Published in final edited form as:

Pediatr Infect Dis J. 2014 August ; 33(8): e207–e212. doi:10.1097/INF.0000000000000288.

White Matter Signal Abnormalities in Children with suspected HIV-Related Neurologic Disease on Early Combination Antiretroviral Therapy

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Abstract

BACKGROUND—The natural history and manifestation of HIV-related neurological disease have been ameliorated by combination antiretroviral therapy (ART). We describe the characteristics of white matter signal abnormalities (WMSA) on magnetic resonance imaging (MRI) in children with HIV-related neurological disease.

METHODS—We reviewed MRI scans of children with suspected HIV-related neurological disease despite early ART, and correlated with clinical, neurodevelopmental data, virological markers and time on ART. These children were also on the Children with HIV Early Antiretroviral (CHER) trial.

RESULTS—MRI scans were performed at a mean age 31.9 months (range 8–54) on 44 children: 10 on deferred and 34 on early treatment arms, commencing ART at mean age of 18.5 and 8 weeks respectively. Multiple high signal intensity lesions on T2 /FLAIR were documented in 22 patients (50%), predominantly in frontal (91%) and parietal (82%) white matter. No differences in neurodevelopmental scores comparing children with and without WMSA were found. Neither lesion load nor distribution showed significant correlation with neurodevelopmental scores or neurological examination. Normal head growth was more common in the WMSA group ($p=0.01$).

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Conflicts of Interest and Source of Funding: No conflict of interest to declare.

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There was a trend for association of WMSA and longer time on ART ($p=0.13$) and nadir CD4% ($p=0.08$).

CONCLUSION—Half of children referred with HIV-related brain disease had WMSA on T2/FLAIR. Our findings of the association with normal head growth and duration of ART require further study. We suspect that WMSA can occur early and that initiating ART by 8 weeks of life may be too late to prevent HIV from entering the CNS.

Keywords

HIV-encephalopathy; HIV-related brain disease; developmental score; white matter signal abnormality; MRI; early ART

HIV-encephalopathy is an AIDS defining event, ^[1] which in its most severe form, presents with developmental delay and motor dysfunction ^[2]. However, with combination antiretroviral therapy (ART), manifestations are likely to be subtle and have not yet been well described in children receiving early ART. It is critical to identify a good marker of HIV-related manifestations in the central nervous system (CNS) ^[3] as early treatment can slow deterioration and partially improve manifestations ^[4, 5]. HIV-encephalopathy demonstrates white matter signal abnormality (WMSA), mainly hyperintensity on magnetic resonance imaging (MRI) ^[6]. In adults treated with ART, resolution of WMSA mirrors clinical improvement ^[7, 8]. The imaging findings in children with HIV-encephalopathy show basal ganglia calcification and atrophy. One limited study (21 children) antedating the availability of ART, demonstrated deep white matter hyperintensity sparing the subcortical U-fibers in a third of children ^[9]. Our aim was to determine the prevalence, distribution and characteristics of WMSA on T2/FLAIR (fluid attenuated inversion recovery) sequences in a larger number of children initiating ART from an early age, but with suspected HIV-related neurological disease. We also sought to correlate WMSA with developmental scores, clinical presentation and laboratory studies.

METHODS

We conducted a prospective study over 2.5-years (August 2007 to April 2010) at Tygerberg Children's Hospital, Cape Town, South Africa on HIV-infected children referred for neuroimaging by their infectious diseases clinicians because of suspicion of HIV-related neurological disease (either poor head growth, long tract signs or neurodevelopmental delay). The Children with HIV Early Antiretroviral (CHER) trial ^[10, 11] took place in the same hospital and contributed all of the children referred for MRI. The CHER trial was a randomized two-center study in which HIV-infected infants between 6 and 12 weeks of age and CD4 $\geq 25\%$ were randomized to one of three strategies: ART deferred until indicated, early limited ART for 40 weeks or early limited ART for 96 weeks. Continuous ART was initiated in the deferred arm or in the early limited ART arms after interruption if the CD4 percentage declined below 20% (25% for ART deferred in the first year of life). Other criteria for continuous ART were Centers for Disease Control (CDC) stage C or protocol-defined severe CDC stage B disease. The latter included bronchiectasis and severe lymphoid interstitial pneumonitis, nephropathy and cardiology. Additional criteria were failure to thrive not meeting CDC stage C, severe oral candidiasis, recurrent pneumonia and any

condition considered severe enough for ART (with approval of the study team). A small group with CD4 < 25% at baseline were recruited in parallel and also received early continuous ART on the recommendation of the study's data safety monitoring board. First-line ART was lopinavir-ritonavir, lamivudine and zidovudine. The majority of 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 CD4 count below 250 cells per mm³ received ART antenatally. Newborn infant received a single dose of nevirapine at birth and zidovudine for 7 days.

Children were in regular follow-up^[10,11] with clinical assessments monthly, including neurological examination and head growth monitoring using CDC growth charts (< 3 years) and World Health Organization (WHO) percentile charts (>3 years). Poor head growth was defined as downward crossing of at least 2 major centiles on CDC charts and 1 centile line on WHO charts. Neurodevelopmental screening assessment was performed every 6 months, and as part of a site-specific neurodevelopmental sub-study, the Griffiths mental development scales (GMDS)^[12] were performed at 12, 18, 30 and 42 months. GMDS quotients were obtained from raw scores or age equivalents, using the United Kingdom Norms with a mean of 100 and standard deviation of 15^[12, 13]. Significant developmental delay was defined as more than 2 standard deviations below the mean (developmental quotient below 70).

Patients were excluded if evidence of current or previous opportunistic CNS infection; CNS neoplasm; neurological disease caused by factors other than HIV; previous anoxic insults; persistent metabolic derangement or inadequate MRI scans (omitted sequences) were present. Post-gadolinium-enhancing lesions such as focal, ring or solid enhancement, enhancement of the dura, meninges or cranial nerves, were excluded from the study. Baseline and clinical data were obtained from participants' medical records. Viral Loads (VL) >750 000 copies/mL were assigned as 750 001 and those <400 copies/mL as 399. Mean VL at baseline from the CHER trial was calculated, and VL closest to scan was categorized as <or >400 copies/mL.

Scans were performed under general anesthesia (standard practice at our institution) on a Siemens Magnetom Symphony 1.5T. Sequences: Axial T2 spin echo (SE), Axial FLAIR, Sagittal T1 SE, Sagittal T2 turbo spin echo (TSE), diffusion weighted imaging (DWI), post gadolinium Axial T1 with a slice thickness of 5mm. A pediatric neuroradiologist, blinded to clinical findings at time of referral, performed the MRI readings. Any non-enhancing WMSA was recorded according to anatomical regions of the brain and topographic white matter fiber involvement. Predefined criteria were used to describe the WMSA as pinpoint lesions, measurable lesions < 1cm, measurable lesions > 1cm or 'larger' confluent lesions difficult to measure. The maximum diameter of the largest measurable lesion in each patient was determined on axial FLAIR sequences, using visual inspection to determine the slice. DWI and apparent diffusion co-efficient (ADC) map was used to determine any diffusion abnormality relating to the lesions. 'Lesion load' was arbitrarily determined by calculating the number of regions involved (divided into 17 zones: frontal, temporal, occipital, parietal left and right, corpus callosum, midbrain, pons, medulla, cerebellar hemispheres, cerebellar

vermis, caudate, lentiform nucleus, thalamus) irrespective of the size and number of the lesions.

Quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) was performed on stored plasma samples of all CHER subjects at screening in a separate sub-study using the RocheCOBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Molecular Diagnostics, Branchburg, New Jersey). CMV values ≥ 150 copies/ml were considered positive for exploring a potential relationship with WMSA.

For statistical analysis, one-way analysis of variance (ANOVA) was conducted to compare continuous measurements between groups with and without WMSA. The Chi-square test was used to compare categorical variables (e.g. gender) between the two groups. Spearman correlations were used to test for relationships between developmental scores and 'lesion load' and also WMSA distribution. Two-way ANOVA was conducted to produce results corrected for gender. Ethics approval, N07/09/208, for the study was obtained from Stellenbosch University.

RESULTS

Forty-four HIV-infected children (22 boys) were studied. Age ranged from 8 to 54 months (mean 31.9 and SD 9.9 months). Average time between referral request and MRI scan was 2.2 months (SD 1.6 months). There were no exclusions due to image quality (motion artifact). MRI demonstrated WMSA on T2/FLAIR in 22 children, 50% of the sample. Demographic, immunologic and virologic data are shown in Table 1, which also shows comparisons in those with and without WMSA.

Prevalence and distribution of WMSA

Sixteen children (73%) with WMSA had a combination of lesions (representative scan in Figure 1a). Three children had only pinpoint lesions (Figure 1b), 1 had only measureable lesions <1 cm and 2 children had confluent lesions. Lesion size ranged from 5 to 12mm, with an average of 7.2mm. In 12 children, the lesions were T1 iso-intense, 3 had T1 hypo-intense lesions and 7 had combinations of lesion intensity. None of the lesions demonstrated enhancement. Predominantly frontal (20; 91%) (Figure 1c) and parietal (17; 77%) distribution was noted in subcortical and deep white matter (Figure 1d). Table 2 summarizes WMSA distribution. Other areas of involvement included the peritrigonal regions in 7 children (32 %), involving both right and left sides (unilateral in one child), left cerebellar hemisphere in 1 child (5%) and left lentiform nucleus in one child (5%). Twelve of 22 (54%) had WMSA in 4 or more zones. The maximum number of zones in a single child was 7.

Developmental score

Assessments were performed at a mean age of 30 (range 11-48) months. Mean scores fell into the low average category with a mean general quotient (GQ) of 81.7 (range 67 – 101). The mean locomotor sub-quotient was 83 (range 50 – 116). The mean language sub-quotient was 79.7 (range from 57 – 118). These mean scores are around 1 standard deviation lower than previously described in HIV-uninfected children at 21 months of age, from this

community^[14] who had means of 95, 99.7 and 93.2 respectively for GQ, locomotor and language. The time between GMDS and MRI ranged from 3.7 months before to 3.4 months after the scan. There was no difference between the groups (with and without WMSA) for time between scan and GMDS ($p=0.87$) or mean age at GMDS assessment ($p=0.46$).

Correlating developmental scores with lesion load and distribution of WMSA

There were no differences in developmental scores in those with and without WMSA (see Table 1). Lesion load also showed no correlation with developmental quotients (lesion load vs. GQ, $p=0.99$; lesion load vs. locomotor, $p=0.80$ and lesion load vs. language, $p=0.50$). However, the child with the most sites involved ($n=7$) also had the lowest overall GQ (67) and locomotor sub-quotient (50), both significantly delayed, with a language sub-quotient of 82, which is below average. This child, with a baseline CD4 of 13.4% and viral load above 750 000 copies/mL at 9.4 weeks of age received continuous ART. There were more boys in the group with WMSA (14 vs. 8), but no differences were found between the groups when controlling for gender on GMDS outcomes (2-way ANOVA results not shown).

Clinical indications, laboratory tests and WMSA

For those with WMSA, significantly fewer (36%) had declining head growth as an indication for neuroimaging referral versus 64% without WMSA ($p=0.01$). There was no difference in the frequency of developmental delay, increased muscle tone or pathological tendon reflexes as a reason for referral between the children with or without WMSA.

There was no difference in baseline CD4 and viral load pre-ART, or CD4 and viral load closest to MRI scan between the groups. Those with the lowest CD4% nadir showed a trend to more WMSA ($p=0.08$), which diminished when controlling for gender ($p=0.28$ from 2-way ANOVA). We also noted a trend for CMV positivity and WMSA ($p=0.055$).

Antiretroviral Therapy

Ten children in the deferred ART arm were referred for MRI. They had initiated ART at a median age 18.5 weeks due to immunological and/or clinical decline, and received ART for a median 114 weeks prior to the MRI. Three in this arm had WMSA^[10, 11]. Thirty-four children were in the early limited ART arms. They commenced early ART at a median age of 8 weeks and received ART for a median of 98 weeks. Of these, 2 children had not yet interrupted, 5 were in the ART interruption phase at time of neuroimaging and 17 had already restarted ART after a period of interruption. Ten children received early continuous ART. Seven with baseline CD4 $\geq 25\%$ had already developed significant HIV-related disease (3 with failure to thrive and four with site-determined HIV-related brain disease). The remaining 3 had a CD4% below 25% at baseline.

One child had changed to second line ART (didanosine, abacavir and nevirapine) for 6 months at 17 months of age (2 years before neuroimaging) and then changed back to first line therapy; abacavir was added at 38 months of age (1 year before neuroimaging), due to virological failure. For those with a baseline CD4% $\geq 25\%$ and initially randomized to early limited ART, there was a trend to more WMSA in those not interrupting ART compared to those who interrupted ART ($p=0.129$, Fisher's Exact 2 tail test).

There was also a trend for more WMSA with longer time on ART (in weeks) with mean (standard deviation) 115.6 (43.7) ($p=0.13$ or $p=0.20$ after controlling for gender). There was no statistical difference when controlling for age and time on ART between the two groups. Of the 26 children randomized to early limited ART, 12 had WMSA and 14 did not.

DISCUSSION

Imaging findings in children with HIV in the pre- and post ART eras include atrophy [1, 15], calcification [16] and more recently, WMSA [17]. We have described, for the first time, the distribution and characteristics of WMSA in children who received early ART in infancy. Fifty percent of those referred for MRI because of concern of HIV-related brain disease, had WMSA on T2/FLAIR MRI. Lesions occurred most commonly in superficial and deep white matter and predominantly in the frontal and parietal lobes. Most importantly, WMSA was present in children with both early limited, early continuous and deferred ART. There was no correlation between the distribution of WMSA or the lesion load with immunological or developmental scores.

There was a surprising association between WMSA and normal head growth ($p=0.01$), rather than acquired microcephaly. However, there was no association with either developmental delay, or increased tone and tendon reflexes. These observations require further investigation in a larger cohort. A possible explanation may be that early ART is neuroprotective and that imaging findings in these children represent arrested brain disease but with ongoing inflammation or low-level viral replication. Unfortunately head circumference-for-age Z-scores, which may have increased our ability to interpret this finding, were not documented over time.

The lack of correlation of WMSA and GMDS scores is possibly due to early identification of suspected HIV-related brain disease by performing the GMDS regularly in all children. Some GMDS scores were in the normal range, as other criteria for neurological compromise were met (poor head growth and acquired symmetric motor deficits). It may also be that the GMDS has insufficient sensitivity to assess the more subtle effects corresponding to WMSA based on T2/FLAIR and the children were too young for more detailed neuropsychological assessments to assess specific domains of functioning. Stability of the GMDS over time is also not clear in South African children, since it was standardized in the United Kingdom [12,13] with varying reports of performance on the GMDS in South Africa [18,19,20,21,22]. We did not collect data on socioeconomic status, but these children are all from similar background low-socioeconomic communities.

There was a trend towards presence of WMSA and time on ART, with longer time on treatment associated with increased WMSA ($p = 0.13$). The association is of unclear significance (power=34%), and requires further study in larger groups as WMSA could either represent more severe disease or cumulative ART toxicity, specifically as all guidelines recommend early continuous ART in all HIV infected infants [23]. Also, a trend towards more WMSA in those who, although randomized to early limited ART remained on continuous ART, suggests more severe HIV disease. No children were on efavirenz, which may be neurotoxic in adults [24]. There was also no correlation between WMSA and different

treatment arms on the CHER trial; however, this is a relatively small descriptive study of clinical referrals, and conclusions cannot be drawn from these small numbers.

There was no correlation between WMSA and viral loads, CD4 counts or CD4% closest to the time of scan. However, the time between the scans and these parameters ranged from 0 – 12 months, because it was not part of the research design to obtain these at the time of scan. There was a trend showing a negative association with nadir CD4%. In adults, nadir CD4 levels correspond to episodes of severely impaired immune function, which place the brain at greatest risk of HIV involvement [25]. The WMSA in our patients may represent damage from HIV during exposure to high viral loads prior to ART, or other pathogens may have accessed the brain. Focal white matter lesions without enhancement or mass effect have increased in HIV-infected children between 1991 and 1998, etiologies including viral encephalitis, focal HIV-encephalopathy and progressive multifocal leukoencephalopathy (PML) [15]. The latter was a problem in the pre-ART era resulting in WMSA, possibly due to delayed initiation of ART and using medications with lower CNS penetration. Differential diagnoses to consider with WMSA include maternal recreational drug exposure, intrauterine CNS infections such as toxoplasmosis, CMV and cerebral malformations with cortical dysplasia [5]. Infants co-infected with CMV and HIV, have a higher rate of progression to symptomatic stages of AIDS as well as higher incidence of encephalopathy [5, 6]. Although we showed a possible link between CMV at 6 weeks of age, data were missing for 6 children with and 3 without WMSA. Also, we could not distinguish congenital from acquired CMV infection. The lack of control subjects is a limitation of our study; however WMSA in children above 1.5 years of age is abnormal [26].

Changes occurring in the CNS in the earlier stages of HIV-1 infection remain poorly understood and the evidence is conflicting. Progressive encephalopathy can be associated with normal imaging studies, [1] and there may even be abnormalities on CT scan in asymptomatic children [1]. HIV leukoencephalopathy, visualized as WMSA on MRI, is a triad of diffuse myelin loss, astroglial proliferation, and infiltration by mono and multinucleated macrophages [8, 27]. The myelin pallor is diffuse, involves deep white matter and spares superficial (subcortical) white matter and corpus callosum [27], in contrast to PML which tends to involve subcortical and periventricular white matter, corpus callosum, internal and external capsules and the myelinated fibres of the deep grey nuclei [28, 29]. Our imaging findings suggest that superficial white matter is not spared as WMSA involving the subcortical white matter was noted in many children in our series. It may be difficult to distinguish from other causes of WMSA such as prenatal/perinatal injury [5], especially in the peritrigonal area, which is susceptible to global hypoxic insults and is also a terminal zone of maturation [30]. However, only 7 (16%) of our patients showed pathological asymmetrical WMSA in the peritrigonal region, with birth asphyxia having been excluded in our study.

Documenting WMSA is important in the clinical management of HIV-infected adults as it provides supporting evidence for HIV-1 associated cognitive motor complex [7], correlates with clinical improvement following ART [7] and suggests that disease regression in patients with AIDS dementia complex on ART can be characterized and monitored by MRI [8]. Currently, neurodevelopmental testing is performed routinely in HIV-infected children to

assess cognitive function and effectiveness of ART in the CNS. By the time cognitive deficits are detected however, significant brain injury may already have occurred [31] as shown in the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial. Here children between 1 and 12 years of age were randomized to early or deferred ART, performed worse than HIV-uninfected control children on intelligence quotient, Beery Visual Motor Integration, Binet memory and Child Behavioral Checklist[32].

The utility of detecting WMSA in children requires prospective study. Qualitative MRI analysis of early white matter changes in HIV-encephalopathy can be difficult [7]. Alternative quantitative imaging (e.g. MRI spectroscopy and relaxometry) can detect encephalopathy, disease progression or improvement on treatment [33]. DTI (Diffusion Tensor Imaging) provides quantitative information on the integrity of white matter tracts and correlates with cognitive impairment in adults [34]. In children, this offers new challenges relating to immaturity of myelination, which may affect measurable fractional anisotropy and because these studies are time consuming. Our limited MRI resources at the time curtailed our capacity to perform these advanced sequences but are included in our continuing work.

CONCLUSION

Our results demonstrate that half of the children referred for suspected HIV-related neurological problems have WMSA on T2/FLAIR, involving mainly the frontal and parietal lobes, superficially and in the deep white matter. The lesion load and distribution did not correlate with the developmental scores or viral load. We suspect that WMSA can occur early and that initiating ART by 7 to 8 weeks of life may already be too late to prevent HIV from entering the CNS.

Acknowledgments

National Research Foundation of South Africa, the Medical Research Council of South Africa, the Harry Crossley Foundation, NIH grant U19A153217 through the Comprehensive International Program of Research on AIDS (CIPRA) network provided funding.

We thank Dr. Avy Violari for careful review of the manuscript and Kennedy Otjombe (Perinatal HIV Research Unit, University of the Witwatersrand) for data extraction. We also thank Dr. Marvin Hsiao, (Department of Medical Virology, University of Cape Town) for sharing the CMV data and Anita Janse van Rensburg (Children's Infectious Diseases Clinical Research Unit) for meticulous data collection and verification. We thank the parents and children taking part in the study and KIDCRU personnel, especially Lugiswa Rosy Khethelo and Mica De Bolt.

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Figure 1.

Axial FLAIR MRI: pin-point white matter signal abnormality (WMSA) (black arrows) in addition to larger measurable lesions (white arrow) of various shapes and sizes all less than 1cm in both of the superior frontal lobes.

Axial FLAIR MRI: multiple bilateral pin point WMSA, involving predominantly subcortical (white arrows) and to a lesser degree deep white matter in the superior frontal lobes.

Axial FLAIR MRI: Two right frontal sub-centimeter focal lesions.

FLAIR MRI: Bilateral parietal WMSA, on the right larger than 1cm (white arrow) and on the left less than 1cm (black arrow) extending from the subcortical to the deep white matter.

FLAIR: fluid attenuation inversion recovery

MRI: magnetic resonance imaging

WMSA: white matter signal abnormalities

TABLE 1

Comparison between children with and without WMSA

	WMSA present (n=22)	WMSA absent (n=22)	p-value	Effect size ***
Male gender (%)	14 (64%)	8 (36%)	0.07*	Cramer's V=0.27
Mean age at MRI (months)	32.8(9.4)	30.9(10.4)	0.53^	0.20
Baseline (before 12 wks of age) mean(SD)				
CD4 absolute count (cells/mm ³)	1756 (778.2)	1859 (984)	0.70^	0.12
CD4%	32.0 (11.9)	35.6 (9.6)	0.27^	0.34
Viral load (copies/mL)	591931(261119)	571449(234191)	0.79^	0.08
Time on ART before MRI (wks) mean(SD)	115.6 (43.7)	94.4 (46.4)	0.13^*	0.48
Mean age of ART initiation (weeks)	10	13.6		
Arms on CHER trial:				
Baseline CD4 ≥25%:				
ART-Def	3	7	0.4	
Early ART until W40	7	7		
Early ART until W96	4	6		
Early continuous ART ≈	5	2		
Baseline CD4 <25%:				
Continuous ART	3	0	NS	
Viral load closest to MRI (%)				Cramer's
<400 HIV RNA (copies/mL)	48%	52%	0.86	V=0.05
>400 HIV RNA (copies/mL)	55%	45%		0.04
Time between Viral Load and MRI (days) Mean (median)	88.5(56.5)	83.3 (50)	0.59**	
CD4 count closest to MRI scan				
Absolute count (cells/mm ³)	1490 (819.6)	1441 (432.2)	0.81	0.08
CD4%	34.2(8.1)	33.8 (9.2)	0.88	0.05
Time between CD4 and MRI (wks) Mean (median)	35.1(18.5)	25.5(17.5)	0.53**	0.18
Nadir CD4 closest to MRI				
CD4 count (cells/mm ³)	1184.3 (680.5)	1048.6(487.5)	0.45	0.23
CD4%	18.9 (6.5)	22.4(6.5)	0.08	0.55
Mean time between scan and nadir CD4 (wks)	89.0(54.4)	68.6(43.2)	0.18	0.43
CMV DNA positive at baseline [§]	6 (75%)	2 (25%)	0.055	
CMV DNA negative at baseline	10 (37%)	17 (63%)		
Reason for MRI request: n (%)				Cramer's
Developmental delay	19(51%)	18 (49%)	0.68	V=0.06
Poor head growth	10 (36%)	18 (64%)	0.01*	0.38
Increased muscle tone	5(42%)	7(58%)	0.50	0.10
Pathological reflexes	14 (48%)	15 (52%)	0.75	0.05

	WMSA present (n=22)	WMSA absent (n=22)	p-value	Effect size ^{***}
Griffiths Mental Development Scales:				
Age at assessment mean (SD) in months	31.0 (8.5)	29.0 (9.3)	0.46	0.23
Time between scan and GMDS in months	3.4 (3.0)	3.2 (4.2)	0.87	0.05
General Quotient	83.2(7.4)	80.3(15.4)	0.44	0.25
Locomotor sub-quotient	81.5(11.9)	84.4(15.1)	0.49	0.22
Language sub-quotient	79.8(8.9)	79.5(13.1)	0.94	0.03

WMSA: white matter signal abnormalities

MRI: magnetic resonance imaging

CHER: children with HIV early antiretroviral therapy

ART: combination antiretroviral therapy

ART-Def: ART deferred therapy

CMV: cytomegalovirus

[^] F-test degrees of freedom 1,42

* Significant p-value

** Mann Whitney U-test

*** Cohen's D unless otherwise specified

[§]CMV 150 copies/mm³; no CMV data for 6 with WMSA and 3 without WMSA

[≈] Received continuous ART although randomized to early limited ART.

TABLE 2

Distribution of WMSA in children with HIV related brain disease by number of patients with at least one lesion in the listed location (note that some patients had more than one site involved)

Location	Cumulative number of patients	Right		Left	
		Superficial	Deep	Superficial	Deep
Frontal	20 (91%)	18 (82%)	5 (23%)	17 (77%)	7 (32%)
Parietal	17 (77%)	11 (50%)	9 (41%)	12 (55%)	8 (36%)
Temporal	1 (5%)	1 (5%)	0	1 (5%)	0
Occipital	3 (14 %)	3 (14 %)	0	1 (5%)	0

WMSA: white matter signal abnormalities