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

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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 (^{1}H MRS) non-invasively measures metabolite levels as potential neurologic biomarkers.
- We used ^{1}H MRS to examine the differences in absolute metabolite levels (AMLs) in normal children and HIV-infected children initiating ART at different ages, and the relation to clinical measures of disease progression.

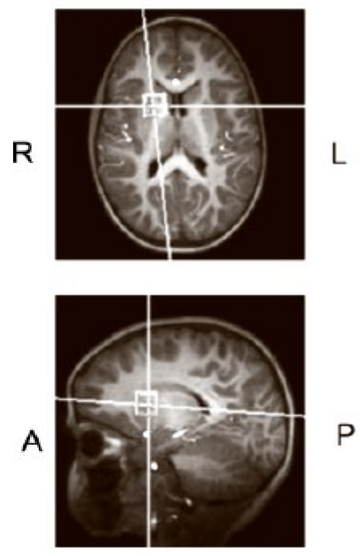
METHODS

Participants

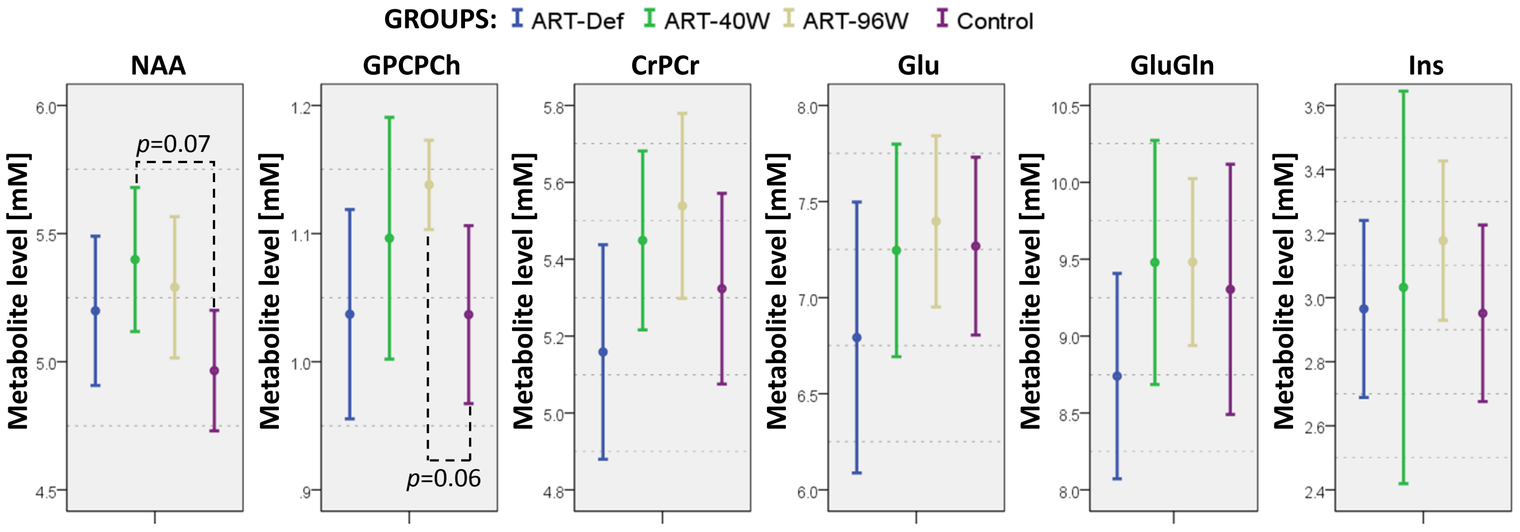
- 34 HIV-infected (Age 5.5±0.3 yrs) IsiXhosa (native African) children from the Children with HIV Early ART efficacy (CHER) drug trial (Medical Research Council, MRC and the Comprehensive International Program for Research on AIDS in South Africa, CIPRA-SA) followed from birth to age 5 yrs [2] and 15 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 restarted 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 (GPCPCh, *cell membrane integrity*), Creatine (CrPCr, *neurocellular metabolism*), Glutamate (Glu), Glutamate+Glutamine (Glu+Gln, *neurotransmitters*) and myo-Inositol (Ins, *neuroreception & cell transport*). MRS data were processed in LCMODEL® with eddy current compensation after offline partial volume correction and spectral frequency & phase correction [4].
- One-way between group ANOVA, regression modelling to control for demographic confounders (age, birth weight and gender) and examination of Pearson correlations with clinical measures of HIV progression were performed in SPSS 22 to study HIV- and/or ART-induced metabolic differences.



RESULTS



One-way between group ANOVA with Post-hoc analyses show

- NAA in ART-40W children tends to be higher than in uninfected controls.
- GPCPCh in ART-96W children tends to be higher than in uninfected controls.

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

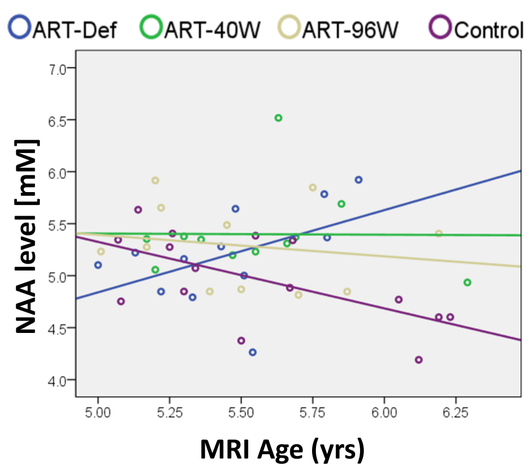


Figure 2: Graph displaying the relationship between NAA in the basal ganglia and Age at time of scanning in the different groups

Relationship between NAA and Age at time of scan

- Increasing age is negatively associated with NAA in uninfected controls (β=-0.6, p=0.02).
- There is a significant age-by-group interaction effect that shows a stronger positive association of NAA with age in the ART-Def children (*slope*=0.8, p=0.008) compared to controls, leading to higher NAA in ART-Def children at higher ages, despite initiating at lower levels than controls.

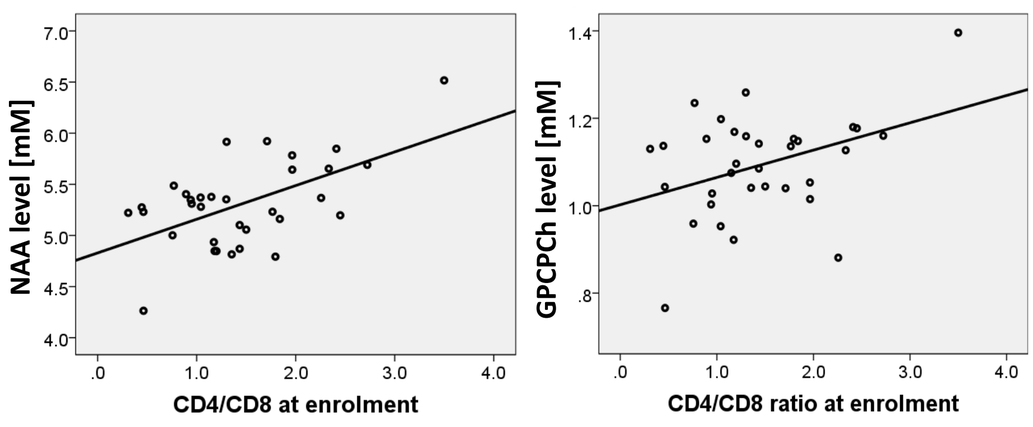


Figure 3: Relationship between the CD4/CD8 ratio in HIV infected infants at the time of enrolment into the CHER drug trial to their levels of NAA (LEFT) and GPCPCh (RIGHT) in the basal ganglia at age 5-6 years.

Relations with clinical measures of HIV infection

- In infected children, lower CD4/CD8 ratio at enrolment is associated with lower NAA (r=0.56, p=0.001) and GPCPCh (r=0.38, p=0.03) levels in BG at age 5 years.
- No other clinical measures (cumulative time on ART, CD4/CD8 ratio at MRI, and occurrence of adverse events) were significantly associated with metabolite levels in this region (all p's>0.2).

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 CD4/CD8 ratio at enrolment and both NAA and GPCPCh 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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