

White Matter Abnormalities in Males with suppressed HIV-Infection on Combination Antiretroviral Therapy compared to Representative Controls

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Objective: HIV-associated morbidity and mortality has decreased significantly following the introduction of combination antiretroviral therapy (cART)¹. Although HIV-associated dementia has become rare in the era of cART, HIV-associated neurocognitive disorder (HAND) remains common and has been reported in 15-50% of HIV-infected patients². It is yet unknown, what neuropathophysiology might underlie HAND in patients on cART. We performed brain diffusion tensor MRI (DTI) scans and neuropsychological assessment in HIV infected patients and comparable uninfected controls to gain more insight into the cognitive function and white matter integrity of middle-aged HIV-infected patients with suppressed viraemia on cART.

Methods/Participants: HIV-infected males (N=70, ≥ 45 years, median age: 53 years, mean estimated HIV-infection duration: 12.6 years) with suppressed viraemia on cART (median years since start ART: 11.1, current mean CD4 count: 606/mm³) were compared to HIV-uninfected men (N=47) of similar age, ethnicity, education and lifestyle. Six cognitive domains: verbal fluency, information processing speed, attention, executive function, memory and motor function were assessed. Cognitive impairment in HIV-patients was identified using the Multivariate Normative Comparison method³. DTI scans were acquired on a Philips 3.0 Tesla Intera system (Philips Healthcare, Best, The Netherlands), using an eight-channel SENSE receiver head-coil. The scanning parameters were TE/TR = 92/7725 ms; diffusion sensitivities of b=0 and b=1000 s/mm²; 55 to 60 continuous (no inter-slice gap) slices; data matrix 112x112; voxel size 2x2x2 mm³; DWI along 64 directions. DWI-data were preprocessed using in-house developed software after which Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps were computed. Voxel-wise statistical analysis of FA and MD data were carried out using tract-based spatial statistics (TBSS), part of FMRIB Software Library (FSL)^{4,5}. TBSS projects all subjects' FA and MD data onto a mean FA tract skeleton, before applying voxel-wise cross-subject statistics. Statistics were performed with non-parametric permutation correction for multiple comparisons, using Threshold Free Cluster Enhancement (TFCE)⁶.

Results: Group comparison on TBSS, after correction for age, showed significantly increased MD in the left inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum and corpus callosum ($p = 0.046$, TFCE-corrected), in the HIV-infected group compared to uninfected controls (Figure 1). In addition, a trend of decreased FA, after correction for age, in cerebral white matter was detected in the HIV-infected group ($p = 0.08$, TFCE-corrected, data not shown). No interaction effect between age and HIV-status was found for both FA and MD. In addition, no differences in MD or FA could be detected between 26 HIV-infected patients with and 44 HIV-infected patients without cognitive impairment. No correlations were found for FA and MD values and cognitive domain scores, after correction for age, in HIV-infected patients.

Conclusion: More microstructural cerebral white matter abnormalities were found in middle-aged HIV-infected patients with suppressed viraemia on cART than in uninfected controls. No association between these brain abnormalities in the patients with HIV and overall cognitive impairment or impairment in any of the individually tested domains could be demonstrated. To what degree these white matter abnormalities in HIV are the result of white matter lesions resulting from small vessel disease will be explored in future analyses, where those voxels affected by such lesions will be masked out of the tract skeleton used.

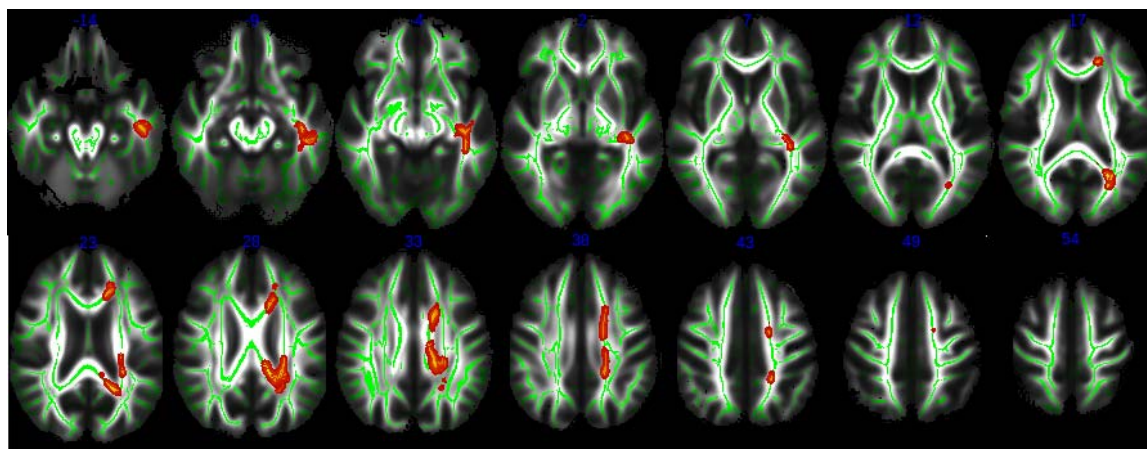


Figure 1: Voxel-wise group comparison using TBSS analysis identified locally increased mean diffusivity (MD) in white matter in HIV-infected patients (shown in red) when compared to representative uninfected controls ($p = 0.046$, TFCE-corrected). The John Hopkins University (JHU) White-Matter Tractography Atlas was used for reference of white matter tracts. Significant voxels within the skeleton are expanded for improved visualization.

References: ¹Palella FJ, et al. *N. Engl. J. Med.* 1998;338(13):853–60. ²Schouten J, et al. *AIDS.* 2011;25(5):561–75. ³Huizenga HM, et al. *Neuropsychologia.* 2007;45(11):2534–42. ⁴Smith SM, et al. *Neuroimage.* 2006;31(4):1487–505. ⁵Smith SM, et al. *Neuroimage.* 2004;23 Suppl 1:S208–19. ⁶Smith SM & Nichols TE. *Neuroimage.* 2009;44(1):83–98.