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The use of visual rating scales to quantify brain MRI lesions in patients with HIV infection

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Abstract

Background and purpose—HIV-infected patients commonly have abnormalities in cerebral white matter which are visible on MRI as hyperintensities (WMH). Visual rating scales (VRS) have been used to quantify WMH in other diseases such as cerebral small vessel disease (CSVD), but not in HIV. Such scales are advantageous because they are applicable to routinely acquired MRIs and so are suitable for large scale studies and clinical care. We sought to establish the utility of three VRS (the Fazekas, Scheltens and van Swieten scales) in HIV.

Methods—The Manhattan HIV Brain Bank (MHBB) is a longitudinal cohort study which performs serial neurologic examinations and neuropsychological testing. All brain MRIs (n=73) performed for clinical purposes on MHBB participants were scored using the three VRS. We assessed reliability, validity, and correlation of the VRS with clinical factors relevant to HIV and CSVD.

Results—The VRS all showed acceptable internal consistency and inter-rater reliability and were highly correlated with one another ($r=0.836-0.916$, $p<0.001$). The Fazekas and Scheltens scales demonstrated more WMH in periventricular regions, and the Scheltens scale also suggested a frontal to occipital gradient, with greater WMH frontally. All three VRS correlated significantly

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with cognitive impairment (global T score). Age and HCV antibody serostatus were the strongest clinical/demographic correlates of WMH, followed by African-American race.

Conclusions—VRS reliably quantify WMH in HIV-infected individuals and correlate with cognitive impairment. Future studies may find routinely acquired brain MRI quantified by VRS to be an accessible and meaningful neurologic outcome measure in HIV.

Keywords

HIV; MRI; white matter hyperintensities; cerebral small vessel disease; neurocognitive impairment

Introduction

The effect of HIV on the brain and its neuroimaging correlates have long been subjects of research. Early studies described atrophy and generalized white matter hyperintensities (WMH), with some reports indicating a predilection for periventricular areas such as the corpus callosum.¹ During this pre-therapeutic era, a particular challenge was distinguishing the features of HIV from those of opportunistic infections (OIs) such as cytomegalovirus (CMV).² With the current use of combination antiretroviral therapy (CART) and resultant immune reconstitution, OIs have become less common. However, as the HIV-infected population ages and accrues vascular risk factors³ such as hypertension, diabetes and dyslipidemia, the differential diagnosis of WMH in the HIV-infected patient is instead complicated by the possibility of cerebral small vessel disease (CSVD).

Recent neuropathologic studies have documented the presence of CSVD in HIV and explored its clinical predictors.^{4,5} Our group found that mean arteriolar wall thickness correlated with hepatitis C virus (HCV) infection, African American race, hypertension, and use of CART.⁴ Others found associations of CSVD with diabetes and use of protease inhibitors (PIs).⁵ There is also an extensive literature exploring the clinical correlations of white matter abnormalities in HIV using morphometric techniques and diffusion tensor imaging. The CHARTER study demonstrated that the volume of abnormal white matter was associated with nadir CD4+ counts and HCV co-infection;⁶ other studies have documented associations of WMH with age, active HCV, a history of AIDS, higher current CD4+ counts, number of years spent with CD4+ counts under 500, and total duration of HIV infection.^{7–9} Hence, there is large overlap between the clinical correlates of CSVD and WMH in HIV-infected cohorts. Furthermore, increases in WMH have observable functional consequences in HIV patients, including neurocognitive difficulties, particularly in the domains of executive function and psychomotor speed.¹⁰

Interestingly, despite the abundance of research using advanced MRI techniques, there has been relatively little work examining the features of WMH on conventional MRIs such as those obtained in the context of clinical care. Outside the realm of HIV research, visual rating scales (VRS) have been employed for this purpose for many years, and continue to be used because of their practicality for application to clinical data, for studies with large numbers of participants, and for studies in which neuroimaging is not the primary focus.¹¹ Among many available scales, three have been used extensively, namely those developed by Fazekas, Scheltens, and van Swieten (Table 1). The Fazekas scale was developed to describe

signal abnormalities in patients with Alzheimer's disease and determine whether they could be differentiated from healthy elderly controls and patients with presumed vascular dementia.¹² This scale is currently used particularly for the quantification of leukoaraiosis due to CSVD.^{13,14} However, some authors have found the Fazekas scale overly simplistic. A more detailed alternative is the Scheltens scale, which added basal ganglia and infratentorial subscales, greater anatomic detail within each subscale, and specificity with regards to size and number of lesions.¹⁵ A third scale, published by van Swieten and colleagues, took a different and relatively simpler approach of defining two anatomic areas, anterior and posterior, but adding greater specificity regarding the MRI slices which should be analyzed.¹⁶

The potential advantages of VRS are the ability to apply them broadly and inexpensively to any routinely acquired brain MRI, and the ability to compare findings across central nervous system (CNS) disease states. However, to our knowledge such scales have been applied infrequently to HIV-infected cohorts. One study (using the Rotterdam Scan Study Scale¹⁷ which quantifies periventricular and subcortical WMH), found that a larger lesion burden was associated with older age and higher systolic blood pressure.¹⁸

In the current study, we applied the Fazekas, Scheltens, and van Swieten scales to brain MRIs, obtained in the course of medical care using routine clinical neuroimaging protocols, from HIV-infected participants enrolled in a longitudinal cohort study (the Manhattan HIV Brain Bank, MHBB). Our goal was two-fold. First, we sought to assess the performance of these scales in HIV-infected adults, including their ability to provide meaningful quantification of WMH and its neuroanatomic distribution, and whether one particular scale was best suited to our population. Second, we aimed to determine whether scores provided by these scales correlated with neurocognitive performance and with HIV-related and vascular risk factors.

Methods

The Manhattan HIV Brain Bank (MHBB)

The MHBB (U24MH100931) is an ongoing prospective cohort study, located in New York City, which was founded in 1998 to be a research resource of neurologic tissues from highly characterized donors. The MHBB cohort and study procedures have been described previously.^{19,20} Briefly, inclusion criteria are designed to target HIV-infected patients with relatively high mortality risk based on clinical judgment, considering issues such as age, co-morbid medical illnesses, and laboratory parameters such as HIV-1 plasma RNA load and CD4+ count. Participants undergo comprehensive assessments at 6–24 month intervals (based on health status and psychosocial stability). This assessment includes: documentation of co-morbid medical conditions; standardized neurologic examination including the United Parkinson Disease Rating Scale (UPDRS),²¹ and the HIV Dementia Motor Score (HDMS);¹⁹ collection of blood for HIV-1 plasma RNA load and CD4+ cell count; determination of lifetime and current substance use disorders using either the Psychiatric Interview for Substance and Mental Disorders (PRISM),²² or Composite International Diagnostic Interview (CIDI);²³ and a battery of neuropsychological tests (as described previously),^{20,24} which has been validated in the assessment of HIV-associated neurocognitive disorders, and

results in a global neuropsychological T score calculated from 6 domain-specific T scores: memory encoding, memory retrieval, speed of information processing, working memory, verbal fluency, and abstraction or executive functioning.

Data collection and MRI analyses

All MHBB procedures are in accordance with the ethical standards of our institutional review board (IRB), and with the Helsinki declaration of 1975, as revised in 2000. All MHBB participants provide written informed consent which includes granting access to their medical records for the purposes of data collection. At our institution clinical records are maintained in an electronic health record (EHR) system with direct access to imaging studies. Using the EHR we retrospectively identified all MHBB participants with axial T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI scans of the brain which had been conducted for clinical purposes. All included MRIs were performed at our center, although not necessarily on the same scanner. MRI protocols varied based on the clinical indication for the scan and the time at which the scan was performed; Scans were acquired within the following parameters: field strength= 1.5–3 Tesla; TE= 127–174 ms; TR= 9500–10000 ms; resolution= 256x192–320x320. The first five MRIs were reviewed jointly by three of the co-authors who are all neurologists (JRP, MSD and AN) in order to standardize the application of the three scales. All MRIs were then reviewed and scored by the same rater (AN). To establish inter-rater reliability a fourth author (USC) independently rated a randomly selected subset of MRIs (n=20). If participants had more than one MRI available for review, we included the MRI closest in time to an MHBB visit. If two MRIs were equidistant from an MHBB visit we used the more recent one.

The following data were extracted from the MHBB database for each participant (using the visit closest in time to the MRI): age, race/ethnicity, duration of known HIV infection, current and nadir CD4+, current antiretroviral regimen, HCV serostatus, lifetime diagnosis of a cocaine or stimulant use disorder, current or past hypertension diagnosis, diagnosis of diabetes or hyperlipidemia, smoking status, the results of neuropsychological testing expressed as global and domain-specific T scores, and the results of neurologic examination expressed as the HDMS and UPDRS.

Statistical considerations

Descriptive statistics including frequencies, ranges, and measures of center (mean and standard deviation or median and interquartile range as appropriate) were performed, including description of the neuroanatomic distribution of MRI lesions as determined using each of the scales. Comparison of lesion burden between brain regions (within an individual scale) was performed using paired samples t-tests. The performance of the scales was assessed by calculating internal consistency reliability (Cronbach's α) for each of the scales, determining their correlation with one another, and assessing inter-rater reliability (Spearman's rank correlations). Associations between each of the three scales and neurocognitive performance and clinical factors were assessed using Spearman's rank correlation and the Mann-Whitney U test as appropriate. Finally, variables found to be associated with one or more of the scales in univariate analyses were entered into

multivariate linear regression models, each with one of the three scales as the dependent variable. All analyses were performed using SPSS version 23.

Results

Participants

Of 496 HIV-infected MHBB participants who consented to have their medical records reviewed, 73 (15%) had received at least one MRI of the brain for clinical purposes, which was viewable in our EHR. These 73 participants were, in general, similar to the larger cohort (table 2), except for a higher prevalence of uncontrolled viremia in the overall cohort, and higher prevalence of smoking and older age in our study patients. Although the cause of this difference is unknown, we speculate that participants who received MRIs may have been more likely to be engaged in clinical care, and therefore have their HIV better controlled. The 73 participants were diverse with regards to sex, race/ethnicity, and age (range: 38–72 years). Most participants had longstanding HIV infection and had experienced significant past immunosuppression. Most were currently treated with CART (88%) and had experienced significant immune reconstitution, with 60% of participants achieving an HIV-1 plasma RNA load under 100 copies/ml, and 80% under 2000 copies/ml. Vascular risk factors were common (table 2). The clinical indications for the MRIs (as listed in the EHR) were as follows: abnormal finding on neurologic examination (26%), concern for CNS infection (18%), cognitive complaints (14%), follow-up of a previously observed neuroimaging abnormality (14%), headache (11%), concern for possible cerebrovascular disease (7%), movement disorder (4%), seizures (5%), and syncope (1%).

Performance of white matter rating scales

A broad range of scores were observed on each of the three scales (table 3). Internal consistency reliability of scales was acceptable for all three scales with the van Swieten scale being the highest, although with regard to this measure the Fazekas scale was at a disadvantage having only two items.

As shown in the figure, the summary scores for all three scales were highly correlated with one another (Fazekas/Scheltens: $r=0.916$, $p<0.001$; Fazekas/van Swieten: $r=0.839$, $p<0.001$; van Swieten/Scheltens: $r=0.836$, $p<0.001$). Similarly sub-scores reflective of similar brain regions were correlated. For example, the sum of the Scheltens's two occipital scores (periventricular and white matter) correlated with van Swieten's posterior score ($r=0.749$, $p<0.001$); and the sum of the Scheltens scale's two frontal scores (periventricular and white matter) correlated with van Swieten scale's anterior score ($r=0.806$, $p<0.001$). Similarly, the periventricular sub-score of the Fazekas scale correlated with the periventricular sub-score of the Scheltens scale ($r=.754$, $p<0.001$), as did the analogous white matter sub-scores ($r=.825$, $p<0.001$). Finally, inter-rater reliability was strong for all three scales: Fazekas ($r=.929$, $p<0.001$), Scheltens ($r=.900$, $p<0.001$), and van Swieten ($r=.882$, $p<0.001$).

Neuroanatomic distribution of MRI lesions

The Scheltens scale has the most complex scoring system and examines the greatest variety of brain regions: periventricular, white matter, basal ganglia and infratentorial. However, the

possible ranges of these sub-scores are not uniform (e.g. 0–6 for periventricular, and 0–24 for infratentorial). Thus, in order to compare the relative lesion burden between these brain regions we expressed each of these scores as a fraction of its maximum value, converting all scores to a scale of 0–1. Using this technique, we found that the lesion burden was highest in the periventricular region (0.62; SD=0.17), followed by the subcortical non-periventricular white matter (0.27; SD=0.27), infratentorial region (0.086; SD=0.15), and basal ganglia (0.044, SD=0.09). The lesion burden as quantified by the Fazekas scale was also greater in the periventricular areas (0.63; SD=0.28) as compared to other white matter (0.42; SD=0.33). The differences between the lesion burden in the periventricular and white matter locations was statistically significant for both the Fazekas ($t=-5.62$, $p<.001$), and Scheltens scales ($t=-12.89$, $p<.001$).

The van Swieten scale approaches the anatomy differently, considering anterior versus posterior brain regions. Using this method there was no difference in lesion burden in these two regions, with the mean value being 1.7 out of 6 for both. However, examination of anterior versus posterior brain regions using the Scheltens scale, in which cerebral lobes are considered individually, suggested a greater burden anteriorly in the white matter with the highest burden in the frontal lobes (mean score of 2.52 out of 6), a moderate burden in parietal (1.84) and temporal (1.23) lobes, and the least burden in occipital lobes (0.82). This anterior to posterior gradient was not observed in the periventricular region in which lesion burden was equal in the frontal and occipital regions (1.3 out of 2 for both).

Of note, in this sample of 73 participants, there were 11 participants whose brain lesions were attributable to another AIDS related disorder (progressive multifocal leukoencephalopathy in 9 participants, and primary CNS lymphoma in 2). These participants were not excluded from the above analyses because these neuroAIDS disorders are an important part of the abnormalities observed in the brain MRIs of HIV-infected individuals, and we wished to document, if possible, that the VRS could still be used in their presence. The analyses described above were subsequently repeated excluding these participants, and the same patterns were observed, namely that the periventricular region had the greatest lesion burden overall, and that the Scheltens scale demonstrated a frontal to occipital gradient, which was not apparent using the van Swieten scale.

Correlation of lesion burden with neurocognitive performance

We found that higher scores on all three rating scales were associated with lower global T scores (Fazekas: $r=-.357$, $p=0.006$, Scheltens: $r=-.336$, $p=0.010$, van Swieten: $r=-.299$, $p=0.022$) indicating poorer cognition. When specific domain scores were examined, memory encoding and memory retrieval emerged as the most closely associated with higher burden of WMH. These domains were significantly associated with all three scales (r range of -0.356 to -0.46 ; $p < 0.01$ for all). The only other domain that showed any independent association with lesion burden was speed of information processing, and the association was only with the Fazekas scale ($r=-.305$, $p=.003$).

In terms of the neurologic examination, there was no association between the HDMS and lesion burden as measured by any of the three scales. There was a trend for higher UPDRS scores among those with greater scores on the Scheltens scale ($r=.24$, $p=.054$), and to a

lesser extent the Fazekas scale ($r=.21$, $p=.095$). There was no apparent correlation of UPDRS score with the van Swieten scale ($r=.125$, $p=.322$). When the Scheltens subscales of were examined individually, the observed association with the UPDRS was found to be driven by the infratentorial ($r=.288$, $p=.02$) and basal ganglia ($r=.242$, $p=.052$) sub-scores.

Correlation of lesion burden with HIV-related and vascular risk factors

For these analyses we excluded participants whose brain lesions were attributed to another AIDS-related disorder, and two additional patients for whom clinical data was not available at the time of the scan ($n=60$ for included participants).

In univariate analyses, only two of the potential risk factors we studied were significantly associated with higher lesion burden as measured by all three scales: age (Fazekas: $r=.303$, $p=0.020$; Scheltens: $r=.293$, $p=.025$; van Swieten: $r=.329$, $p=.011$), and HCV antibody positivity (Fazekas: $U=248$, $p=0.003$; Scheltens: $U=259$, $p=.006$; van Swieten: $U=275$, $p=.010$). There was also a trend for higher lesion burden among participants of African-American race (compared to white race) as measured by all three scales (Fazekas: $U=325$, $p=0.063$; Scheltens: $U=323$, $p=.063$; Van Swieten: $U=335$, $p=.085$), and a trend for an association of higher lesion burden with lower current CD4+ count as measured by the Fazekas ($r=-.219$, $p=.092$) and van Swieten scales ($r=-.230$, $p=.077$), but not the Scheltens scale ($r=-.181$, $p=.167$). There was no association of lesion burden with HIV-1 plasma RNA load, years of HIV infection, nadir CD4+ count, use of PIs, cocaine/stimulant use, diabetes, hyperlipidemia, or current or past diagnosis of hypertension.

Multivariate linear regression was performed with each of the three scales as the dependent variable (table 4) and with the following independent variables (as identified in the univariate analyses as potentially significant): age, HCV antibody status, current CD4+ cell count, African-American race. Age remained a significant predictor of lesion burden in all three models, and HCV antibody status was either significant or at trend level in all three models. African-American race was at trend level in the Fazekas scale model only, and current CD4+ count did not significantly contribute to any of the three models.

Discussion

In this study we sought to explore the utility of applying VRS in the assessment of brain MRI white matter lesions in HIV-infected adults. Our rationale was that such scales are commonly used in other CNS diseases such as Alzheimer's dementia and cerebrovascular disease, and establishing their use in HIV would permit inter-disease comparison, and also provide a scalable and clinically applicable alternative to the automated quantitative MRI techniques currently used in HIV research. We found that despite their differences, all three scales (Fazekas, Scheltens, and van Swieten) performed well. The scales provided a range of scores that were suitable for capturing the lesion burden present in our participants without significant floor or ceiling effects, they displayed acceptable internal consistency and inter-rater reliability, and showed significant correlation with one another with regard to total score and relevant sub-scores. Further supporting their validity, all three scales were also associated with neurocognitive impairment, as reflected by the global T score derived from a comprehensive neuropsychological assessment. These data are consistent with previous

studies reporting associations between WMH and global neurocognitive ability in HIV.¹⁰ Additionally, we report the novel finding that WMH burden is associated with memory functions in HIV patients, which aligns with data from non-HIV older adult samples with memory complaints.^{25,26}

Our VRS analyses revealed significant periventricular WMH burden, as well as an anterior-posterior gradient, aligning with results from prior studies using more advanced MRI sequences and analysis techniques.^{8,27,28} Periventricular WMH have been associated with cardiovascular disease in previous studies,^{29,30} and thus might reflect vascular effects in our sample. Moreover, greater anterior than posterior WMH burden is consistent with evidence that HIV is associated with frontostriatal compromise.^{31,32} Yet, DTI and morphometric studies commonly reveal widespread effects of HIV throughout the brain.^{31–38} Interestingly, it has been suggested that WMH may represent a more advanced form of white matter pathology than the subtler, more extensive forms detected by DTI.^{10,39} Future studies are needed to further clarify the clinical relevance of regional white matter lesions in HIV+ samples, as well as to examine the relation of WMH burden to DTI findings.

In terms of factors to support the use of one VRS over the other, several observations can be made, although given the relatively small sample size, definitive recommendations would not be appropriate. The Fazekas scale is the simplest, and in our experience was the fastest scale to apply. Despite its simplicity, the Fazekas scale was the most strongly correlated with cognitive dysfunction, and was also highly correlated with the more complex Scheltens scale. We found the Scheltens scale significantly more laborious to apply, largely due to the anatomic specificity required. However its additional sub-scales, infratentorial and basal ganglia, were significantly correlated with motor dysfunction (UPDRS) in our sample, which is particularly relevant to HIV where motor dysfunction is an important part of CNS manifestations.¹⁹ Also the anatomic specificity allowed us to detect an anterior-to-posterior gradient in lesion burden (with anterior regions being more affected). The van Swieten scale was relatively simple to apply, but did not provide any clear advantage over Fazekas, and overall displayed the weakest correlations with the other two scales and with our markers of neurocognitive and motor dysfunction. The Fazekas scale was also the most closely linked to our clinical/demographic risk factors of interest, maintaining strong associations in multivariate analyses with older age and HCV antibody positivity, and a trend level association with African American race. These same factors were previously found to be associated with pathologic evidence of CSVD in our cohort.⁴ The observation of race-related differences in white matter lesion burden is consistent with previous findings in patients with high cardiovascular risk,⁴⁰ and neurologic patient samples.⁴¹ Moreover, the observation of age- and HCV-related associations with WMH load lends support to recent findings in HIV-infected adults.⁷

The WMH measured in this study may represent structural damage due to vascular disease. In the general population, WMH are likely caused by traditional vascular risk factors,⁴² and WMH have been associated with vascular outcomes, including stroke,^{43,44} mortality,^{45,46} cognitive impairment,^{47,48} and functional impairment.^{49–51} Our findings bear certain similarities to prior studies among community-dwelling individuals which have shown a predominance of WMH in the periventricular region,^{52–54} as well as greater burdens with

increasing age.⁵⁵ One of the goals of this study was to describe the ability of imaging scales developed in non-HIV populations to reliably quantify WMH burden among HIV-infected adults. Further study would clarify the etiologies of WMH in this population, and ways in which patterns of WMH in the brain may differ from non-HIV infected individuals.

This study has important limitations, most of which pertain to issues of sample size and selection bias. First, our cohort is not a population-based sample. Given that this is a brain bank study, our inclusion criteria are designed to favor participants with higher mortality risk. Furthermore, this study examines a subset of our brain bank participants who differed from the overall cohort in that they were slightly older, more likely to smoke, and had somewhat lower HIV-1 viral loads. If these differences are indeed clinically relevant, potential explanations could be that older participants and smokers are more likely to experience neurologic events that lead to MRI scans, and that lower HIV-1 viral loads are indicative of stronger engagement in clinical care, increasing the likelihood of receiving an MRI. However this is speculative. Second, we did not study HIV-negative controls. We made this choice for reasons of practicality; our focus was use of the VRS in HIV-infected individuals and our cohort contains an insufficient number of HIV-negative controls with neuroimaging. However, we acknowledge that the lack of a control group limits our ability to analyze whether the distribution of WMH in our patients is particular to HIV. Third, the MRIs described herein were all performed for clinical purposes, albeit for a diverse set of indications. Thus it is uncertain if our findings would be generalizable to healthier HIV-infected populations without clinical indication for brain MRI. Future research should include these participants and larger sample sizes.

In summary, VRS are useful in the quantification of WMH in the brain MRIs of HIV-infected adults. Using these scales we were able to determine the anatomic distribution of WMH in our participants (i.e. greatest in the periventricular area, and with a predilection for frontal lobes), and its clinical/demographic correlates, (i.e. age, HCV antibody positivity, and African-American race). The Scheltens scale may offer advantage in neurologically-focused studies, for which greater anatomic detail may be required, and motor dysfunction may be an intended focus. However, given its ease of use and stronger correlation with cognitive impairment, the Fazekas scale may be preferable for general purposes. For example, in multi-center studies of medical outcomes of HIV, brain MRI coupled with the Fazekas scale could provide an objective, accessible neurologic measure which could be performed broadly. The simple and straightforward nature of quantitative analysis of conventional MRI, and the attendant need for less training would also be suitable for clinical practice where advanced techniques (such as DTI or BOLD) which require greater post-processing may be difficult to use. Thus future research is needed to further validate the use of VRS in large, diverse groups of HIV-infected individuals, and to determine whether VRS can predict clinical neurologic outcomes in HIV as they do in other populations.

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References

1. Broderick DF, Wippold FJ, Clifford DB, Kido D, Wilson BS. White matter lesions and cerebral atrophy on MR images in patients with and without AIDS dementia complex. *AJR American J Roentgenol.* 1993; 161:177–81.
2. Holland NR, Power C, Mathews VP, Glass JD, Forman M, McArthur JC. Cytomegalovirus encephalitis in acquired immunodeficiency syndrome (AIDS). *Neurology.* 1994; 44:507–14. [PubMed: 8145923]
3. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet.* 2013; 382:1525–33. [PubMed: 24152939]
4. Morgello S, Murray J, Van Der Elst S, Byrd D. HCV, but not HIV, is a risk factor for cerebral small vessel disease. *Neurol Neuroimmunol Neuroinflammation.* 2014; 1:e27.
5. Soontornniyomkij V, Umlauf A, Chung SA, et al. HIV protease inhibitor exposure predicts cerebral small vessel disease. *AIDS.* 2014; 28:1297–306. [PubMed: 24637542]
6. Jernigan TL, Archibald SL, Fennema-Notestine C, et al. Clinical factors related to brain structure in HIV: the CHARTER study. *J Neurovirol.* 2011; 17:248–57. [PubMed: 21544705]
7. Seider TR, Gongvatana A, Woods AJ, et al. Age exacerbates HIV-associated white matter abnormalities. *J Neurovirol.* 2016; 22:201–12. [PubMed: 26446690]
8. Su T, Caan MW, Wit FW, et al. White matter structure alterations in HIV-1-infected men with sustained suppression of viraemia on treatment. *AIDS Lond Engl.* 2016; 30:311–22.
9. Heaps-Woodruff JM, Wright PW, Ances BM, Clifford D, Paul RH. The impact of human immune deficiency virus and hepatitis C coinfection on white matter microstructural integrity. *J Neurovirol.* 2016; 22:389–99. [PubMed: 26689572]
10. Watson C, Busovaca E, Foley JM, et al. White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV. *J Neurovirol.* 2017; 23:422–9. [PubMed: 28101804]
11. Scheltens P, Erkinjuntti T, Leys D, et al. White matter changes on CT and MRI: an overview of visual rating scales. European Task Force on Age-Related White Matter Changes. *Eur Neurol.* 1998; 39:80–9. [PubMed: 9520068]
12. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR American J Roentgenol.* 1987; 149:351–6.
13. Boulouis G, Charidimou A, Jessel MJ, et al. Small vessel disease burden in cerebral amyloid angiopathy without symptomatic hemorrhage. *Neurology.* 2017; 88:878–84. [PubMed: 28130469]
14. Kongbunkiat K, Wilson D, Kasemsap N, et al. Leukoaraiosis, intracerebral hemorrhage, and functional outcome after acute stroke thrombolysis. *Neurology.* 2017; 88:638–45. [PubMed: 28130468]
15. Scheltens P, Barkhof F, Leys D, et al. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci.* 1993; 114:7–12. [PubMed: 8433101]
16. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry.* 1990; 53:1080–3. [PubMed: 2292703]
17. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry.* 2001; 70:9–14. [PubMed: 11118240]
18. McMurtray A, Nakamoto B, Shikuma C, Valcour V. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc.* 2008; 17:212–7.
19. Robinson-Papp J, Byrd D, Mindt MR, et al. Motor function and human immunodeficiency virus-associated cognitive impairment in a highly active antiretroviral therapy-era cohort. *Arch Neurol.* 2008; 65:1096–01. [PubMed: 18695060]
20. Ryan EL, Morgello S, Isaacs K, Naseer M, Gerits P. Neuropsychiatric impact of hepatitis C on advanced HIV. *Neurology.* 2004; 62:957–62. [PubMed: 15037699]

21. Fahn, S., Elton, RL. UPDRS program members. Unified Parkinsons Disease Rating Scale. In: Fahn, S.Marsden, CD.Goldstein, M., Calne, DB., editors. Recent developments in Parkinsons disease. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153-63.
22. Hasin DS, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry*. 1996; 153:1195–01. [PubMed: 8780425]
23. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*. 1994; 28:57–84. [PubMed: 8064641]
24. Carey CL, Woods SP, Rippeth JD, et al. Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. *Clin Neuropsychol*. 2004; 18:234–48. [PubMed: 15587671]
25. Biesbroek JM, Weaver NA, Hilal S, et al. Impact of Strategically Located White Matter Hyperintensities on Cognition in Memory Clinic Patients with Small Vessel Disease. *PloS One*. 2016; 11:e0166261. [PubMed: 27824925]
26. Freeze WM, Jacobs HI, Gronenschild EH, et al. White Matter Hyperintensities Potentiate Hippocampal Volume Reduction in Non-Demented Older Individuals with Abnormal Amyloid-beta. *J Alzheimers Dis JAD*. 2017; 55:333–42. [PubMed: 27662299]
27. Thompson PM, Dutton RA, Hayashi KM, et al. 3D mapping of ventricular and corpus callosum abnormalities in HIV/AIDS. *NeuroImage*. 2006; 31:12–23. [PubMed: 16427319]
28. Cloak CC, Chang L, Ernst T. Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV. *J Neuroimmunol*. 2004; 157:147–152. [PubMed: 15579292]
29. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. *Biol Psychiatry*. 2008; 64:273–80. [PubMed: 18471801]
30. Yoshita M, Fletcher E, Harveyet D. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*. 2006; 67:2192–8. [PubMed: 17190943]
31. Pfefferbaum A, Rosenbloom MJ, Rohlfing T. Frontostriatal fiber bundle compromise in HIV infection without dementia. *AIDS*. 2009; 23:1977–85. [PubMed: 19730350]
32. Pomara N, Crandall DT, Choi SJ, Johnson G, Lim KO. White matter abnormalities in HIV-1 infection: a diffusion tensor imaging study. *Psychiatry Res*. 2001; 106:15–24. [PubMed: 11231096]
33. Chang L, Wong V, Nakama H, et al. Greater than age-related changes in brain diffusion of HIV patients after 1 year. *J Neuroimmune Pharmacol Off J Soc NeuroImmune Pharmacol*. 2008; 3:265–74.
34. Chen Y, An H, Zhu H, et al. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. *NeuroImage*. 2009; 47:1154–62. [PubMed: 19376246]
35. Cohen RA, Harezlak J, Schifitto G, et al. Effects of Nadir CD4 Count and Duration of HIV Infection on Brain Volumes in the HAART Era. *J Neurovirol*. 2010; 16:25–32. [PubMed: 20113183]
36. Cordero DM, Towe SL, Chen NK, et al. Cocaine dependence does not contribute substantially to white matter abnormalities in HIV infection. *J Neurovirol*. 2017; 23:441–50. [PubMed: 28251596]
37. Müller-Oehring EM, Schulte T, Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Callosal degradation in HIV-1 infection predicts hierarchical perception: a DTI study. *Neuropsychologia*. 2010; 48:1133–43. [PubMed: 20018201]
38. Zhu T, Zhong J, Hu R, et al. Patterns of white matter injury in HIV infection after partial immune reconstitution: a DTI tract-based spatial statistics study. *J Neurovirol*. 2013; 19:10–23. [PubMed: 23179680]
39. Maillard P, Fletcher E, Lockhart SN, et al. White Matter Hyperintensities and their Penumbra Lie Along a Continuum of Injury In The Aging Brain. *Stroke J Cereb Circ*. 2014; 45:1721–6.
40. Nyquist PA, Bilgel MS, Gottesman R, et al. Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovasc Dis Basel Switz*. 2014; 37:244–50.
41. Howard J, Battaglini M, Babb JS, et al. MRI correlates of disability in African-Americans with multiple sclerosis. *PloS One*. 2012; 7:e43061. [PubMed: 22900088]

42. Hofer E, Cavalieri M, Bis JC, et al. White Matter Lesion Progression: Genome-Wide Search for Genetic Influences. *Stroke*. 2015; 46:3048–57. [PubMed: 26451028]
43. Ntaios G, Lip GY, Lambrou D, et al. Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation. *Neurology*. 2015; 84:1213–9. [PubMed: 25695964]
44. Windham BG, Deere B, Griswold ME, et al. Small Brain Lesions and Incident Stroke and Mortality: A Cohort Study. *Ann Intern Med*. 2015; 163:22–31. [PubMed: 26148278]
45. Kuller LH, Arnold AM, Longstreth WT Jr, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. *Neurobiol Aging*. 2007; 28:1307–15. [PubMed: 16857296]
46. Kuller LH, Lopez OL, Becker JT, Chang Y, Newman AB. Risk of dementia and death in the long-term follow-up of the Pittsburgh Cardiovascular Health Study-Cognition Study. *Alzheimers Dement J Alzheimers Assoc*. 2016; 12:170–83.
47. Hachinski V. World Stroke Day 2008: ‘little strokes, big trouble’. *Stroke*. 2008; 39:2407–20. [PubMed: 18723419]
48. Longstreth WT, Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002; 33:2376–82. [PubMed: 12364724]
49. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005; 53:649–54. [PubMed: 15817012]
50. Baune BT, Schmidt WP, Roesler A, Berger K. Functional consequences of subcortical white matter lesions and MRI-defined brain infarct in an elderly general population. *J Geriatr Psychiatry Neurol*. 2009; 22:266–73. [PubMed: 19690323]
51. Pohjasvaara TI, Jokinen H, Ylikoski R, et al. White matter lesions are related to impaired instrumental activities of daily living poststroke. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2007; 16:251–8.
52. Wakefield DB, Moscufo N, Guttmann CR, et al. White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. *J Am Geriatr Soc*. 2010; 58:275–81. [PubMed: 20374403]
53. Moscufo N, Guttmann CR, Meier D, et al. Brain regional lesion burden and impaired mobility in the elderly. *Neurobiol Aging*. 2011; 32:646–54. [PubMed: 19428145]
54. Zheng JJ, Delbaere K, Close JC, et al. White matter hyperintensities are an independent predictor of physical decline in community-dwelling older people. *Gerontology*. 2010; 58:398–6.
55. Habes M, Erus G, Toledo JB, et al. White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain J Neurol*. 2016; 139:1164–79.

Figure.

Correlations between visual rating scales

All three visual rating scales were highly correlated with one another (Fazekas/Scheltens: $r=0.916$, $p < 0.001$; Fazekas/van Sweiten: $r=0.839$, $p < 0.001$; van Sweiten/Scheltens: $r=0.836$, $p < 0.001$).

Table 1

Summary of MRI rating scales

Fazekas scale	Scheltens scale	van Swieten scale
<u>Periventricular hyperintensities (0–3)</u> 0= no lesions 1= pencil thin lining 2= smooth halo 3= irregular with extension into deep white matter <u>Deep White Matter Hyperintensities (0–3)</u> 0= no lesions 1= punctate foci 2= beginning confluence of foci 3= large confluent areas	<u>Periventricular hyperintensities (PVH 0–6)</u> Frontal (0–2) Occipital (0–2) Bands lateral ventricles (0–2) 0= absent 1= 5mm 2= > 5mm and <10mm <u>Deep White Matter Hyperintensities (WMH 0–24)</u> Frontal (0–6) Parietal (0–6) Occipital (0–6) Temporal (0–6) <u>Basal ganglia hyperintensities (BG 0–30)</u> Caudate nucleus (0–6) Putamen (0–6) Globus pallidus (0–6) Thalamus (0–6) Internal capsule (0–6) <u>Infra-tentorial foci of hyperintensities (IFT 0–24)</u> Cerebellum (0–6) Mesencephalon (0–6) Pons (0–6) Medulla (0–6) 0= absent 1= < 3mm, 5 lesions 2= < 3mm, > 6 lesions 3= 4–10mm, 5 lesions 4= 4mm, > 6 lesions 5= > 11mm, >1 lesion 6= confluent	<u>Anterior white matter (0–6) at the levels of:</u> Choroid plexus (0–2) Cella media (0–2) Centrum semiovale (0–2) <u>Posterior white matter (0–6) at the levels of:</u> Choroid plexus (0–2) Cella media (0–2) Centrum semiovale (0–2) 0= no lesions or a single lesion 1= multiple focal lesions 2= multiple confluent lesions scattered throughout the white matter

Table 2

Participant characteristics as compared to the larger cohort

	Study sample (n=73)	Overall MHBB cohort ^d (n=424)	p-value
Gender			0.95 ^b
Male	60%	62%	
Female	40%	38%	
Race			0.30 ^b
African-American	49%	53%	
White	51%	42%	
Other	0%	5%	
Ethnicity			0.54 ^b
Hispanic/Latino	34%	31%	
Non-Hispanic/Latino	66%	69%	
Age (years) ^c	54 (8.6)	52 (7.7)	0.04 ^d
Duration of known HIV infection (years) ^c	18 (7.5)	18 (5.2)	0.69 ^d
Nadir CD4+ count (cells/mm ³) ^c	153 (171)	132 (196)	0.39 ^d
Current CD4+ count (cells/mm ³) ^c	402 (308)	337 (349)	0.14 ^d
HIV plasma RNA load (copies/mL) ^e	27 (20, 754)	160 (20, 39700)	0.005 ^f
Vascular risk factors			
Hypertension	42%	35%	0.07 ^b
Diabetes	20%	18%	0.33 ^b
Hyperlipidemia	35%	30%	0.25 ^b
Smoking	57%	32%	<0.001 ^b

MHBB = Manhattan HIV Brain Bank; CD = cluster of differentiation; HIV = human immune deficiency virus; RNA = ribonucleic acid

^aExcluding participants who were part of the sample for this study^b χ^2 analysis^cValues expressed as mean (standard deviation);^dIndependent samples t-test^eValues expressed as median (interquartile range)^fMann-Whitney U test

Table 3

Characteristics of scores on three MRI white matter rating scales

Scale	Range of possible scores	Range of observed scores	Mean (SD)	Internal consistency reliability (Cronbach's α)
Fazekas	0–6	1–6	3.1 (1.6)	0.65
Scheltens	0–84	3–39	13.4 (9.8)	0.77
van Swieten	0–12	0–11	3.4 (3.4)	0.90

SD = standard deviation

Table 4

Multivariate analysis of clinical factors associated with brain MRI T2 lesion burden

	B (unstandardized)	SE	β (standardized)	p-value
Model 1: Fazekas scale as outcome				
Age in years	0.051	0.019	0.304	0.011
HCV antibody status	1.015	0.346	0.339	0.005
Current CD4+ cell count	−0.001	0.001	−0.140	0.235
African-American race (as compared to white)	0.610	0.345	0.205	0.083
Model 2: Scheltens scale as outcome				
Age in years	0.327	0.124	0.320	0.011
HCV antibody status	4.489	7.096	.243	0.050
Current CD4+ cell count	−0.004	0.004	−0.135	0.273
African-American race (as compared to white)	2.693	2.232	0.147	0.233
Model 3: van Swieten scale as outcome				
Age in years	0.124	0.046	0.325	0.009
HCV antibody status	1.583	0.828	0.230	0.061
Current CD4+ cell count	−0.002	0.001	−0.180	0.143
African-American race (as compared to white)	1.115	0.826	0.163	0.183

HCV = hepatitis C virus; CD = cluster of differentiation; SE = standard error