HIV Clinical Factors and Cardiovascular Disease Risk Predict White Matter Hyperintensity Burden

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ABSTRACT

Cardiovascular disease (CVD) risk factors such as hypertension are highly prevalent in people with HIV (PWH) and have been linked to an elevated risk of white matter hyperintensities (WMH), a measure of small vessel disease. We investigated factors associated with WMH burden (measured as total WMH volume, or WMHv) in PWH and demographically matched controls. Consistent with previous findings, WMH is prevalent in middle-aged to older PWH on cART and with successful viral suppression and WMHv strongly correlates with CVD risk and age. Additionally, WMHv is higher in African Americans with HIV and correlates with current CD4/CD8 ratio and HIV disease duration.

METHODS

Participants. 97 PWH and 37 demographically matched controls participated in this study (Table 1). The majority of PWH were on cART and had undetectable viral load (<20 copies/mL) (Table 2).

Table 1. Participant demographics.

	PWH (n=97)	PWoH (n=37)	p-value
Age, Mean (SD)	56.2 (6.5)	54.5 (7.4)	.210
Sex, % Female	24.7	27.0	.786
Race, % African American	62.9	56.8	.515
Education, Mean (SD)	14.2 (3.1)	14.6 (2.9)	.463
CVD risk (%), Mean (SD)	19.5 (8.7)	16.5 (9.8)	.089*

Table 2. HIV clinical factors.

	n	Mean (SD)
CD4 nadir, median (IQR)	96	194.5 (52 – 360)
Viral Load, % Detectable	95	27.7
cART Adherence, (%)	97	97.9
CD4/CD8 Ratio, median (IQR)	95	0.85 (0.60 – 1.16)
Disease Duration	97	25.6 (9.3)

Calculating CVD risk. The Framingham General Cardiovascular Risk Profile was used to calculate CVD percent risk. It includes age, body mass index (BMI), systolic blood pressure (SBP) status and treatment, smoking status, and diabetes status.

MRI collection and preprocessing. T1-weighted structural MRI images (1x1x1 mm^3) were collected and CAT12 software was used to obtain WMH volume (WMHv) and gray matter volume (GMv).

Statistical analyses. Non-parametric ANCOVA and regressions were performed in SPSS to investigate the effects of HIV status, age, sex, race, education, HIV clinical factors and CVD percent risk on WMHv, normalized by total intracranial volume (TIV). Parametric multiple linear regressions were performed in R to investigate the effects of WMHv, HIV status, age, sex, race, education, and HIV clinical factors on GMv, normalized by TIV. Mediation analysis for age as a predictor of GMv via WMHv was performed in SPSS.

CVD percent risk, age, race, CD4/CD8 ratio, and HIV disease duration are predictors of white matter hyperintensity burden.

Figure 1. Higher CVD percent risk and older age are associated with worse WMH burden (higher WMHv).

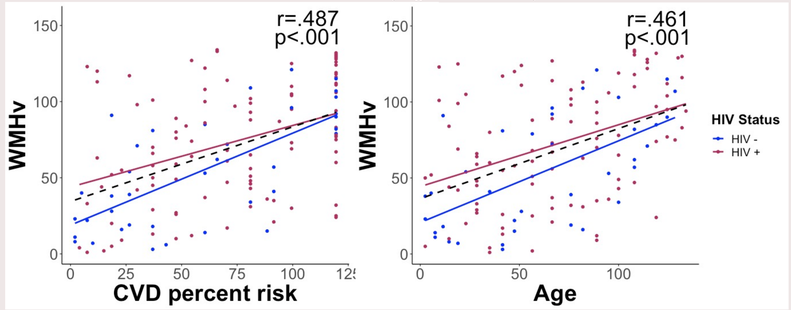


Figure 2. African American race is a strong predictor of WMH burden. HIV status is a marginally significant predictor with a small effect size (h_p^2 = .025).

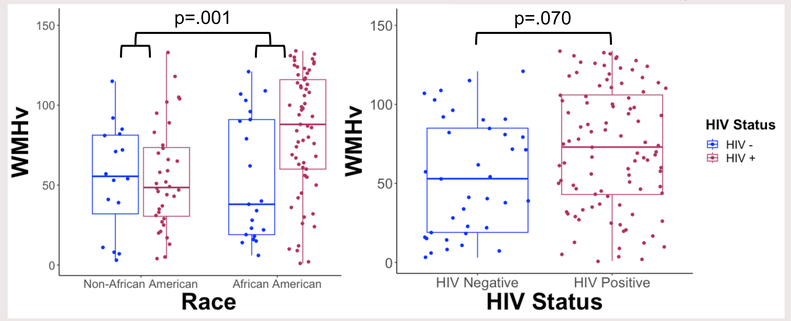


Figure 3. Lower current CD4/CD8 ratio and longer disease duration correlate with worse WMH burden.

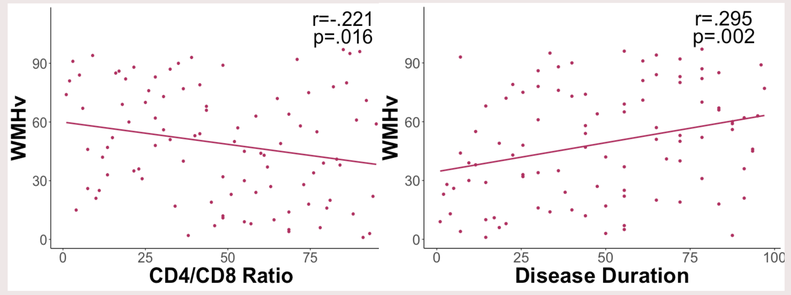


***Figure axes are represented as rank values from non-parametric tests**

RESULTS

Table 3. p-values of significant predictors of WMHv and GMv in all participants.

Predictors of WMHv		Predictors of GMv	
HIV status	.070	**HIV status**	.289
Age	<.001	**Age**	.001
Race	.001	**Sex**	<.001
CVD percent risk	<.001	**WMHv**	<.001

Table 4. p-values of significant predictors of WMHv in PWH. Additionally, WMHv is a strong predictor of GMv in PWH (p<.001).

Predictors of WMHv in PWH	
Age	<.001
Race	<.001
CVD percent risk	<.001
CD4/CD8 Ratio	.016
Disease Duration	.002

Figure 4. Mediation analysis for age as a predictor of GMv via WMHv.

Relationship	Unstandardized B	p-value
A	.00017268	.00003277
B	-2.87206509	.00000714
C	-.0097368	.00161770
Total Effect	-.00146962	.00000386

CONCLUSIONS

Across PWH and controls, WMH burden is significantly associated with higher CVD percent risk, older age, and African American race, while lower total GMv is significantly associated with older age, total WMHv, and male sex. Mediation analysis reveals an indirect effect of age on total GMv through total WMHv. There is a non-significant trend for higher WMH burden in PWH compared to demographically matched controls (p=0.070). In PWH, WMH burden is significantly associated with lower CD4/CD8 ratio and longer disease duration in addition to CVD percent risk, age, and African American race.

Implications and Future Directions. In addition to common cardiovascular disease risk factors, HIV clinical factors (CD4/CD8 ratio and disease duration) may contribute to small vessel disease in PWH, suggesting a need to further improve immune function with novel and more effective treatment. Furthermore, WMH burden disproportionally affects African American PWH, reaffirming the need for equitable HIV healthcare in the forms of equal access and health education.

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