

Assessment of Antiretroviral Therapy Effects in Early HIV Infection by Diffusion Tensor Imaging

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Target audience: Researchers interested in the sensitivity of diffusion imaging to anti-retroviral treatment effects in Human Immunodeficiency Virus (HIV).

Purpose: Antiretroviral therapy (ART) has reduced AIDS-related deaths worldwide¹; however, neurocognitive impairment is evident in nearly 50% of patients receiving treatment². This may reflect limited penetration of ART through the blood brain barrier resulting in reduced treatment efficacy in the central nervous system. The neuroprotective benefit of ART, therefore, is not well characterized. Evidence suggests that some agents used in ART regimens may actually be neurotoxic^{3,4}. In order to assess the effects of treatment on the brain, this study used diffusion imaging to study treated and untreated HIV+ subjects and age matched controls.

Methods: 50 HIV seropositive (25 treated, 25 treatment naïve) and 20 age-matched seronegative control participants were examined. Recency of infection was determined using an early infection assay (Blood Systems, San Francisco, CA). Imaging data were acquired using a 3T scanner (maximum gradient slew rate: 200mT/m/sec; maximum gradient strength 40mT/m; Siemens Health Care, Erlangen, Germany) equipped with a 12 channel receive-only head coil. A sagittal MP-RAGE sequence [TR/TI/TE=2300ms/900ms/2.91ms, flip angle=9 degrees, field of view=256x256 mm, slice thickness=1mm, in-plane resolution=1mm isotropic; slices=176] and axial DTI [slices=72, slice thickness=2mm, in-plane resolution=2mm isotropic, field of view=256x256 mm, TR/TE=9600/90, GRAPPA=2, scan time=10min:53s, total diffusion gradient=40 mT/m, diffusion weighting=0, 1000 sec/mm²] data were acquired. Voxel-wise analysis was performed in Statistical Parametric Mapping (Wellcome Trust, London, UK). A voxel was considered significant if $p < 0.005$ and only if contained in a cluster of 50 adjacent significant voxels (corresponding to a minimum 0.4 cm³ volume). A neuropsychological test battery included the macro-neurological examination which has been used by the AIDS Clinical Trials Group for studies of neurological manifestations of HIV infection.⁵

Results: The HIV (32.6 ±9.6 years) and control (31.8±8.9 years) groups did not differ significantly in age ($p = 0.75$) or in educational status ($p = 0.74$). Based on early assay values, the HIV cohort was estimated to be infected, on average, less than one year and the length of infection did not differ in ART naïve and treated HIV subgroups. CD4 cell counts did not differ significantly between ART and ART naïve subjects ($p = 0.912$), however, as expected, plasma viral load was significantly higher in naïve subjects ($p = 0.00008$). Significant diffusion restrictions were identified bilaterally in cerebellum in HIV compared to control group (Figure 1). Comparison of the 25 treated HIV, 25 treatment naïve HIV, and control subjects indicated that cerebellar diffusion restrictions were more pronounced in the treated group. The HIV group ($n=50$) had weaker performance in six of the fourteen neuropsychological tests including: Digit Symbol (0.0002), Rey Complex Figure Recall ($p = 0.002$), Verbal Fluency ($p = 0.009$), Letter Number Sequencing ($p = 0.02$), Grooved Pegboard Dominant ($p = 0.04$), and Grooved Pegboard Non-Dominant ($p = 0.02$). All p values are False Discovery Rate corrected. The HIV subgroup on ART ($n = 25$) did not differ significantly from the ART naïve subgroup ($n = 25$) on any of the fourteen neuropsychological tests.

Discussion: This quantitative *in vivo* brain imaging analysis indicates cerebellar diffusion restrictions in HIV subjects infected, on average, less than one year. Comparison of controls ($n = 20$) to treated ($n = 25$) and untreated ($n = 25$) HIV subjects indicated that subjects on ART showed more extensive cerebellar diffusion restriction than both controls and treatment naïve individuals. While the entire HIV+ group ($n = 50$) differed in six of the fourteen NP tests when compared to controls, the treated and treatment naïve subgroups did not differ significantly on any NP test.

Conclusion: These findings indicate that diffusion changes occurs early in HIV infection and patterns of diffusion changes appear to differ in individuals who are treatment naïve and those who have initiated therapy. Diffusion changes measured by MRI exist between treated and untreated individuals in the first year of infection that were not detectable in neuropsychological performance tests. MRI may be more sensitive to sub-clinical changes in HIV and may be useful in assessing neuro-protective strategies. Further studies are needed to explore how these early changes evolve longitudinally and their prognostic significance for long term neurologic outcome.

References: 1. UNAIDS Report on the Global Aids Epidemic. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2010. 2. Heaton RK, Clifford DB, Franklin DR Jr, et al. Neurology 2010; 75(23): 2087-2096 3. Clifford DB. Neurology 2010;74(16):1248- 1249. 4. Robertson, K. R., Z. Su, et al. (2010). Neurology 74(16): 1260-1266. 5. Seigny JJ, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. Neurology 2004;63(11):2084-2090.



Figure 1: Diffusion restrictions (orange) were identified in cerebellum in early HIV infection compared to controls subjects.