	NA	NA	NA	NA