**Effects of ART timing and HIV progression on Neurometabolite levels in Basal Ganglia at age 5 years**

K. Mbugua 1,2, J. M. Holmes 1,2, A.T. Hesu 3, F. Little 4, M. F. Cotton 5, E. Dobbels 4, A.J.W. van der Kouwe 6, B. Laughton 7, E.M. Meintjes 1,2

1 MRC/UCT Medical Imaging Research Unit, University of Cape Town, South Africa, 2 Department of Human Biology, University of Cape Town, South Africa, 3 Department of Statistical Sciences, University of Cape Town, South Africa, 4 Children’s Infectious Diseases Clinical Research Unit, Department of Paediatrics & Child Health, Tygerberg Children’s Hospital & Stellenbosch University, South Africa, 5 Athinoula A. Martinos Centre for Biomedical Imaging, Massachusetts General Hospital, Boston MA, USA, 6 Oxford Centre for Clinical Magnetic Resonance Research (OCMR), Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, UK

**INTRODUCTION**

- The human blood brain barrier remains largely impervious to Anti-Retroviral Treatments (ARTs), making the brain a reservoir for HIV. Furthermore, secondary HIV infection mechanisms cause chemical imbalances and toxicity, thereby affecting normal neurocellular development and function [1].

- Although early ART improves the HIV prognosis, its long-term effects in combination with brain HIV damming remain unclear, especially in the Basal Ganglia (BG), which are a prime site for neurocellular activity and proliferation. These effects appear to be magnified in children in neurodevelopment (below age 5 years), causing metabolite imbalances that lead to neuropathies, and complex cognitive, motor, and behavioural disorders [2].

- Proton Magnetic Resonance Spectroscopy (1H MRS) non-invasively measures metabolite levels as potential neurologic biomarkers.

- We used 1H MRS to examine the differences in absolute metabolite levels (AAMLS) in normal children and HIV-infected children initiating ART at different ages, and the relation to clinical measures of disease progression.

**METHODS**

**Participants**

- 34 HIV-infected (Age 5.5±0.3 yrs) IsiXhosa (native African) children from the Children with HIV Early ART efficacy (CHER) drug trial (Medical Research Council, MRC and the Comprehensive International Program for Research on AIDS in South Africa, CIPRA-SA) followed from birth to age 5 yrs [2] and 15 matched controls (Age 5.6±0.5 yrs, 12 exposed/3 unexposed).

- Groupings: 12 ART deferred at birth until clinically symptomatic (ART-Def), 11 ART administered from age 12-40 weeks (ART-40W), 11 ART administered from age 12-96 weeks (ART-96W) and 15 HIV-negative controls. Interruption was in accordance with CHER protocols and ART was re-started if certain clinical/immunological criteria of HIV presented.

**Imaging and Analysis**

- Single Voxel Spectroscopy on Siemens 3T Allegra MRI using a real-time motion & B0-corrected Point Resolved Spectroscopy Sequence (PRESS) in right basal ganglia (3).

- Landmark metabolite biomarkers measured were N-Acetyl-Aspartate (NAA, marker for neuronal integrity), Choline (GPCPCr, cell membrane integrity), Creatine (CrPCr, neurocellular metabolisms), Glutamate (Glu), Glutamate+Glutamine (Glu+Gln, neurotransmitters) and myo-Inositol (Ins, neuroreception & cell transport).

**RESULTS**

**One-way between group ANOVA with post-hoc analyses show**

- NAA in ART-40W children tend to be higher than in uninfected controls.

- GPCPCr in ART-96W children tend to be lower than in uninfected controls.

**CONCLUSIONS**

- 80% of the uninfected controls that provided data for the basal ganglia were exposed to HIV in utero and ART perinatally as part of treatment for prevention of mother to child transmission (PMTCT) which may explain the low NAA levels observed in controls compared to HIV-infected children.

- Delaying early ART may cause and sustain neuronal as well as neurocellular loss or damage arising from HIV infection. However, our data suggests that abnormal neuronal development may be partially reversed after initiating ART, as is evident in the stronger association between NAA and age in the group whose ART was deferred compared to all other groups.

- More advanced disease stage in HIV infected infants appears to hinder normal neuronal and neurocellular development, as characterised by the association between CDA/Cr ratio at enrolment and both NAA and GPCPCr at the later ages 5-6 years in all treatment arms. This association also demonstrates that early damage or abnormal development may not be fully reversible irrespective of the timing of ART. Longitudinal studies are needed to see whether observed patterns continue with increasing age.

**References**


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**Figure 1:** Mean absolute metabolite levels (plus 95% confidence intervals) in the right basal ganglia.

**Figure 2:** Graph displaying the relationship between NAA in the basal ganglia and Age at time of scanning in the different groups.

**Figure 3:** Relationship of NAACr ratio in HIV infected infants at the time of enrolment into the CHER drug trial to their levels of NAA (LEFT) and GPCPCr (RIGHT) in the basal ganglia at age 5-6 years.