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Initiation of antiretroviral therapy after the critical neuronal developmental period of the second postnatal year affects white matter microstructure in adolescents living with HIV

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Abstract

Rapid maturation of major white matter pathways occurs in the first 2 years of life, indicating a critical neuronal developmental period. The impact of initiating antiretroviral therapy (ART) in children perinatally infected with HIV-1, after the age of 2 years on neurocognitive functioning and white matter development in adolescence has not been studied. 46 adolescents who initiated ART during the first 2 years of life (<2yrs), and 79 adolescents who initiated ART after 2 years of age (>2yrs), with perinatally acquired HIV were enrolled in the Cape Town Adolescent Antiretroviral Cohort. Adolescents completed a comprehensive neurocognitive battery testing a number of cognitive domains. Diffusion tensor imaging (DTI) was done to determine fractional anisotropy (FA), mean diffusivity (MD), axial diffusion (AD) and radial diffusion (RD) in a region of interest analysis.

Neurocognitive performance was similar between adolescents who initiated ART <2yrs or >2yrs. There was a trend towards attention (p=.07) and working memory (p=.05) being poorer in the group who initiated ART >2yrs. FA was lower in the >2yrs group in the superior corona radiata (p=.03), and the external capsule (p=.04). MD was higher in the >2yrs group in the cerebral peduncle (p=.02), the superior corona radiata (p=.01) and the superior fronto-occipital fasciculus (p=.03). RD was higher in the >2yrs group in the superior corona radiata (p=.02), the cerebral peduncle (p=.01) and the superior fronto-occipital fasciculus (p=.01). However the higher AD in the >2yrs group in the superior corona radiata was not in the expected direction (p=.01). Initiation

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of ART after the neuronal development period of the second postnatal year is associated with white matter alterations on neuroimaging.

Keywords

adolescent; HIV; neuroimaging; antiretroviral therapy; neurodevelopment

Introduction

Human brain development in the first 2 years after birth is extremely dynamic and likely plays an important role in neurodevelopmental disorders (Knickmeyer et al. 2008). Brain white matter (WM) maturation is a complex and long-lasting process that begins in the fetal period and continues into adulthood. The most significant period of WM myelination occurs between mid-gestation and the second postnatal year (Brody et al. 1987). Diffusion tensor imaging (DTI) has detected rapid maturation of major WM pathways in the first 2 years of life, that is very likely related to rapid grey matter growth and functional maturation, indicating a critical neuronal developmental period of life (Geng et al. 2012). The impact of initiating antiretroviral therapy (ART) in children perinatally infected with HIV-1, after the age of 2 years on neurocognitive functioning and WM development in adolescence has not been studied.

HIV-infected children and adolescents continue to have the largest gaps in treatment (Davies and Pinto 2015). All children should receive ART as early as possible, preferable from birth irrespective of clinical stage or immunological status. However, context-specific differences in treatment guidelines and access to ART over the past two decades have resulted in great variability in use of ART among perinatally infected adolescents living with HIV. The goals of ART go beyond averting death and severe morbidity, to optimizing health (Davies and Pinto 2015). Studies from sub-Saharan Africa, where ART is generally started later, have reported neurodevelopmental delay (Bagenda et al. 2006) and neurocognitive impairment in adolescents living with HIV compared to uninfected peers (Hoare et al. 2016). Early initiation of ART in infancy has been shown to positively impact neurodevelopment; however, children continue to be diagnosed with HIV outside of the early infancy period and can experience subtle to severe neurocognitive deficits despite ART (Crowell et al. 2014). Early viral suppression has been associated with a positive impact on cognitive functioning during childhood (Crowell et al. 2015). Worryingly an MRI study found that WM structural abnormalities occur very early after birth, and even initiation of ART by eight weeks of age may be too late to prevent HIV from damaging WM in the central nervous system (CNS; (Ackermann et al. 2016). Second line ART, increased viral load, low CD4 counts and poor cognitive function have been associated with poor WM integrity as measured by DTI in youth living with HIV in South Africa (Hoare et al. 2015a).

DTI, an MRI imaging method, provides a distinct rapid, non-invasive method to assess the microstructural integrity of WM (Wycoco et al. 2013) making it particularly amenable for use in children. Common DTI metrics include fractional anisotropy (FA) and mean diffusivity (MD). Higher MD and lower FA are traditionally representative of poorer

directional diffusion suggesting alterations in neuronal microstructure. Axial diffusivity (AD) and radial diffusivity (RD) are additional DTI-derived metrics corresponding to diffusion parallel and perpendicular to the direction of the WM tract, respectively (Song et al. 2002). Major fiber tracts all show increasing FA values and decreasing RD and AD during normal development in the first 2 years of life. The changing rates of the diffusion indices are faster in the first year than the second year for all tracts. RD and FA show larger percentage changes in the first and second years than AD (Geng et al. 2012). Myelin loss (measured in DTI by an index of RD) and axonal damage (measured in DTI by an index of AD) are both also observed in WM injuries, such as have been previously described in adolescents living with HIV (Uban et al. 2015; Cohen et al. 2016). Prior DTI studies conducted in South Africa to investigate WM alterations in youth living with HIV compared to healthy HIV uninfected controls have found higher MD and lower FA, representative of poorer directional diffusion and higher RD and lower AD, suggestive of myelin loss and axonal damage in HIV infected youth (Hoare et al. 2012; Hoare et al. 2015b). The WM differences were widely distributed and included the cerebral peduncle, internal capsule, corona radiata, sagittal stratum, external capsule, superior longitudinal fasciculus, fronto-occipital fasciculus and the corpus callosum (Hoare et al. 2012; Hoare et al. 2015b).

The aim of this study was to explore the impact of initiating ART after 2 years of age on brain WM development and neurocognitive functioning in early adolescence using DTI in perinatally infected adolescents in the Cape Town Adolescent Antiretroviral Cohort (CTAAC). We expected to see a trend of differing levels of WM microstructural damage and neurocognitive function associated with the age of ART initiation, due to the protective nature of ART on the developing brain. We used a region of interest (ROI) analysis based on regions affected in prior analyses in South Africa.

Methods

Participants

Adolescents enrolled in CTAAC, a prospective cohort study of perinatally infected HIV-infected adolescents on ART were eligible for inclusion in this study. Adolescents were recruited from primary care sector health care service in Cape Town. Inclusion criteria were: aged 9-11 years, perinatally infected, use of ART for at least 6 months, knowledge of their HIV status and able to provide informed parental consent and participant assent. Adolescents were sampled consecutively and were not recruited based on disease complexity or virological suppression/unsuppression. Exclusion criteria were: an uncontrolled medical condition, such as poorly controlled diabetes mellitus, epilepsy, or active tuberculosis requiring admission; an identified CNS condition (other than HIV), such as past or current TB meningitis or bacterial meningitis, documented cerebrovascular accident, lymphoma; a history of head injury with of loss of consciousness greater than 5 minutes, or any radiological evidence of skull fracture; a history of perinatal complications such as hypoxic ischemic encephalopathy or neonatal jaundice requiring exchange transfusion, or neurodevelopment disorder not attributed to HIV. Adolescents with a history of psychosis and severe depression were also excluded. Depression was measured using the Becks Youth Inventory. Participants were enrolled from August 2013 to April 2015 at the

Research Centre for Adolescent and Children Health at Red Cross Children's Hospital, South Africa. Baseline health and sociodemographic questionnaires were administered. Recent CD4 and viral load results and date of initiation of ART were abstracted from care records. Ethical approval was obtained from the University of Cape Town's Faculty of Health Sciences research ethics committee.

Measures

Questionnaires were administered by study staff to adolescent/parent or guardian dyads at enrolment. Where appropriate, separate questionnaires were administered to an adolescent and their accompanying parent/guardian in separate rooms. Interviews were conducted in the participants home language, in private rooms by trained counsellors with extensive experience working with HIV infected children. Each of these questionnaires has been used in the local population, with evidence of good reliability in isiXhosa speaking populations (Hoare et al. 2016).

Neurocognitive assessment

Each participant was assessed using a battery of standardized neurocognitive tests used in paediatric neuropsychological assessment and research in South Africa. Tests were administered in the children's home language. Test instructions were translated and back-translated into isiXhosa, and test administration complied with International Test Commission guidelines (Bartram 2001). Where possible neurocognitive measures were adjusted for age by using age-adjusted scaled scores in the scoring of the tests. General intellectual functioning was measured using the Wechsler Abbreviated Scale of Intelligence (WASI: (Axelrod 2002). The following tests were used to examine cognitive domains: Fingertip Tapping subtest from the NEPSY-II (Brooks et al. 2009), Grooved Pegboard Test (Bryden and Roy 2005), Subtests from the Wechsler Intelligence Scale for Children (WISC-IV; (Wechsler 2003) measured information processing speed, The Rey Complex Figure Test (RCFT(Watanabe et al. 2005) , the Boston Naming Test – Short Form-South Africa (BNT-SF-SA(Roth 2011), category and phonemic fluency, immediate and delayed recall trials of the RCFT and the Hopkins Verbal Learning Test-Revised (HVLT-R: (Benedict et al. 1998), WISC-IV Digit Span backwards (DS backwards) subtest, the Color Trails Test 2 (CTT2) and the NEPSY-II Inhibition subtests.

Using data from the test battery, as well as theoretical knowledge about the construct(s) each test is meant to test, we created ten separate composite cognitive domains: general intellectual functioning, attention, working memory, visual memory, verbal memory, language, visual spatial ability, motor coordination, processing speed and executive function. To determine the statistical strength of each cognitive domain, we conducted Cronbach's alpha tests on various combinations of neuropsychological tests to determine which neuropsychological tests had strong inter-relatedness (or internal consistency) within a specific domain. For the Cronbach's alpha tests we only used the total scaled scores of the tests, and/or subtests, for each of the individual neuropsychological tests. Scaled scores were used because they take into account the child's age, gender and the various developmental changes happening in the different age groups. To compute the individual test scaled scores,

we used the individual test publisher norms. Where test publisher norms were not available (for example; for the HVLT) we converted the test raw score into a *z*-score.

A Cronbach's alpha value of 0.7 was considered high and deemed as an indication of good inter-relatedness between the tests. The Cronbach's alpha tests were only done for domains in which there were more than one neuropsychological test measuring performance in that domain. The domains of language and visual spatial ability, each consisted of only one neuropsychological test from the battery, and thus Cronbach's alpha values are not reported for these two domains. Tests which did not contribute well to the cognitive domains with regards to the Cronbach's alpha value were excluded from the individual composite cognitive domain scores.

Composite cognitive domain scores were calculated by averaging the scores of the all tests that comprised each domain, so that a single score for each domain was determined for each participant (Phillips et al. 2018). We used the CTAAC control sample (n=44) means and standard deviations to convert all scaled and T-scores of the individual neuropsychological tests into *z*-scores. The CTAAC controls were HIV-uninfected, but recruited form the same community/schools and matched for age, gender, SES and years of education (Phillips et al. 2018).

DTI acquisition

Diffusion weighted imaging was performed at the Cape Universities Brain Imaging Centre on a 3T Siemens Allegra scanner within seven days of neuropsychological assessment. A single-channel transmit-receive head coil was used with the following parameters: TR=8800ms, TE=88ms, field-of-view of 220mm, $1.8 \times 1.8 \times 2.0$ mm^3 image resolution, 65 slices, 0% distance factor and 2× Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration. Images were acquired in an axial orientation with 30 gradient directions at b=1000mm/s^2, and 3 directions with b = Omm/s^2 The acquisition was repeated 3 times to allow for redundancy in data. A multi-echo Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted image was acquired with the following parameters: FOV=256 × 256mm, TR=2530ms, TE = 1.53/3.21/4.89/6.57ms, TI=1100ms, flip angle=7°, 144 slices, inplane resolution = $1.3 \times 1.0mm^2$ and slice thickness of 1.0mm.

DTI preprocessing and statistical analysis

Diffusion weighted images were corrected for eddy current distortion within FMRIB Software Library (FSL) 5.0.1 and imported into MATLAB R2013b for processing. This entailed the affine registration to the average b=0mm/s^2 image of the first acquisition. For each of the acquisitions, outlier data points were determined by calculating the Z-values at the 25^{th} and 75^{th} percentile of the registered diffusion image. Any data points that were 3 SD from the mean were excluded. The corrected images were exported to FSL 5.0.1 after correction. In FSL 5.0.1 images underwent brain extraction in the Brain Extraction Toolbox (BET) to remove any non-brain tissue and fit a linear tensor model to produce FA, MD, AD and RD maps.

FA images were analysed with the Tract-based Spatial Statistics (TBSS) pipeline (Smith et al. 2006). Each participant's FA was registered to a study-specific target. This target was

determined by registering each participant to every other participant. The mean square displacement coefficient of each image was calculated and the participant with the lowest mean displacement was chosen as a representative target for the group. After registration to the study-specific target, each image was then up-sampled to Montreal Neurological Institute (MNI) space, taking into account the previous transformation parameters. An average FA was created and thinned to produce a mean FA skeleton with a threshold of 0.2. This skeleton is representative of the centres of WM tracts common to the group. Registration and skeleton projection were also applied to the MD, AD and RD images as described above. We used a ROI analysis based on regions affected in prior analyses in South Africa. Regions selected were the cerebral peduncle, internal capsule, corona radiata, sagittal stratum, external capsule, superior longitudinal fasciculus, fronto-occipital fasciculus, and the cingulum. The WM ROI's as determined by the John Hopkins University (JHU) WM atlas (Mori et al. 2005) were exported to SPSS 25.

Statistical analyses were performed using SPSS 25 software (IBM, Armonk, NY, USA). Demographic data and neurocognitive domains were analyzed using independent sample T tests for continuous variables and Chi-squared tests for categorical variables. Neuroimaging data were analysed in mixed factor ANOVAS, incorporating age of ART initiation as a between subjects factor, and brain hemisphere (L or R) as a within subjects factor. This approach allowed for a reduction in the number of total tests run, by approximately a factor of 2. Log transformed viral load was tested for associations with cognitive domain scores, and also DTI scores, to be aware of a potential confound.

After these initial analyses, we investigated the associations between DTI measures that were significantly different in adolescents who initiated ART >2yrs, and neurocognitive domains that were sensitive to age of initiation. Thus, the significant DTI regions were tested for associations with significant domain scores. Whether these associations differ in groups stratified according to ART initiation group is also noted. Two tailed partial correlations were run in SPSS 25, and the correlation coefficients were adjusted for gender, age, and current school grade.

A sample size of at least 45 HIV infected adolescents in each group was based on detecting a significant difference in whole brain mean FA; the proposed sample size would allow >80% power to detect differences of >0.0.

Results

46 HIV infected adolescents who initiated ART under the age of 2 years (<2yrs) and 79 HIV infected adolescents who initiated ART after the age of 2 years (>2yrs) completed neurocognitive testing and DTI. Other than duration of treatment, demographic characteristics were similar between adolescents who initiated ART <2yrs and >2yrs (Table 1).

In the group that initiated ART <2yrs (n=46), the range of age of initiation was 0.25yrs - 1.98yrs. For the group that initiated ART >2yrs (n=79), the range of age of initiation was

2.05yrs - 10.98yrs. See supplemental figure for visual depiction of the age range distributions.

Neurocognitive performance was similar between adolescents who initiated ART <2yrs and >2yrs. There was a trend towards attention (p=.07) and working memory (p=.05) being poorer in the group who initiated ART >2yrs (Table 2). Log transformed viral load was not significantly associated with any of the cognitive domains, and the inclusion of log transformed viral load as a control variable in the analyses did not alter the results or p-values.

There was no significant difference between the groups in whole brain mean FA (p=.93) and whole brain mean MD (p=.26). However, there were differences at the regional level (Table 3). Log transformed viral load was included as a control variable in this analysis.

FA was reduced in the >2yrs group in the superior corona radiata (p=.03) and increased in the external capsule (p=.04), suggesting an increased risk of WM alterations in this group. MD was increased in the >2yrs group in the cerebral peduncle (p=.02), the superior corona radiata (p=.01), and the superior fronto-occipital fasciculus (p=.03)

RD was increased in the >2yrs group, in the superior fronto-occipital fasciculus (p=.01), the cerebral peduncle (p=.01), and the superior corona radiata (p=.02) suggesting myelin loss in these structures. The <2yrs group however (AD reduced) had greater axonal damage in the superior corona radiata (p=.01).

Additional analyses

Only the significant ROIs from Table 3 and the trending cognitive domains from Table 2 were included in these additional analyses. The results of these correlation tests are presented in Table 4. The stratified test produced slightly different results compared to the combined sample. In the >2yrs group, none of the associations between DTI value and cognitive domain, as listed in Table 4A, survived. However, in the <2yrs group, there were numerous significant associations. The full list of significant associations by stratified group is in Tables 4B and 4C.

Working memory and attention were positively correlated with FA and AD in the external capsule, cerebral peduncle and superior fronto-occipital fasciculus.

However, in the <2yrs group MD and RD were positively correlated with attention in the cerebral peduncle, which is not in the expected direction.

Discussion

To our knowledge, this is the first exploratory study of brain WM integrity and cognition in a homogeneous sample of adolescents with a narrow age range (9-11 years) examining the effect of age of initiation of ART in childhood on early adolescent brain development. This study suggests that initiation of ART >2yrs increases the risk of WM alterations in the CNS. The similar performance in neurocognitive domains suggests that neurocognitive tests may not be as sensitive as DTI in detecting brain alterations caused by perinatal HIV infection.

Neuroimaging studies show that even when ART is initiated in childhood, there are alterations in brain structure in children living with HIV, compared to uninfected peers (Hoare et al. 2014). Few neuroimaging studies have been done in children within the critical stage of early adolescent brain development between 9 and 11 years (Nwosu et al. 2018).

Neurocognitive performance was similar between adolescents who initiated ART <2yrs and >2yrs in this study, however there was a trend towards attention and working memory being poorer in the group who initiated ART >2yrs. Working memory and attention were positively correlated with FA and AD in the external capsule, cerebral peduncle and superior fronto-occipital fasciculus. However, in the <2yrs group MD and RD were positively correlated with attention in the cerebral peduncle, which is not in the expected direction. The interpretation of DTI measures in the developing adolescent brain is complex. The organization of WM during normal adolescent development is dynamic, and understanding these findings would be aided by our longitudinal study, which is currently underway. Despite the evidence for the benefit of early ART on neurodevelopment in early childhood, it remains unclear if this positive effect will persist through adolescence. Findings of the cognitive benefit of ART have been reported by Puthanakit et al. (2013) who examined cognitive outcomes of youth (median age 9 years) with early and deferred ART after 3 years of follow-up. Children with moderate immunosuppression and no AIDS-defining illness randomized to early ART when ≥1 year of age did not differ from children for whom ART was deferred until immunological or clinical progression. The window of opportunity for a positive effect of ART initiation on neurocognition in adolescence may remain in infancy. HIV infected infants initiated on early ART (<3 months) have been reported to have significantly better locomotor and neurodevelopment at approximately one year of age compared to infants on deferred ART, despite careful monitoring and ready access to ART in the latter(Laughton et al. 2012). Virologic suppression during infancy or early childhood has also been associated with improved neurocognitive outcomes in school-aged children living with HIV(Crowell et al. 2015). Very few adolescents in the current study were initiated on treatment under 3 months of age, due to poor access to ART prior to 2004 in South Africa and older treatment guildelines (see supplementary figure). The children in this study were bom between 2002 and 2004. ART has become increasingly available since the implementation of the South African Comprehensive HIV and AIDS Care, Management and Treatment Plan in 2004. During the first year after the implementation very few children were accessing ART (Meyers et al. 2007). It is therefore reasonable to assume that the majority of children who were initiated on ART<2yrs in this study were commenced on treatment as they became immunosuppressed or developed an AIDS defining illness at an earlier age than the children initiated on treatment >2yrs, which may explain the lack of significant differences in cognitive functioning between the groups.

DTI studies have examined WM in children living with HIV compared to an uninfected control group. In children with HIV, even when long-term clinically and virologically controlled, lower brain volumes and poorer WM integrity has been reported compared to matched controls (Cohen et al. 2016). HIV infected children have WM abnormalities measured by FA, despite early ART, suggesting that ART does not fully protect the WM from either peripartum or in utero infection (Ackermann et al. 2016). In contrast to adults, the corticospinal tracts were predominantly involved rather than the corpus callosum

(Ackermann et al. 2016), similar to the findings in the current study. WM signal abnormalities can occur early and initiating ART by 8 weeks of life may be too late to prevent HIV from entering and damaging the CNS (Ackermann et al. 2014). Children on early-interrupted ART had lower FA compared with those receiving continuous treatment (Ackermann et al. 2016).

Few studies have investigated WM abnormalities in adolescents living with HIV. Older HIV infected adolescents have higher risk of alterations in WM microstructure compared to typically developing adolescents, and certain alterations were related to past disease severity (Uban et al. 2015). Relative to uninfected controls, HIV infected adolescents have also demonstrated significantly reduced FA in the corpus callosum, superior and posterior corona radiata, and superior longitudinal fasciculus(Li et al. 2015). Moreover, FA values in the frontal WM were negatively correlated with the duration of ART and were positively associated with the age at onset of ART (Li et al. 2015). No alterations were found in the current study in the ROIs sagittal stratum, internal capsule, cingulum, superior longitudinal fasciculus and the corpus callosum, as in previous studies conducted in Cape Town (Hoare et al. 2015b). However, the current study is unique as it examines the effect of age of initiation of ART in childhood on early adolescent WM development. The FA, MD and RD findings are in the hypothesized direction with initiation of ART >2yrs increasing the risk of WM alterations in the ROI. However, the <2yrs group had greater axonal damage in the superior corona radiata. The majority of adolescents who were initiated on ART<2yrs in this study may have been commenced on treatment as they became immunosuppressed or developed an AIDS defining illness at an earlier age than the children initiated on treatment >2yrs, which may explain the increased damage in these structures. In addtion the interpretation of DTI measures in the developing adolescent brain is complex. The organization of WM during normal adolescent development contributes to the observed development of diffusion properties, which may cause decreased RD, increased AD and greater increased FA. The AD increase in the superior corona radiata of the <2yrs group was not revealed suggesting that axonal myelination is a dominant process in white matter maturation in the examined age group. Biological basis of diffusion measures and their changes is not quite clear (Geng et al. 2012).

Several limitations of this study should be emphasized. First the exploratory and cross sectional design of the study, which makes the causal relationships posited here difficult to prove. However, longitudinal follow-up is under way to better understand the impact of age of initiation of ART in childhood on brain remodeling typically seen in later adolescence. Second, there are limitations associated with DTI as a quantitative imaging technique. FA probably reflects some changes in some aspects of connectivity, although we cannot really say what precise aspect, and into which direction the change occurred (Jones et al. 2013). Third, although other congenital infections and incidental CNS abnormalities were excluded as far as possible on history, clinical examination and on clinical review of the MRI scans; it remains a possibility that there may be some overlapping effects of undiagnosed conditions such as congenital CMV.

Conclusion

These findings suggest that initiation of ART after the neuronal development period of the second postnatal year is associated with WM alterations in the CNS. The similar performance in neurocognitive domains suggests that initiation of ART after infancy may not be sufficient to protect adolescents from neurocognitive impairment previously observed in the CTAAC cohort (Phillips et al. 2018).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflicts of Interest and Source of Funding:

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Table 1:

Demographic and clinical characteristics of the NeuroHIV CTAAC cohort by age of initiation

	Age of initiation ART <2yrs N=46	**Age of initiation ART >2yrs N=79**	**P-value**
Age, Mean (SD)	10.43 (0.83)	10.49 (0.82)	.65
ART age of initiation in years, Mean (SD)	1.05 (0.54)	4.98 (2.41)	.00
ART duration in years, Mean (SD)	9.44 (0.73)	5.75 (2.38)	.00
Current school grade, Mean (SD)	4.09 (1.11)	4.32 (1.05)	.25
Current CD4, Mean (SD)	872.3 (414.54)	989.7 (457.75)	.16
Current viral load	Median=0, IQR=40	Median=0, IQR=40	.12
Gender	Male=29 (63%)	Male=37 (47%)	.08
Home language	isiXhosa=43 (93%)	isiXhosa=71 (90%)	.80
ART line regimen (1st, 2nd, and 3rd line regimens)	34 on 1st; 8 on 2nd; 4 on 3rd	66 on 1st; 10 on 2nd; 3 on 3rd	.36

Independent T-tests were used to examine group differences on continuous variables and Chi Square tests were used in the case of categorical variables.

Table 2:

Neurocognitive domains scores in adolescents who initiated ART <2yrs and >2yrs

	Age of initiation ART <2yrs N=46 Mean (SD)	**Age of initiation ART >2yrs N=79 Mean (SD)**	**P-value**
General Intellectual functioning	−0,61 (0,73)	−0,66 (0,74)	.70
Attention	−0,56 (0,82)	−0,28 (0,81)	**.07**
Motor co-ordination	0,03 (1,07)	−0,04 (0,96)	.69
Visual memory	−0,40 (0,79)	−0,50 (0,79)	.49
Verbal memory	−0,52 (1,04)	−0,43 (1,24)	.70
Working memory	−0,64 (0,48)	−0,44 (0,64)	**.05**
Language	−0,36 (0,96)	−0,34 (1,11)	.92
Visuo-spatial function	−0,45 (0,71)	−0,34 (0,89)	.49
Processing speed	−0,69 (0,56)	−0,60 (0,73)	.45
Executive function	−0,61 (0,58)	−0,48 (0,73)	.31

Results highlighted in bold show a trend towards significance at p<.05

Independent T-tests were conducted

Table 3:

Significant ROI differences in FA, MD, AD and RD in adolescents who initiated ART <2yrs and >2yrs

ROI	DTI scalar	<2yrs mean (SD)	>2yrs mean (SD)	P-value
Superior corona radiata	FA	7,31E-1	7,11E-1	.03
	AD	1,93E-3	2,00E-3	.01
	MD	1,55E-3	1,62E-3	.01
	RD	1,35E-3	1,43E-3	.02
External capsule	FA	3,85E-1	3,66E-1	.04
Cerebral peduncle	MD	1,53E-3	1,58E-3	.02
	RD	1,30E-3	1,37E-3	.01
Superior fronto-occipital fasciculus	MD	1,36E-3	1,41E-3	.03
	RD	1,13E-3	1,21E-3	.01

FA=fractional anisotropy MD=mean diffusivity AD=axial diffusion RD=radial diffusion

ROIs reported here combine left and right hemisphere values

Table 4:

Neurocognitive domains that displayed a significant association with DTI measurements within HIV+ adolescents

Brain structure	DTI scalar	Clinical variable	Pearson correlation	P-value
A. Combined sample (N=125)				
External capsule RH	FA	Working memory	0.18	.04
Cerebral peduncle LH	AD	Attention	0.19	.02
	AD	Working Memory	0.17	.05
Superior fronto-occipital fasciculus RH	FA	Attention	0.17	.04
B. <2yrs (N=46)				
Cerebral peduncle RH	MD	Attention	0.33	.04
	RD	Attention	0.35	.02
Superior fronto-occipital fasciculus LH	AD	Working memory	0.31	.05
C. >2yrs (N=79)				
No findings				