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ABSTRACT

BACKGROUND AND PURPOSE: Fractional anisotropy in the frontal white matter, corpus callosum, and internal capsule is abnormal in human immunodeficiency virus–positive (HIV+) adults. We describe the distribution and nature of white matter abnormalities in a cohort of children who started antiretroviral therapy within the first year of life and the benefit of early treatment by using DTI measures (fractional anisotropy and mean, axial, and radial diffusion).

MATERIALS AND METHODS: DTI was performed on children in a neurodevelopmental substudy from the Children with HIV Early Antiretroviral trial. Voxel-based group comparisons were obtained to determine regions where fractional anisotropy and mean diffusion differed between HIV+ and uninfected children. Associations of DTI parameters with the timing of antiretroviral therapy initiation were examined.

RESULTS: Thirty-nine HIV+ children (15 boys; mean age, 5.4 years) and 13 controls (5 boys; mean age, 5.7 years) were scanned. Two clusters with lower fractional anisotropy and 7 clusters with increased mean diffusion were identified in the HIV+ group, with symmetric distribution predominantly due to increased radial diffusion, suggestive of decreased myelination. Corticospinal tracts rather than the corpus callosum were predominantly involved. Children on early-interrupted antiretroviral therapy had lower fractional anisotropy compared with those receiving continuous treatment.

CONCLUSIONS: HIV+ children at 5 years of age have white matter abnormalities measured by fractional anisotropy, despite early antiretroviral therapy, suggesting that early antiretroviral therapy does not fully protect the white matter from either peripartum or in utero infection. In contrast to adults, the corticospinal tracts are predominantly involved rather than the corpus callosum, possibly due to early antiretroviral therapy. Continuous early antiretroviral therapy can limit white matter damage.

ABBREVIATIONS: AD = axial diffusivity; ART = antiretroviral therapy; CC = corpus callosum; CHER = Children with HIV Early Antiretroviral trial; CST = corticospinal tract; FA = fractional anisotropy; HIV = human immunodeficiency virus; HIV+ = human immunodeficiency virus–positive; MD = mean diffusivity; RD = radial diffusivity

White matter structural abnormalities can be assessed by using quantitative parameters determined from DTI.[1] Fractional anisotropy (FA) provides information about the microstructural integrity of highly oriented microstructures but is not specific to the type of injury. Mean diffusivity (MD) is a measure of average molecular motion independent of any tissue directionality.

Loss of axonal integrity decreases FA and increases MD; however, increased FA may also indicate loss of complexity in the underlying axonal matrix due to loss of crossing and other nonparallel fibers. Increased radial diffusivity (RD), a marker of excessive axonal packing attenuation and/or poor myelination,[2] and

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decreased axial diffusivity (AD), an index of axonal damage, occur in human immunodeficiency virus (HIV)-associated WM injury.[3-5] FA in the frontal subcortical WM, corpus callosum (CC), and internal capsule is abnormal in HIV-positive (HIV+) adults.[6-8] Those with the most advanced HIV disease have the highest diffusion constant elevations and the largest anisotropy reductions, specifically in the CC and frontal WM.[6] Most early studies used a priori ROI analyses. Subsequently, more widespread WM damage has been shown by using voxelwise and whole-brain analyses.[1,3,7,9,10] Animal neuro-AIDS models also show WM damage: Macaques show reduced FA in the CC genu,[11] and mice have reduced FA (mainly due to increased RD) and increased MD in the CC.[12]

Few studies have used DTI to examine HIV-associated alterations in WM in children. Lower FA and higher MD and RD in the CC and higher MD in the superior longitudinal fasciculus have been demonstrated in antiretroviral therapy (ART)-naïve children (8–12 years of age) compared with age-matched controls,[13] while ART failure was associated with decreased FA in the left superior and right posterior corona radiata and decreased AD in the left inferior cerebellar peduncle in 50 children on first-line ART (6–15 years of age).[14] Regional and whole-brain decreases in FA and increased MD and RD, compared with controls, have been reported in HIV+ children and adolescents (6–20 years of age),[15,16] irrespective of treatment status.[15] Regional alterations were related to past disease severity, measured by nadir CD4%, and peak viral loads.[16] ART-naïve children (6–11 years of age) showed reduced myelin compared with children on ART (6–16 years of age) but were also younger.[15] These studies did not document ART history.

Adolescents stable on ART ($n = 15$, 13–17 years of age; mean age at ART initiation, 9.5 years) had lower FA in the CC, superior and posterior corona radiata, frontal and parietal WM, pre- and postcentral gyrus, and superior longitudinal fasciculus (mainly due to increased RD) than controls ($n = 26$).[17]

Despite consistent evidence of HIV-related WM alterations, studies have included wide age ranges over developmental phases when both WM volume and FA demonstrates notable increase.[18-20] Few studies have controlled adequately for age or ART regimens. To date, no DTI studies have been performed in younger children, and none, in children receiving standardized early ART (within the first year of life), to our knowledge.

The aim of the present study was to determine the spatial distribution and nature of WM abnormalities at 5 years of age in a cohort of HIV+ children beginning ART well within the first year of life. An additional aim was to explore the association of the timing of ART initiation and DTI-derived parameters (FA, AD, RD), to interrogate the potential protection of early ART on WM microstructures.

We hypothesized poorer WM integrity when starting ART after 12 weeks of age.

MATERIALS AND METHODS

Subjects

We present data for 52 of 62 children enrolled in a neurodevelopmental substudy of the Children with HIV Early Antiretroviral (CHER) trial[21,22] in Cape Town, South Africa. The group comprised HIV+ children on ART and age-matched controls from a parallel vaccine study, with informed consent from parents or caregivers.[23]

Exclusions were the following: 6 HIV+ subjects with mixed ancestry (the genetic determinants of ethnicity could influence brain growth and maturity and we felt that having a more homogeneous study population and control group would remove bias), 1 HIV+ child whose structural image was motion-corrupted, 1 control child with incidental periventricular leukoencephalopathy, and 2 HIV+ children with data intersection instabilities.

The CHER trial was a 2-center study in which HIV+ infants between 6 and 12 weeks of age and CD4 ≥ 25% were randomized to 1 of 3 treatment strategies: ART-deferred until indicated, early-limited ART for 40 weeks, and early-limited ART for 96 weeks. Infants with a CD4% < 25% were enrolled into a separate group (Part B), initially to be randomized into ART for 40 weeks and ART for 96 weeks but then retained on early-continuous ART. The entire cohort comprised 451 HIV-infected infants younger than 12 weeks of age. Four hundred eleven infants had baseline CD4 ≥ 25%, of whom 377 were reported in the main trial.[22]

Continuous ART was initiated in the ART-Deferred arm when the CD4 declined below 25% in the first year of life and 20% thereafter or for the Centers for Disease Control severe stage B or C disease. These criteria also applied to restarting ART in the ART for 40 weeks and ART for 96 weeks arms. Because some children in ART-Deferred began ART early, we stratified children into those starting ART after (late ART) or before 12 weeks (early ART), irrespective of the treatment arm. In addition, because some in the ART for 40 weeks and ART for 96 weeks arms met the end points during primary therapy, the early ART group was subdivided into those with or without treatment interruption.

First-line ART was lopinavir-ritonavir, lamivudine, and zidovudine. Most mothers had participated in the prevention of mother-to-child transmission program, which included zidovudine antenatally from 32 weeks and single-dose nevirapine at delivery. Mothers with a CD4 count below 250 cells per cubic millimeter received ART antenatally. Neonates received a single dose of nevirapine at birth and zidovudine for 7 days.

Children were in regular follow-up with 3 monthly clinical assessments.

Baseline laboratory and clinical data at enrollment and within 6 months of MR imaging scan, including CD4, CD8 parameters, and viral load, were obtained from participant medical records and the CHER data base. A viral load of >750,000 copies/mL was assigned as 750,001, and that with <400 copies/mL, as 399 (viral suppression).

Ethics approval for the study was obtained from ethics boards of all institutions involved.

MR Imaging Data Acquisition

The children were imaged on a 3T MR imaging scanner by using structural T1 imaging followed by 2 DTI acquisitions with opposite phase-encoding directions by using a twice-refocused spin-echo sequence.[24] The 3D EPI-navigated[25] multiecho MPRAGE[26] sequence was acquired in a sagittal orientation with the following parameters: FOV = 224 × 224 mm, 144 sections, TR = 2530 ms, TE = 1.53/3.19/4.86/6.53 ms, TI = 1160 ms, flip

Table 1: Sample characteristics of HIV-infected children[a]

	Late ART (>12 wk)	Early ART (<12 wk) Interrupted	Early ART (<12 wk) Not Interrupted	*P* Value
No.	13	16	10	
Sex	4 M/9 F	5 M/11 F	6 M/4 F	.30
Age at scan (yr)	5.3 (0.30)	5.4 (0.24)	5.6 (0.43)	.20
Age ART started (wk)	36 (17)	8 (2)	8 (2)	<.01[b]
Time on ART (wk)	241 (22)	203 (59)	285 (22)	<.01[b]
Time interrupted (wk)[c]	NA	85 (90)	NA	
Clinical measures at baseline				
CD4 count	2064 (711)	1969 (1118)	1720 (978)	.57
CD4%	37 (7)	35 (10)	30 (13)	.21
CD8 count	1751 (1109)	1460 (675)	1978 (945)	.34
VL > 750,000 (%) (No.)	69 (9)	56 (9)	40 (4)	.37
400 < VL < 750,000 (%) (No.)	31 (4)	44 (7)	60 (6)	
Clinical measures within 6 mo of scan				
CD4 count	1027 (392)	1110 (460)	1289 (592)	.58
CD4%	37 (8)	34 (7)	36 (10)	.49
CD8 count	902 (450)	1083 (544)	1087 (625)	.57
VL > 750,000 (%) (No.)	8 (1)	0	0	.14
400 < VL < 750,000 (%) (No.)	23 (3)	6 (1)	0	
Suppressed VL (%) (No.)	69 (9)	94 (15)	100 (10)	

Note:—NA indicates not applicable; VL, viral load.
[a] Values are mean (SD).
[b] Significant.
[c] Calculated up to the time of scanning in 3 children who had not restarted ART.

angle = 7°, voxel size = 1.3 × 1.0 × 1.0 mm^3. DWI was performed in 30 directions with b=1000 s/mm^2, voxel size = 2 × 2 × 2 mm^3, TR/TE = 9500/86 ms, and 4 volumes with b = 0 s/mm^2.

Data Analysis

Preprocessing. Diffusion-weighted volumes with signal dropout or motion-corrupted sections were removed,[27] and the diffusion-encoding scheme was adjusted, with a constraint that the same volumes be removed in both DTI acquisitions. Coregistration and susceptibility correction were performed.[28,29] Briefly, coregistration of individual volumes to the first unweighted image was performed by using linear affine (12 *df*) transformation (FMRIB Linear Image Registration Tool, FLIRT; http://www.fmrib.ox.ac.uk/) in FSL (http://www.fmrib.ox.ac.uk/fsl). Subsequently, these images were imported to Matlab (MathWorks, Natick, Massachusetts) for susceptibility correction and outlier rejection.[29] Outliers of each acquisition were examined by first calculating *z* scores on the basis of 25 and 75 percentile limits; data points above 3 SDs beyond the mean were discarded. The 2 acquisitions were combined into a single corrected image; FA, MD, and eigenvalue (e_1, e_2, and e_3) images were generated. The first eigenvalue (e_1) was AD; the remaining 2 were used to compute RD ($e_{23} = [e_2 + e_3] / 2$).

Coregistration. The FA images were first coregistered to corresponding structural images to achieve intrasubject alignment. Structural images of all subjects were then coregistered to a "most representative" control image; then they were subsequently coregistered to the National Institutes of Health pediatric MRI Data Repository T1-template image for children 4.5–8.5 years of age, with an isotropic resolution of 1.0 × 1.0 × 1.0 mm^3 by using linear (FLIRT) and nonlinear (FMRIB Nonlinear Registration Tool, FNIRT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT) coregistration algorithms in FSL.[30] FA images were warped by using the same transforms for intersubject alignment. The same transforms were applied to MD, AD, and RD images. A WM binary mask was generated for each subject by applying an FA threshold of 0.2. Individual masks were multiplied to generate a final binary image representing WM regions with FA ≥ 0.2 in all subjects. The binary image was multiplied by the coregistered FA and MD images of each subject to localize statistical analyses, explained below, to the same WM regions.

Statistical Analysis. Voxel-based group comparisons were performed in FSL to determine regions where FA and MD differed significantly between HIV+ and control children and between HIV+ children starting ART late or early and those with and without interruption. To account for multiple comparisons when determining significant clusters, we used the AlphaSim command (http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) in Analysis of Functional Neuro Images (AFNI; http://afni.nimh.nih.gov/afni) with an overall significance level of α = .05 and an individual voxelwise significance level of P = .01. Full width at half maximum values ranged between 3.8 and 5.2 mm across the masked thresholded WM masks, and we performed 5000 Monte Carlo simulations.[31] Clusters of at least 258 mm^3 were significant at these levels.

Locations of clusters showing group differences were identified by using the Harvard-Oxford cortical and subcortical and Johns Hopkins University WM tractography atlases provided in FSL and an MR imaging atlas of human WM anatomy.[32,33] For each cluster, average FA and MD and corresponding AD and RD values were extracted.

Categoric variables were summarized by using frequency and percentage of frequency distributions overall and by group. Continuous measurements were summarized by using means and SDs. Variables were compared between the groups by using ANOVA and χ^2 tests.

RESULTS

After exclusions, we present data for 13 healthy controls (mean age, 5.7 ± 0.5 years; 5 boys) and 39 HIV+ children (mean age, 5.4 ± 0.3 years; 15 boys). Demographic and clinical data of HIV+ children are presented in Table 1.

Ten children receiving early ART fulfilled the criteria for continuous ART. ART in 16 children was interrupted after primary therapy, and 3 had not restarted ART by the time of MR imaging. Parents of 1 child randomized to ART at 96 weeks initially withheld ART without knowledge of the investigators. This child was included in the late-treatment group.

Four children started ART under Part B; treatments of 2 were interrupted, and 2 were on continuous ART.

Table 2: Clusters in which FA was lower in HIV+ children compared with controls[a]

Cluster Location/CST	Size (mm^3)	Coordinates	AD			RD		
			HIV+	Control	*P* Value	HIV+	Control	*P* Value
Right internal capsule	365	27, −23, −1	1.18 (0.03)	1.20 (0.03)	.10	0.60 (0.10)	0.56 (0.02)	<.001
Right parietal lobe	294	19, −24, 42	1.18 (0.06)	1.22 (0.07)	.08	0.60 (0.04)	0.56 (0.03)	<.001

[a] Values are mean (SD).

Table 3: Clusters in which HIV+ children had significantly greater MD compared with controls[a]

Cluster Location	Size (mm^3)	Coordinates	AD			RD		
			Control	HIV+	*P* Value	Control	HIV+	*P* Value
ILF/SLF								
Right temporal	7503	32, 0, −24	1.19 (0.03)	1.23 (0.03)	.001	0.62 (0.02)	0.65 (0.03)	<.001
Left putamen	6916	−29, −26, −2	1.20 (0.03)	1.25 (0.03)	.001	0.59 (0.02)	0.62 (0.03)	<.001
CST								
Right brain stem	916	21, −15, −9	1.25 (0.04)	1.29 (0.03)	.01	0.58 (0.02)	0.63 (0.02)	<.001
IFOF								
Left temporal	555	−37, −10, −17	1.19 (0.05)	1.25 (0.04)	.003	0.66 (0.02)	0.70 (0.04)	<.001
Forceps minor								
Left frontal	336	−19, 43, 14	1.20 (0.06)	1.24 (0.06)	.04	0.63 (0.03)	0.67 (0.05)	.0030
Left frontal	266	−17, 42, −1	1.22 (0.06)	1.26 (0.06)	.05	0.62 (0.03)	0.65 (0.05)	.0040
UF								
Right frontal	330	15, 38, −12	1.19 (0.05)	1.25 (0.06)	.003	0.64 (0.03)	0.67 (0.04)	.0046

Note:—ILF/SLF indicates inferior/superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus.
[a] Values are mean (SD).

The cumulative period on ART was longest for those receiving early-continuous ART.

Eighty-seven percent ($n = 34$) had viral load suppression (<400 copies/mL). Of the 13% ($n = 5$) unsuppressed at MR imaging, 4 were in the late-ART group (with viral load of 3590, 5980, 8870, and >750,000 HIV RNA copies/mL) and 1 was in the early ART-interrupted group (204,000 HIV RNA copies/mL).

Imaging

On the T1-weighted MR images, structural abnormalities were identified in 3 HIV+ children (mild cerebellar atrophy, mild generalized atrophy, pineal multilobed cyst), and none in controls.

Two clusters were identified in the right corticospinal tract (CST), where FA was lower in HIV+ children than in controls (mean FA, 0.42 ± 0.03 versus 0.46 ± 0.03; and 0.43 ± 0.04 versus 0.49 ± 0.04). Differences in FA were attributable to increased RD ($P < .001$, Table 2). Left-sided similar clusters were seen, however, not surviving cluster-size correction. The FA and RD values in these clusters for the child with viral load > 750,000 HIV RNA copies/mL at scan were below the group average (excluding this child) but not the lowest overall. FA values did not differ significantly between the other 4 unsuppressed children and the remaining group.

Seven clusters showed higher MD at $P < .01$ in infected children than in controls, the largest being 7503 mm^3, which included several tracts. Both AD and RD contributed to the increased MD (Table 3).

Comparison of FA between Children Starting ART before and after 12 Weeks of Age

Against our hypothesis, children starting ART later did not demonstrate poorer white matter integrity as measured by FA. Rather, 1 cluster was identified in the brain stem in the left CST, where FA was lower in early compared with late ART initiation. When comparing early-continuous and early-interrupted ART individually against late ART, we found lower FA only in the early-interrupted ART group, suggesting that interruption is harmful to WM. No regions showed FA differences between early-continuous and late ART. The reduced FA in the children on early-interrupted ART was attributable to increased RD and AD.

DISCUSSION

We demonstrated WM areas with significantly reduced FA in HIV+ children initiating ART at a median age of 4 months compared with uninfected controls.

No Frontal or Parietal White Matter Predilection for Abnormal Findings

Our findings confirm the presence of FA abnormalities found in HIV+ adults and adolescents but differ in volume and distribution. Young children on early ART had very few regions with abnormal FA. The predilection for frontal lobe involvement described in adults[34-38] was not seen possibly due to the small sample size, specifically the control group ($n = 13$). We previously reported multifocal WM signal abnormalities on standard T2-weighted MR imaging sequences in frontal (91%) and parietal WM (82%) of HIV+ children at a mean age 31.9 months.[39] Twenty of these children are also included in the present study. Ten had WM signal abnormality on FLAIR.[39] Unfortunately, a limitation in the present study was the absence of FLAIR, thus an inability to assess interval WM signal change. However, the absence of frontal and parietal involvement in FA does suggest interval improvement on ART.

Although clusters showing left-sided FA differences did not survive cluster-size correction, FA reductions were bilateral in the CST. The MD differences were more widely distributed and included the inferior longitudinal fasciculus (bilateral), CST, inferior fronto-occipital fasciculus, forceps minor, and uncinate fasciculus.

Because frontal WM myelination continues into adulthood, children demonstrate inherently lower frontal FA values than adults.[40] To exclude frontal predominance of WM abnormality being maturational,[41] we determined areas of significant FA difference between HIV+ children and age-matched controls by using voxelwise group comparisons. The predominant contribution to decreased FA was RD, while the increased MD was due to both RD and AD, indicating both reduced myelin and loss of axonal integrity.[42]

The age difference between the HIV+ and control groups was only a few months, not considered clinically significant. Our study has a much narrower age range than previous studies, facilitating improved comparison with controls representing the age-related normally developing brain.

Children's Ages and ART Relevance

The higher FA values in those beginning ART after 12 weeks was surprising because we expected this finding in those beginning ART before 12 weeks. However, the difference was attributable to ART interruption, possibly negating the benefits of early ART, rather than neurotoxicity due to longer ART exposure.[43-45]

The timing of the interruption may be important with reference to WM maturation. Three phases of maturation are observed by FA: rapid change in the first 3–6 months, slower change until 24 months, and relative stability thereafter. Most WM tracts are formed at birth; then they increase in size together with FA during 24 months.[46] Deep WM structures such as the CC and internal capsule have high FA at birth, which rapidly rises. In contrast, frontal WM has low FA, increasing to intermediate values around 24 months. In neonates, the CST is present within the brain stem, but the size and intensity are much lower than in the older brain.[47] Postmortem studies, however, have shown that the CST and the superior cerebellar peduncles mature early.[48,49] ART was interrupted at 40 weeks (around 10 months of age); this interruption may have coincided with a critical stage of CST maturation.

Notably, we found no CC involvement in HIV+ children. HIV-associated FA abnormalities in the CC have been reported in adults and in children.[6,7,8,13] In contrast, our children started ART early compared with those in other studies. Most interesting, CC volume and thickness were similar to those in controls in a study by Andronikou et al,[50] which included the 20 HIV+ children previously reported. The CC genu demonstrates a variable growth spurt at 2 months of age, followed by similar growth in the splenium by 4–6 months, with myelination being visible on T1-weighted MR imaging from 4–6 months.[51] Our data support early ART being neuroprotective for the CC.

That no FA differences were noted between the late and early-continuous groups may have been a "survivor effect." Eight children in the ART-Deferred arm died in the first year of life and were not studied. In addition, those on early-continuous rather than early-limited ART were more severely affected by HIV, having already reached a trial end point during primary ART, thus being ineligible for interruption. All participants on continuous therapy had suppressed viral loads at the time of scanning. Notably, those from Part B had a baseline CD4 below 25% and therefore had more advanced HIV. Nevertheless, the early-interrupted children had the most WM damage, suggesting that WM is more vulnerable at the time that ART interruption occurred.

Our data strongly suggest that WM damage, though not prevented by early ART, can be ameliorated or reversed, possibly through reduced neuroinflammation.[52] The children in this study are enrolled in a longitudinal neuroimaging study that includes DTI at age 7 and 9 years, which will provide vital information on the continuous effect of ART and/or HIV as well as answer questions relating to the influence of white matter maturation.

CONCLUSIONS

HIV+ children at 5 years of age have WM fiber abnormalities measured by FA despite early ART, suggesting that early ART does not fully protect the WM from either peripartum or in utero infection. In contrast to adults, the CSTs of children are predominantly involved rather than the CC, possibly due to early ART. Continuous ART can limit WM damage.

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