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Sources of Active Brain White Matter Injury in Virally Suppressed HIV Infection Revealed Through Fixel-Based Analysis

Running head: HIV and white matter injury

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Abstract

Background: To better understand HIV and cardiovascular disease (CVD) effects on brain white matter during HIV infection, advanced diffusion imaging and comprehensive predictor analyses are essential.

Setting: Prospective observational cohort study

Method: 84 virally suppressed people with HIV infection (PWH) and 48 uninfected controls underwent T1-weighted, FLAIR, and diffusion MRI at baseline and 24 months later (75 PWH and 40 controls). White Matter Hyperintensity (WMH) volumes were derived from structural scans. Fixel-based analysis tract-based metrics included fibre density (FD), fibre cross-section (FC) and fibre density and cross-section (FDC).

Results: Relative to controls, mixed models showed significant reductions ($p<.05$ - $p<.01$) of FC, and lower FDC to a lesser extent, in multiple long cortical association tracts, and within striatal- and thalamic-frontoparietal connections in PWH at both time points. Higher CVD risk was associated with reduced FC in the arcuate fasciculus and FDC in the cingulate gyrus ($p<.05$). In PWH, more severe cognitive impairment and

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longer duration of HIV disease was associated with worse FDC across multiple tracts ($p<.03 – p<.001$). Lower baseline CD4 counts was associated with lower FD in the frontal association tracts ($p<.05 – p<.005$). Higher WMH volume was associated with higher CVD risk (periventricular $p<.001$, deep $p<.03$), but not HIV status.

Conclusions: Major brain white matter tracts are impacted by HIV status, HIV duration, cognitive impairment, baseline CD4, and CVD risk to a lesser extent, despite equal WMH burden between infection groups. Our study provides further evidence of active immuno-vascular underpinning of HIV neuropathogenesis on fine white matter structure despite controlled HIV.

Key words: HIV; viral suppression; diffusion imaging; brain white matter; cardiovascular disease risk; aging; Fixel-based analysis

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Background

White matter injury occurs despite controlled HIV infection. However, the extent of this injury and nature are not well understood as associated factors are increasingly multifactorial. Even in people with HIV (PWH) with low medical and psychiatric confounds, there are multiple sources of potential white matter injury during chronic HIV infection including normal and abnormal brain ageing[1], microvascular disease from cardiovascular factors[2-4], immunological factors from HIV[5], antiretroviral neurotoxicity, low grade viral replication and viral reservoirs' activity.

Existing white matter imaging studies in HIV have not systematically considered CVD factors despite their importance on brain white matter health[6] and their higher prevalence in HIV. Studies have shown cross-sectionally lower fractional anisotropy (FA) and higher mean diffusivity (MD) in PWH with increased tobacco use[7] and overall cardiovascular risk factors[4]. Conversely, better cardiorespiratory health was associated with higher FA and higher axonal density in multiple white matter tracts in PWH[8].

Moreover, previous studies have included non-virally suppressed participants and mostly conducted cross-sectional studies, and as such, baseline age, follow-up time, and HIV duration effects cannot be differentiated. This has led to conflicting results[9]. In the few existing longitudinal studies, some have found stable FA and MD metrics in PWH over six months in younger-to-middle aged adults[9], in small samples of cognitively normal PWH[10], and in larger multicentre studies over 24 months in older adults[11]. By contrast, age-related longitudinal reduction in FA was observed in PWH in the superior longitudinal fasciculus only[12]. Over a four-year follow-up, PWH had greater increases in MD in posterior regions compared to HIV-negative controls[13]. Thus, although

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generally baseline differences are present, longitudinal changes remain unclear. Additionally, considering middle to older aged adults when vulnerability from aging and lifestyle factors are likely to synergistically contribute to white matter injury.

In addition to these limitations, HIV studies have relied on the main established measures of white matter integrity by DTI (FA and MD) which can be spuriously altered by unintended factors such as reduced crossing fibres, reduced crossing fibres angles, or increased free water within white mattertracts[14]. These may occur in HIV due to white matter volume loss, ventricular enlargement, or changes in white matter cellularity. To overcome this non-specificity, newer methods such as fixel-based analysis[15] provide information about fiber populations within each MRI voxel, generating measures of white matter fibre density (FD), fibre cross section (the log is used; logFC) and a composite of fibre density and cross section (FDC) measure. The advantage of these measures is that they are more reliable and have improved biological plausibility[15]. The utility of fixel based analysis in providing an improved rendition of brain white matter health has only been used in two studies in treated[16] and untreated PWH[17]. Neither of these studies evaluated the key contribution of CVD risk, and both were cross-sectional. Furthermore, while WMH are used in clinical practice as markers of white matter injury, they represent only the extreme of tissue injury[18]. By contrast, DTI provides measures of more subtle white matter dysfunction.

Finally, most HIV studies have not concomitantly assessed white matter tract outcomes and white matter hyperintensity (WMH). PWH are at increased risk of higher WMH severity compared to age-controls[19,20], yet this has only been associated with diffusion metrics in one study. Increased WMH volumes in PWH aged 60+[21] were associated with lower FA, controlled for HIV and age, but viral control of this sample was variable

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and longitudinal effects on FA were not considered, perhaps due to small follow-up samples.

To address the identified limitations with prior work the three aims of the current study were: (1) to use FBA to examine white matter tract microstructure metrics in PWH compared to HIV-negative (HIV-) participants who were closely comparable for demographic and lifestyles factors and were screened for any major medical or psychiatric confounds; (2) assess longitudinal associations of white matter metrics with CVD risk, HIV-associated neurocognitive disorder (HAND), and HIV disease factors (HIV duration, AIDS, Nadir CD4, Baseline CD4, Baseline CD8), and; (3) assess longitudinal WMH volume associations with HIV status and CVD risk. We hypothesised that: (1) Across the whole sample, white matter metrics would be reduced over time and with HIV status and higher CVD risk, and; (2) Within PWH, white matter metrics decline over time would be exacerbated with more severe HAND and worse immunological factors, and; (3) WMH volume would be increased with HIV status and with higher CVD risk.

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Methods

Study design: Prospective observational cohort study which is part of the HIV and Brain Aging Research Program at the Sydney St. Vincent's Hospital and The University of New South Wales Human. The institutions' Research Ethics Committees approved our protocol (08/SVH/90). All individuals provided written informed consent before study participation.

Participants

At baseline, 84 virally suppressed and clinically stable PWH and 48 HIV- participants screened for any major medical and psychiatric confounds completed clinical, neuropsychological, and imaging assessments. Of those, 75 PWH and 40 HIV- returned for follow-up assessments two years later between 2009-2014. Descriptions of our HIV and Brain Aging Research Program inclusion, exclusion, and confounding comorbidity exclusion were published previously[22]. The HIV- controls were comparable to the PWH in terms of age, education, geographic, and lifestyle factors[22]. Only males were included in the study, and all but one participant identified as Caucasian.

Procedures

All study assessments have been published in previous publications[22 22,23 24,25]. In brief, at both timepoints blood was drawn to assess HIV viral load, and CD4+ and CD8+ counts and MRI scans were performed. At baseline online was assessed HAND clinical category and CVD assessment. To describe CVD risk, we used the 2008 10-year Framingham cardiovascular risk score[26], and also within the PWH sample, the 12-month Data Collection on Adverse events of Anti-HIV Drugs (DAD) score[27]. We used

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the 2007 HAND diagnostic criteria[24] adapted to the global deficit score methods and functional data[22] to classify asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). Due to small numbers of participants with HAD, we combined the MND and HAD categories in subsequent analyses. Framingham risk scores were positively skewed (Figure S1) and thus were log-transformed for all subsequent analyses.

Neuroimaging acquisition and processing

Imaging was acquired at St. Vincent's Hospital, Sydney Medical Imaging Department on a Phillips 3T Achieva TX scanner collecting T1-weighted anatomical images, T2 FLAIR, and diffusion images[25]. An overview of the processing pipeline is presented in **Figure 1** and details are provided in supplemental material. Structural T1 scans were used to correct for EPI distortions of the DWI images and then corrected DWI images were processed[28] to derive tract-based metrics[29] of FD, FDC, and logFC. FLAIR scans were used for WMH segmentation[30] and the regional distribution was calculated based on freesurfer[31] processing of T1 scans. WMH volumes were positively skewed and thus log-transformed for all subsequent analyses.

Statistical analyses

All analyses were performed in R 4.1.2 (R Core Team, 2021) using linear mixed models with random intercepts using the nlme package[32]. The Framingham CVD risk score was log-transformed to approximate a normal distribution. Estimated total intracranial volume (ICV) was used as a covariate for models including the logFC and FDC metrics[33]. For analysing tract metrics with FBA, we created models using FD, logFC,

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and FDC as dependent variables and examined all three-way and two-way interactions between time (categorial variable as baseline vs follow up), HIV status, and CVD risk and dropped interaction terms if not significant. Subsequently within the PWH sample, we examined all tract metrics associations with HIV factors (HAND group, HIV duration, history of AIDS, Nadir CD4+ cell count, CD4+ cell count, and CD8+ cell count). Again, all two- and three-way interactions with time and CVD were assessed and dropped if not significant. All q-values reported are false-discovery rate[34] (FDR) corrected[35] (alpha = 0.05) across tracts within each predictor of interest (i.e., CVD, HIV, and HIV factors) separately. We used the same analysis procedure for assessing contributions to periventricular and deep WMH volume. The Framingham CVD risk score includes age, and so age was not included independently as a covariate in primary analyses to avoid multicollinearity. However, we performed secondary analysis to separate the effect of non-modifiable (i.e., age) and modifiable CVD risk factors. Models were constructed as detailed above, but with additional terms for baseline age, and the residual of CVD risk regressed against age to represent modifiable CVD risk factors.

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Results

Demographic, clinical, neuroimaging, and laboratory characteristics of the study samples are presented in **Table 1 and 2**. There were no significant demographic or clinical differences between those who did and did not attend follow-up.

WM tract metrics are reduced with time, HIV status, and CVD risk factors

Over time, there was a small and significant main effect of time reflecting decline in all tract metrics across all tracts independently of HIV status and CVD risk factors (**Figure 2 and S2, top panel**). CVD risk was associated with reduced fibre cross section in arcuate fasciculus and both reduced fibre density and cross section in the cingulate gyrus (**Figure 2 and S2, middle panel**). Additional significant main effects for HIV status were observed with a reduction of fibre cross section in multiple cortical association tracts and striatal- frontoparietal and thalamic-frontoparietal connections (**Figure 2 and S2, bottom panel**). There were no statistically significant two- or three-way interactions between time, HIV infection, or CVD on tract metrics, meaning that the white matter metrics did not evolve over time as a function of HIV status or CVD risk or their combination.

WM tract metrics are associated with worse HAND and HIV disease factors in PWH

Compared to cognitively normal PWH, participants with ANI had reduced fibre cross section in the superior thalamic radiation only (Figure 3 and S3, top panel), while the combined MND and HAD subgroup had widespread reductions in fibre density and

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cross section across many cortical and subcortical association tracts (**Figure 3 and S3, bottom panel**). There were no significant interactions between time, HAND categories, and CVD risk, meaning that the white matter metrics did not evolve over time as a function of HAND categories or CVD risk or their combination. However, there was a significant two-way interaction showing participants with a longer HIV duration had a significantly greater reduction in fibre metrics over time across multiple tracts, and independently of baseline age. (**Figure 4 and S4, top panel**). Higher CD4 cell count was associated with higher fibre density in frontal tracts (**Figure 4 and S4, middle panel**), whilst lower CD8 cell count was associated with lower fibre cross-section in temporo-parietal and occipital tracts (**Figure 4 and S4**, **bottom panel**). There were no significant interaction effects (with age or time) or main effects for past AIDS status or nadir CD4 count.

WMH volume: Association CVD risk and time, but not HIV status

Periventricular WMH volume increased over time (Estimate = 0.083, SE = 0.027, p = 0.002) and with CVD risk (Estimate = 0.643, SE = 0.172, p < 0.001), but not with HIV status (Estimate = -0.155, SE = 0.218, p = 0.479). Deep WMH volume increased with CVD risk only (Estimate = 0.613, SE = 0.281, p = 0.031), but not with time (Estimate = 0.121, SE = 0.086, p = 0.164) or HIV status (Estimate = -0.208, SE = 0.354, p = 0.558). There were no significant interactions between time, HIV status, and CVD risk on either periventricular or deep WMH volume.

Secondary analyses

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We performed secondary analyses to separate non-modifiable (i.e., age) and modifiable risk factors from the Framingham 2008 CVD risk score. The residual of the CVD risk score with age regressed out was strongly correlated with almost all CVD risk factors (Supplemental Table 1). Findings on tract metrics were similar with regards to HIV, HAND severity, and HIV disease factors (**Figures S5 and S6**). Differences were observed for CVD risk on tract metrics. CVD risk excluding age reduced the observed effects in frontal tracts, suggesting these were more related to age than modifiable CVD risk factors. Conversely, there was reduced FD in the thalamic-precentral tract related to modifiable CVD risk factors. For WMH volumes, the prior main effects of CVD risk were due to age for periventricular (Estimate = 0.0672, SE = 0.0142, $p < 0.001$) and deep (Estimate = 0.083, SE = 0.023, $p < 0.001$) WMH volumes; no effects were observed for HIV status or CVD risk excluding age.

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Discussion

The current longitudinal observational study quantified the effects of HIV and CVD on both white matter tracts and WMH volume in a sample of clinically stable, virally suppressed PWH and their HIV- counterparts who were screened for any major medical or psychiatric confounds. This work addresses the methodological limitation of previous studies in two ways by: 1. Measuring the white matter integrity with FBA[9]. Fixel based analysis represents a more refined quantification of the white matter integrity by improving the resolution of crossing fibres and consequently improves the biological specificity and significance of the following findings. 2. The inclusion of CVD factors which have not been systematically tested in previous DTI studies in PWH.

Using FBA, we found that over the study period, all white matter microstructure declined for the whole sample which we interpret as normal aging effects on the white matter across the two-year period in this 45-69 age group. However, over and above these time-related changes, HIV infection status was associated with additional white matter microstructural abnormalities across the two-year study. These white matter microstructural abnormalities were linked to current HIV-related immune compromise and activation (lower current CD4+ T cells and higher CD8+ T cells), HAND severity (MND+HAD had widespread impact, ANI had a restricted impact in the superior thalamic radiation), and to a lesser extent, CVD risk. Within the PWH group, baseline HIV duration was associated with worsening white matter microstructure over the study period potentially reflecting active immuno-senescence, rather than legacy effects as both AIDS status and nadir CD4 did not contribute to the white matter microstructure

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changes. In parallel, WMH volume did not systematically vary between PWH and HIV-controls nor those with HIV and greater CVD risk versus those with lower CVD risk. WMH volume, however, increased by CVD risk independently of HIV status. This effect was of greater magnitude for the periventricular WM, which also increased during the study period. This work demonstrates that some CVD-driven increase in clinically apparent white matter disease (i.e., WMH), the fine white matter microstructure shows widespread abnormalities only in PWH. These findings assist in resolving the inconsistencies in the previous DTI and HIV literature which for the most part did not use FBA[36] and WMH volume at the same time.

More specifically, our study shows that CVD and HIV infection status lead to impaired white matter microstructure in different brain regions and that both represent independent risks likely reflecting differing neuropathological mechanisms. HIV infection status was associated with widespread reductions in cortical association tracts and subcortical-parietal tracts, whereas increased CVD risk factors were associated predominantly with reduced fibre cross-section (i.e., size) in association tracts. Moreover, age-controlled CVD risk factors were associated with reduced fibre density in the thalamic-premotor tract. Diffuse reduced fibre size due to HIV infection status is consistent with earlier work in this dataset which noted lower white matter volume in frontal regions[37]. Our work extends that of prior fixel based analysis in younger and less treated samples which found reduced FD in limited frontal and corticospinal tracts[16] and reduced metrics in motor tracts[17]. As such, we demonstrate widespread alterations in white matter microstructure in this older sample with longer HIV duration, despite clinical stability and viral suppression. To the best of our knowledge, the current study is the first to assess CVD factors while measuring tracts with fixel based analysis in

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PWH. Age-independent CVD findings of reduced fibre density are consistent with general population studies where both inherited[38] and acquired[39] primary vascular brain disease is associated with reduced fibre density. The thalamic pre-motor tract may reflect afferent thalamus injury. The thalamus is an integrative structure relaying information between the deep grey matter and the cortex. It is particularly vulnerable to small cerebral disease injury with potential impact on motor, sensory, motivational and a wide range of cognitive functions[40] depending on the locations of the injury. More broadly, CVD is more likely to cause ischemic injury, which in acute disease is more likely to involve myelin rather than axonal loss[41], and thus in chronic disease may be detected as reduction in tract cross-section than density. By contrast, HIV as a neurotropic virus may involve both axons and oligodendrocytes and cause more widespread microstructural changes. Regionally, CVD risk factors have been associated more with frontal WMH[42], potentially due to increased frontal vulnerability of perforating arterioles[43], which is consistent with the findings here. Neuropsychologically, such neurological complications may be difficult to distinguish from HIV-related changes, hence the importance of MRI assessment. Additionally, there were no interactions with HIV×age or CVD risk and/or age or HIV×CVD risk× and/or age (CVD and age considered together or separately), suggesting no accelerated white matter atrophy in older PWH during the study period including in those who had greater CVD burden. This level of relative brain health stability across two years has been previously demonstrated in another cohort with sustained viral suppression[11].

In this study we show that mild to moderate HAND (MND+HAD; HAD was at early stage in all cases) was associated with widespread reductions in FC and FDC, corroborating our previous work a DTI-based model of FA and MD[25]. The fixel based

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analysis further demonstrated more extensive fibre cross section and density alterations in the MND+HAD cases relative to both ANI and controls, again reflecting probable atrophy. Such a wide involvement of the white matter microstructure is consistent with the diffuse type of cognitive impairment which predominantly affects high order cognitive abilities in patients with moderate HAND or at the level of functional integration[44]. Furthermore, in most of these cases, there was no evidence of progression over time or age over the two-year period[45]. In ANI, we found restricted white matter microstructure abnormalities as reduced fibre cross section in the superior thalamic radiation. Both HIV and CVD effects contribute to this finding. The restricted level of white matter injury may be specific to ANI rather than its location within the wider frontal, superior and parietal white matter tracts bundles[37].

We demonstrate that current HIV factors were more important in influencing white matter microstructure abnormalities than any legacy HIV disease markers (that is AIDS and nadir CD4). Longer baseline HIV duration associated with more rapid decline over time in white matter fibre density and volume (i.e., HIV duration and time interaction on reduce fibre density in multiple tracts). This finding occurs in the context where higher current CD4+ count was associated with higher frontal tract density, whereas higher CD8+ count was associated with lower tract volume in mostly posterior tracts. When taken together, the HIV duration finding may be indicative of ongoing immune-senescence[46], rather than a legacy effect. This was also despite controlling for CVD risk factors (including age), emphasising that this independent HIV effect is the driver of progressive alterations in white matter microstructure. Cross-sectionally increased HIV duration has been associated with lower traditional DTI metrics of FA and MD[4,47], however to our knowledge this has not been investigated longitudinally especially using

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FBA. The overall neuropathology implications of these findings are that chronological age, current HIV disease factors (lower immune recovery, immune activation, and immune senescence), and CVD risk factors are actively driving alterations in white matter density and atrophy.

We found no significant differences in periventricular or deep WMH volume between PWH and HIV- participants controlling for CVD risk in agreement with a previous study in well controlled PWH[48], and using quantitative methods for WMH volume measurement[49,50]. By contrast, in large virally-controlled samples of PWH on cART, significant increases with HIV status were found using visual rating scales[19,51]. It is plausible that visual rating studies may be relatively more specific to such differences because higher Fazekas visual WMH grading is given by volume and confluence, and therefore, those with more severe disease may have a ceiling effect on large confluent areas. This creates a restricted range of values which put weights at the severe end of the spectrum of WMH distribution. This is supported by other work finding a quadratic relationship between visual rating scales and WMH volumetric measures[52]. In contrast to rating scales, WMH assessed by automated volumetric measures have a wider range of values. In other words, the WMH volumetric measures are more sensitive but perhaps less specific, and results may vary slightly depending on the composition of the samples especially for non-HIV factors. Importantly, the absence of difference in WMH with HIV status despite widespread tract metrics highlights that subtle white matter impairment may be present without clinically apparent white matter injury.

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There are several limitations to this study. While our sample reflect the demographics of the majority of PWH in Australia, we acknowledge that there is a lack of representation of women and some minorities living with HIV. Migrants from high HIV prevalence countries are included in this sample, but they reflect those who are highly educated. Our study was based on a 32-direction acquisition protocol and a single b-value. This means that contrary to multishell acquisitions, our FD metric was less specific than optimal. While using automated tract derivations is advantageous and has been used in more marked structurally neurodegenerative conditions such as Alzheimer's disease[38], striatum and thalamic projections may be less reliable given the known atrophy of these structures in HIV. Additionally, while this is a valuable longitudinal neuroimaging sample of PLWH there are several limitations. It remains relatively underpowered to detect two and three-way interactions. It remains possible that HIV may contribute to excess structural changes over time, albeit at a smaller effect size than is able to be determined here. The use of only two timepoints limits the assessment of non-linear acceleration in PLW with age. Lastly, the variability in follow-up assessments may increase the uncertainty of estimates, but this was equivalent between groups and thus is unlikely to bias group comparisons.

In conclusion, in this sample of PWH who has long-term viral suppression, the fine integrity of white matter tracts revealed by fixel-based analysis is impacted across cortical association tracts and subcortical-parietal tracts as well as thalamic pre-motor tract, due to active HIV disease-related processes of HIV infection, including longer age-corrected HIV duration and baseline CD4+ T cells and CD8+ T cells, and to a lesser extent CVD. Our study indicates that assigning only a CVD origin to fine white matter injury in PWH is likely not correct. At the same time, the burden of WMH does

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not differ as a function of HIV status or the interaction of HIV status and CVD risk. CVD risk had however a similar impact on WMH burden between HIV status infection groups. This report provides further evidence of the complex immuno-vascular underpinning of HIV neuropathogenesis in virally suppressed PWH.

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Conflict of Interest

DJ, AC, KL, and CDR have no conflict of interest to declare

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Authors' contributions

All authors contributed to the study design, data interpretation, and provided critical revision of the manuscript. C.D.R., B.J.B., and L.A.C. were involved in data acquisition. D.J. conducted the imaging and statistical analyses and drafted the manuscript. All authors approved the final version of the manuscript.

AI-tools did not contribute to this manuscript.

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Supplementary Material-https://links.lww.com/QAI/C741

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Figure 1: Summary of neuroimaging pipeline

Figure 1 Legend: Steps in processing of structural and diffusion imaging. Final tract metrics were fibre density (FD), fibre cross-section (FC) and both fibre density and cross-section (FDC).

Figure 2: Effects of HIV status, CVD risk on tract metrics

Figure 2 Legend: Effect estimate values and standard error for long cortical association tracts, striatal- frontoparietal tracts and thalamic-frontoparietal tracts. Darker shaded values are statistically significant (FDR $p<0.05$), lighter shaded values are not statistically significant. Tracts included: corpus callosum (CC), uncinate fasciculus (UF), arcuate fascicle (AF), anterior thalamic radiation (ATR), superior thalamic radiation (STR), cingulate gyrus (CG), corticospinal tract (CST), superior longitudinal fascicle (SLF), middle longitudinal fascicle (MLF), inferior longitudinal fascicle (ILF), inferior occipito-frontal fascicle (IFO), optic radiation (OR); striatal (ST) and thalamic (T) tracts to cortical regions: fronto-orbital (FO), prefrontal (PREF), premotor (PREM), precentral (PREC), postcentral (POST), parietal (PAR), and occipital (OCC).

Figure 3: Effects HAND clinical categories on tract metrics

Figure 3 Legend: Effect estimate values and standard error for long cortical association tracts, striatal- frontoparietal tracts and thalamic-frontoparietal tracts. Darker shaded values are statistically significant (FDR $p<0.05$), lighter shaded values are not statistically significant. Tracts included: corpus callosum (CC), uncinate fasciculus (UF), arcuate fascicle (AF), anterior thalamic radiation (ATR), superior thalamic radiation (STR), cingulate gyrus (CG), corticospinal tract (CST), superior longitudinal fascicle (SLF), middle longitudinal fascicle (MLF), inferior longitudinal fascicle (ILF), inferior occipito-frontal fascicle (IFO), optic radiation (OR); striatal (ST) and thalamic (T) tracts to cortical regions: fronto-orbital (FO), prefrontal (PREF), premotor (PREM), precentral (PREC), postcentral (POST), parietal (PAR), and occipital (OCC).

Figure 4: Effects of HIV disease factors on tract metrics

Figure 4 Legend: Effect estimate values and standard error for long cortical association tracts, striatal- frontoparietal tracts and thalamic-frontoparietal tracts. Darker shaded values are statistically significant (FDR $p<0.05$), lighter shaded values are not statistically significant. Tracts included: corpus callosum (CC), uncinate fasciculus (UF), arcuate fascicle (AF), anterior thalamic radiation (ATR), superior thalamic radiation (STR), cingulate gyrus (CG), corticospinal tract (CST), superior longitudinal fascicle (SLF), middle longitudinal fascicle (MLF), inferior longitudinal fascicle (ILF), inferior occipito-frontal fascicle (IFO), optic radiation (OR); striatal (ST) and thalamic (T) tracts to cortical regions: fronto-orbital (FO), prefrontal (PREF), premotor (PREM), precentral (PREC), postcentral (POST), parietal (PAR), and occipital (OCC). CD4+ and CD8+ results reported x 10.

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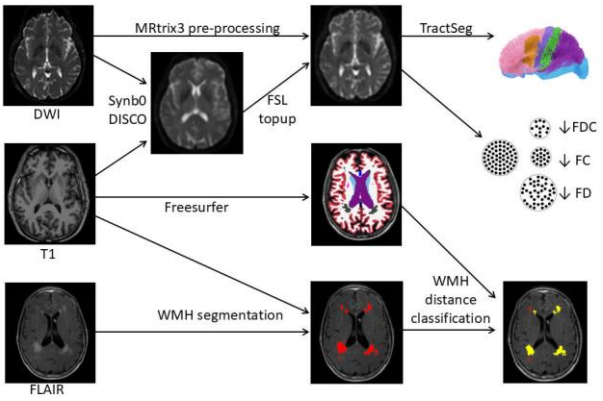

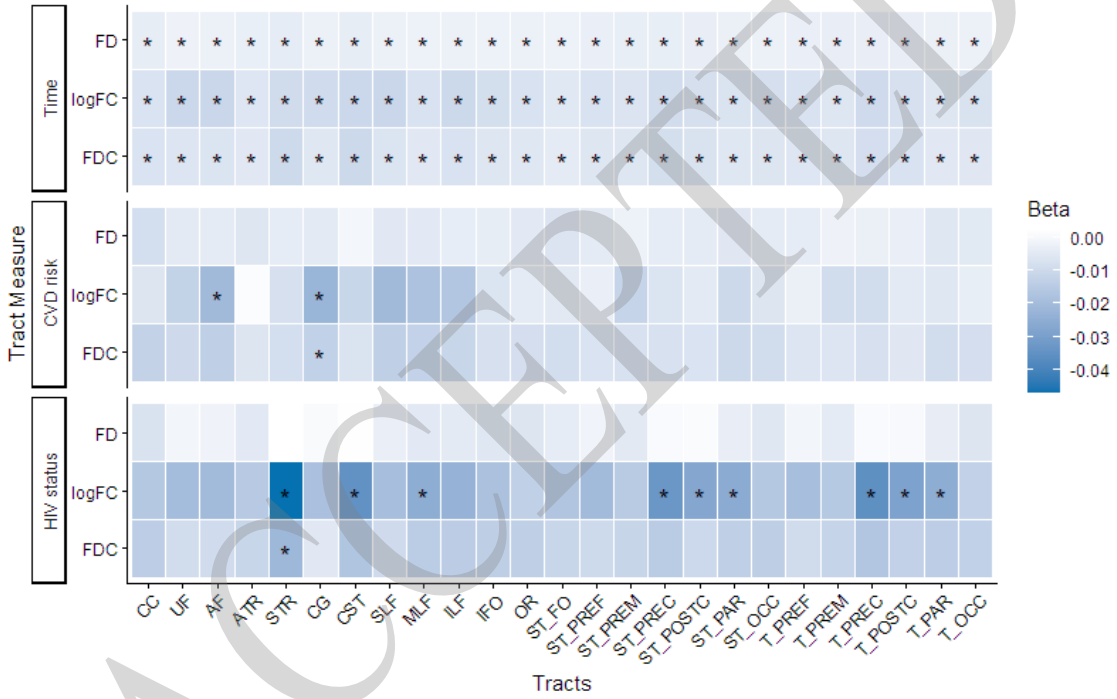

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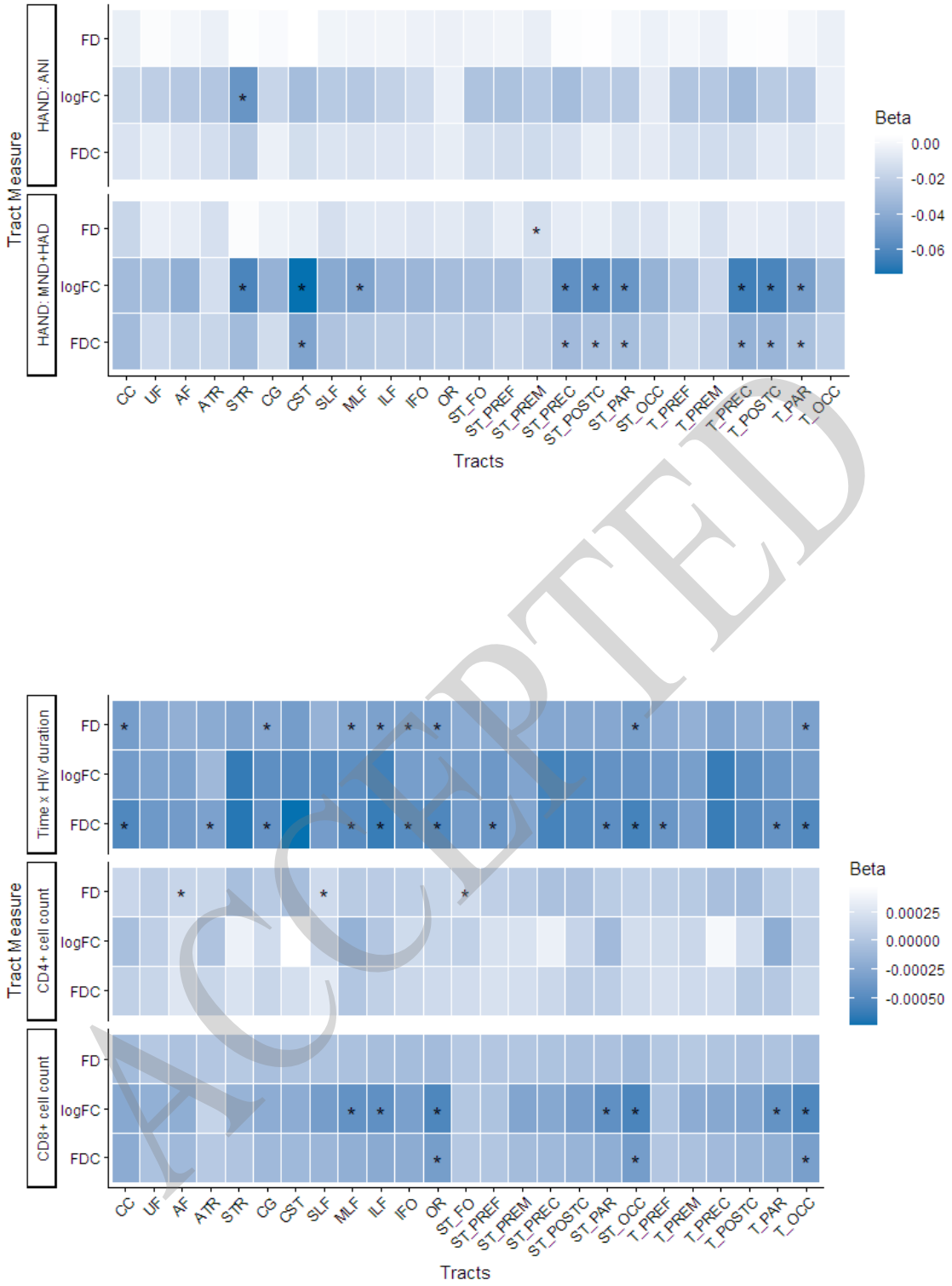

Table 1. Demographic, cardiovascular, and neuroimaging information in the study samples

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		HIV-		PWH		*p*
Baseline						
	n	48		84		
		M	SD	M	SD	
	Age (years)	53.3	6.34	54.4	6.45	0.334
	Age range	45-67		45-69		
	Education (years)	15.2	2.57	14.3	2.68	0.060
	Framingham high risk (%)	19		49		<0.001
	DAD high risk (%)	-		10		
	Cardiovascular event (%)	0		12		
	Cardiovascular medication (%)	21		31		
	Periventricular WMH (mm^3)	267	347	460	1061	0.308
	Deep WMH (mm^3)	139	389	186	625	0.654
Follow-up						
	n	40		75		
		M	SD	M	SD	
	Age (years)	55.6	6.61	56.1	6.19	0.701
	Age range	45-67		45-68		
	Education (years)	15.1	2.63	14.4	2.56	0.158
	Test-retest interval (months)	25.4	5.5	25.8	5.77	0.66
	Test-retest interval range	11.6-40.6		14.5-40.7		

VIQ: Verbal IQ; WMH: White matter hyperintensities

Participants (n=17) across both groups did not return for follow-up due to claustrophobia, new MRI contraindications, were unavailable, or did not wish to participate. There were no significant demographic or clinical differences between those who did and did not attend follow-up.

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Table 2. Laboratory, clinical and HIV disease characteristics

Measure	HIV-		PWH	
	Median/%	Range	Median/%	Range
Baseline				
Total cholesterol (nmol/L)	4.8	(3.1-8.2)	5.2	(2.4-8.1)
HDL cholesterol (nmol/L)	1.3	(0.9-1.9)	1.2	(0.5-2.5)
Systolic blood pressure (mm Hg)	119	(90-164)	130	(96-160)
Current smoker	6%	NA	20%	NA
Antihypertensive use	21%	NA	24%	NA
Serum glucose (nmol/L)			4.9	(3.4-8.2)
Triglycerides (nmol/L)			1.6	(0.5-11.3)
Median HIV duration (years)			20	(4-30)
Median current cART duration (months)			24	(6-156)
Median nadir CD4+ cell count (cells/µl)			180	(0-490)
Median CD4+ cell count (cells/µl)			528	(77-1476)
Median CD8+ cell count (cells/µl)			822	(51-2132)
Median CD4/CD8 ratio			1.71	(0.16-8)
Protease/Integrase inhibitor use			45%	
Historical AIDS			27%	
Plasma HIV RNA undetectable (<50 copies/ml)			98%	
CSF HIV RNA undetectable[1] (<50 copies/ml)			97.22%	
NP normal			49%	
ANI			36%	
MND+HAD			15%	
Follow-up				
Median CD4+ cell count (cells/µl)			670	(136-1936)
Median CD8+ cell count (cells/µl)			844	(285-2352)
Median CD4/CD8 ratio			1.35	(0.45-4.2)
Plasma HIV RNA undetectable across study (<50 copies/ml)			88%	
Change in cART during study period			13%	

[1]CSF was obtained in 36 patients.
NP-normal: neuropsychologically-normal, ANI: Asymptomatic Neurocognitive Impairment, MND: Mild Neurocognitive Disorder, HAD: HIV-associated dementia.

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