Recovery of HIV encephalopathy in perinatally infected children on antiretroviral therapy

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ABBREVIATIONS

ART	Antiretroviral therapy
CHER	Children with HIV Early AntiRetroviral treatment
HCZ	Head circumference z-score
HIV	Human immunodeficiency virus
HIVE	Human immunodeficiency virus encephalopathy
PCR	Polymerase chain reaction
UMN	Upper motor neuron

AIM To describe the trajectory of clinical signs in children who developed human immunodeficiency virus encephalopathy (HIVE) after starting early antiretroviral therapy (ART).

METHOD This was a retrospective case-cohort description of HIVE among Cape Town participants from the Children with HIV Early AntiRetroviral treatment (CHER) trial. Criteria for HIVE diagnosis were at least two of: (1) acquired central motor deficit, (2) impaired brain growth, and (3) failure to attain or loss of developmental milestones in the absence of an alternative aetiology.

RESULTS Of 133 surviving participants who initiated ART at a median age of 9 weeks and who were followed until a median age of 6 years, 20 (12%) developed HIVE at a median age 31 months (interquartile range 19–37). In these, the first neurological deterioration was noticed at a median age of 19 months, when 16 were on ART and nine had undetectable HIV viral load for a median of 12 months. Signs of upper motor neurons were present in 18, of whom 12 resolved and four had persistent spastic diplegia; 19 had motor delay, of whom 14 resolved; 12 had language delay, of whom 11 resolved; and 16 had impaired brain growth, of whom only five recovered. For the 16 participants already on ART at HIVE diagnosis, regimens were not altered in response to diagnosis.

INTERPRETATION HIVE may occur despite early ART initiation and virological suppression and then resolve on unchanged ART, most likely as intrathecal inflammation subsides.

Human immunodeficiency virus encephalopathy (HIVE) is the most severe neurological manifestation of HIV in children and can be ameliorated by combination antiretroviral therapy (ART).[1,2] The patterns initially described for HIVE in the pre-ART era were static, plateau, or sub-acute progressive,[3] none of which recovered. ART has dramatically reduced the incidence of HIVE, especially when started in the first few weeks of life;[4,5] however, HIVE still occurs.[6,7] The manifestations and clinical course are variable, presumably related to individual differences in the underlying timing of infection and mechanism of neuronal insults.[8–11] Typical patterns of progression in the era of early ART have not been clearly defined. We report the longitudinal progression of clinical signs in a cohort of children from a clinical trial who developed HIVE despite receiving ART from an early age.

METHOD

We reviewed the clinical notes of participants from the Children with HIV Early AntiRetroviral treatment (CHER) trial[12,13] with confirmed HIVE, and documented their clinical course from earliest deterioration. The CHER trial started in July 2005 and formally ended on 31st August 2011 with participants followed for an additional 14 months to October 2012. In the CHER trial, 411 infants with CD4 T cells of at least 25% and below 12 weeks of age were randomized to immediate ART for 40 (ART-40W) or 96 weeks (ART-96W) followed by planned interruption, or ART was deferred until clinical or immunological deterioration (Fig. S1, online supporting information). A further 40 infants with CD4 T cells less than 25% and below 12 weeks of age were randomized to ART-40W or ART-96W. ART comprised lopinavir/ritonavir, zidovudine, and lamivudine. The 'ART was deferred' arm was stopped by the Data Safety Monitoring Board in 2007. The Cape Town site contributed 151 (33%) participants (Fig. S2, online supporting information), of whom 133 survived past infancy and were included in the current analysis. Beyond the trial close-out (September 2011),

Cape Town participants remained in active follow-up at the research site. The trial was approved by the Health Research Ethics Committees of Stellenbosch University, the University of the Witwatersrand, and the Medicines Control Council of South Africa. Informed written consent was obtained from caregivers.

In the CHER trial, participants were reviewed clinically every 4 weeks until week 24, every 8 weeks until week 48, and then every 12 weeks. Review included ART adherence, growth monitoring, and a neurological examination. The following developmental domains were assessed every 6 months: gross motor, language, fine motor, and personal–social functioning, using the locally developed Molteno Adapted Scale.[14,15] More frequent neurodevelopmental assessments were performed when an abnormality was suspected.

HIVE diagnosis was determined using the criteria listed below by a blinded end-point review committee during the CHER trial and by a team of experts, both outside CHER (RvT, paediatric neurologist) and investigators from CHER (BL, MFC, ED, and SI), after the end-point review committee was disbanded (Fig. S2).

Criteria for HIVE were at least two of the following three findings in the absence of an alternative aetiology: (1) acquired central motor deficit manifesting as upper motor neuron (UMN) signs, specifically pathological reflexes (abnormally brisk reflexes plus abnormal spreading of reflexes, crossed adductor response or sustained clonus), increased tone, gait disturbance, ataxia or paresis, with evidence of previously normal neurological examination; (2) impaired brain growth manifesting as acquired microcephaly (reduction in serial head circumference z-score [HCZ] below one standard deviation [SD] from baseline), or generalized brain atrophy demonstrated on radiological imaging; (3) failure to attain or loss of developmental milestones on two consecutive visits 3 months apart, using a Molteno Adapted Scale-derived developmental quotient (developmental age divided by chronological age×100) of less than 70 in a developmental domain, with evidence of a previously normal quotient. Pre-ART criteria from the Centers for Disease Control and Prevention required only one of the above three findings for a diagnosis of HIVE.[16] However, we used more stringent diagnostic criteria and excluded doubtful or incomplete cases. Alternative aetiologies were excluded after careful clinical, laboratory, and radiological investigation. In addition, psychosocial, nutritional, or maternal causes were excluded. We also actively sought to exclude confounders. Social deprivation and lack of stimulation from caregivers is common in our setting and could contribute to neurodevelopmental delay.[17] As poverty, poor education, depression, and HIV-associated neurological disorder may all contribute to mothers not caring adequately for their children, we looked for recent changes in the mothers or their circumstances that could explain developmental delay. Four participants were excluded on this basis.

Where neurodevelopmental milestones were recorded in the absence of a Molteno Adapted Scale, these were retrospectively plotted to obtain a Molteno Adapted Scale developmental quotient for that individual domain. This approach provided additional fine-grain detail for description of cases. UMN signs were scored as follows: 0, normal; −1, brisk reflexes; −2, extremely brisk or spreading reflexes or increased tone; −3, crossed adductor response; −4, clonus (at least three beats) or Babinski/up-going plantar response. Gait disturbance related to UMN dysfunction was scored −5. UMN function was considered abnormal if the score was not greater than −2. The presence of brisk reflexes alone was considered insufficient evidence of central motor deficit. We considered a child to have neuromotor deficit when there was a gross motor quotient of less than 70 and/or a UMN score no greater than −2.

What this paper adds

- Despite suppressive antiretroviral therapy, children can develop human immunodeficiency virus encephalopathy,
- The most common manifestations are motor deficits and impaired brain growth.
- Most experience improvement, with many resolving without additional intervention.

World Health Organization growth parameter z-scores for age and sex were used to determine weight-for-age z-score, height-for-age z-score, weight-for-height z-score, body mass index-for-age z-score, and HCZ (WHO AnthroPlus: https://www.who.int/growthref/tools/en/).

We defined the date of first neurological concern, when a developmental quotient less than 70 or UMN signs (see above) were first documented. The date of nadir for clinical signs was the date of lowest developmental quotient and/or lowest UMN score. The date of first improvement was the earliest date where this was documented. Normalization of development was defined as return of developmental quotient to at least 90. Normalization of central motor deficit was defined as return of UMN score to zero. Time to recovery in each domain was calculated from the first nadir date in that domain.

The onset of acquired microcephaly was the date at which head circumference measurement departed from the usual z-score line and progressively dropped by more than 1 SD. Recovery was defined as return to within 1 SD of baseline HCZ.

HIV RNA polymerase chain reaction (PCR) viral load testing in plasma was performed on stored specimens from 2005 to 2007 and routinely 3 to 6 monthly after 2007 using a Roche AmpliPrep/COBAS Amplicor assay (Roche Molecular Systems, Pleasanton, CA, USA). The lower limit of detection was 400 copies/mL in routine specimens and 40 copies/mL in retrospectively assayed stored specimens. Cumulative time with unsuppressed HIV RNA viral load was calculated with the assumption that, following an undetectable HIV RNA viral load, viral load remained undetectable until the next viral load test.

Cytomegalovirus PCR viral load was measured using the Roche COBAS AmpliPrep/COBAS TaqMan cytomegalovirus PCR (Roche Molecular Diagnostics, Branchburg, NJ,

Table 1: Demographics, immunological status, and anthropometry of human immunodeficiency virus encephalopathy (HIVE) cases vs non-cases

	HIVE cases, *n*=20	Non-cases, *n*=113	*p*
Sex (male)	8 (40%)	51 (45%)	0.67
Received nevirapine at birth	17 (85%)	106 (94%)	0.17
Received zidovudine at birth	18 (90%)	104 (92%)	0.76
Birthweight (kg)	2.8 (2.6–3.0)	3.0 (2.7–3.3)	0.03
Mode of delivery			
Normal Vertex delivery	17 (85%)	79 (70%)	—
Caesarean section	3 (15%)	15 (13%)	
Unknown	0	19 (17%)	
Baseline $\log_{10}$ HIV RNA viral load (copies/mL)	5.9 (5.8–5.9)	5.9 (5.6–5.9)	0.58
Cytomegalovirus detectable in pre-enrolment plasma (specimens available for *n*=118 participants: 18 cases, 100 non-cases)	7/18 (39%)	25/100 (25%)	0.22
Nadir CD4 (cells/mm^3)	688 (446–912)	708 (532–998)	0.15
Nadir CD4%	21% (15–25%)	21% (16–26%)	0.55
Cumulative months with low CD4 or CD4%[a]	5 (0–14)	2 (0–8)	0.59
CHER arm allocation (ART-Def; ART-40W; ART-96W)	5; 10; 5	33; 38; 42	0.35
Median age at onset of HIVE (mo)	31 (19–37)	n/a	
Age at first ART initiation (wks)	9 (8–10)	9 (7–12)	0.76
Cumulative time on ART (y)	5 (5–5)	5 (3–5)	0.47
Duration interrupted ART (mo) (9/20 cases [<50%] had interrupted ART)	0 (0–8)	2 (0–8)	0.45
Cumulative time with unsuppressed HIV RNA PCR viral load (mo)	20 (17–36)	24 (11–34)	0.96
Total time in follow-up (y)	6 (6–7)	6 (3–7)	0.11
Virally suppressed at last recorded visit	17 (85%)	78 (69%)	0.14
Nadir head circumference-for-age z-score	−0.9 (−1.7 to −0.2)	−0.5 (−1.3 to 0.2)	0.80
Weight-for-age z-score			
At trial entry	−1.0 (−1.9 to −0.7)	−0.9 (−1.8 to 0.0)	0.45
Nadir	−2.1 (−3.1 to −1.6)	−1.6 (−2.5 to −0.7)	0.32
Height-for-age z-score			
At trial entry	−1.9 (−2.8 to −1.3)	−1.4 (−2.3 to −0.6)	0.59
Nadir	−2.7 (−3.2 to −2.2)	−1.8 (−2.6 to −1.4)	0.95
Weight-for-height z-score			
At trial entry	0.5 (−0.1 to 1.2)	0.5 (−0.3 to 1.2)	0.40
Nadir	−1.2 (−2.7 to −0.4)	−0.6 (−1.8 to 0.1)	0.23
Body mass index-for-age z-score			
At trial entry	−0.4 (−1.0 to 0.3)	−0.2 (−1.1 to 0.6)	0.72
Nadir	−0.7 (−1.8 to −0.2)	−0.8 (−1.7 to −0.1)	0.17
Zenith	2.1 (1.2–2.4)	1.7 (0.9–2.7)	0.36

All variables are given as median (interquartile range) or *n* (%) unless stated otherwise. Time measurements (y/mo/wks) are rounded to the nearest whole number. [a]As defined in text. CHER, Children with HIV Early AntiRetroviral treatment; ART, antiretroviral therapy; ART-Def, ART was deferred; PCR, polymerase chain reaction.

USA).[18] Children with positive cytomegalovirus DNA PCR tests but unmeasurable viral loads were assumed to have a cytomegalovirus viral load equal to the lower limit of detection (150 copies/mL).

Lymphocyte subsets were measured every 3 to 6 months. Cumulative time with low CD4 T cell absolute count or CD4% was defined as CD4 <1000 cells/mm^3 or CD4% <25% for <12 months of age; CD4 <750 cells/mm^3 or CD4% <20% for 12 to 35 months of age; CD4 <500 cells/mm^3 or CD4% <20% for greater than 36 months of age.

Statistical analysis

Frequencies were determined for categorical variables whereas medians and interquartile ranges (IQRs) were calculated for continuous measures. Categorical measures stratified by status of HIVE were compared by Fisher's exact test; continuous measures were compared by the *t*-test for normally distributed data and the Mann–Whitney *U* test for skewed data. The progression of developmental deterioration and UMN signs are presented graphically covering the periods before and after nadir measures. All tests of hypotheses were conducted at the 0.05 level of significance. All statistical analysis was done using Stata Statistical software release 15 (StataCorp LLC, College Station, TX, USA).

RESULTS

In 133 Cape Town CHER participants who were followed until a median age (IQR) of 6 years 2 months (4y 8mo–6y 7mo), ART was initiated at a median age (IQR) of 9 (7–12) weeks. Undetectable HIV RNA viral load was attained at a median (IQR) of 6 (6–19) months later. HIVE was recognized in 20 out of 133 (15%) participants. The origin of cases is depicted in Figure S2. Cases are compared with non-cases in Table 1. For HIVE, the median (IQR) age when neurological deterioration was first noticed was 19 (16–22) months. At this time 16 out of 20 cases were on ART, of whom nine had undetectable viral load for a median (IQR) of 12 (9–14) months before onset. There were

seven on ART with a detectable viral load greater than 1000 copies/mL. Of the four cases not on ART, three were in interruption phase (all ART-40W) and one was not yet on ART (Table 2).

UMN signs were present in 18 out of 20, of whom 12 recovered fully over a median (IQR) of 3 years 11 months (2y 11mo–5y), one had partial recovery and four had ongoing spastic diparesis (Table 3). Gross motor delay was present in 19 out of 20, of whom 14 recovered fully over a median (IQR) of 1 year 8 months (1y 1mo–2y 7mo), and one was lost to follow-up. Language delay was present in 12 out of 20, of whom 11 recovered fully over a median (IQR) of 1 year 11 months (1y 5mo–2y 2mo). Impaired brain growth was present in 15 out of 20, of whom five recovered over a median (IQR) of 2 years (1y7mo–2y 7mo). Progression of neurological deterioration and recovery is presented in Table 3. Progression of UMN signs is shown in Figure 1 and the gross motor quotient in Figure 2 for HIVE cases. Figure S3 (online supporting information) presents the pattern of language quotient recovery in those affected. Four cases included were previously described.[11] Of 484 developmental domain assessments, 73 (15%) were plotted retrospectively. Most of these (50 out of 73, 68%) were gross motor milestone assessments.

ART regimens were not altered when neurological deterioration was noted as there were no alternatives. By the end of follow-up, five cases had switched from trial-prescribed ART (zidovudine, lamivudine, and lopinavir/ritonavir): three switched to didanosine, abacavir, and efavirenz or nevirapine owing to assumed virological failure following poor adherence; all later switched back to zidovudine, lamivudine, and lopinavir/ritonavir after viral resistance testing and achieving an undetectable viral load after adherence intervention; all three improved neurologically after resuming first-line ART and achieving viral suppression. One child was switched from zidovudine to stavudine owing to anaemia; he continued to deteriorate neurologically for 10 months after the switch. First neurological improvement was noted 17 months after the switch. One was switched to abacavir owing to asymptomatic hyperlactataemia discovered after full resolution of gross motor abnormalities; the mild hyperlactatemia subsequently resolved.

Among the 16 cases with impaired brain growth, HCZ did not return to premorbid levels, with only five recovering to within 1 SD of their premorbid HCZ. Median (IQR) HCZ at 5 years of age was −1.1 (−1.0 to −1.4) SD below their baseline HCZ; however, this did not correspond with neurological recovery. Radiological progression of the six cases with generalized brain atrophy could not be determined as follow-up imaging was not routinely performed. Magnetic resonance imaging was performed on 17 out of 20 cases to exclude alternative diagnoses.

Cytomegalovirus was detectable in seven out of 18 cases with an available pre-enrolment plasma specimen, of whom only three had a cytomegalovirus viral load above 150 copies/mL. There was no difference in cytomegalovirus viral load between cases and non-cases (p=0.64) or in the proportion with detectable cytomegalovirus between cases and non-cases (p=0.22). One child with HIVE had cytomegalovirus pneumonia at 2 months of age with a good response to ganciclovir. Birthweight was marginally lower in cases than non-cases (Table 1).

Table 2: Antiretroviral therapy (ART) treatment status at onset of human immunodeficiency virus encephalopathy (HIVE)

	HIVE cases, n=20
ART-Def treatment status at onset of HIVE	
Started ART	4
Not yet started ART	1
ART-40W treatment status at onset of HIVE	
On ART not yet interrupted	0
On uninterrupted ART (site decision to maintain ART)	3
In protocol-defined interruption phase	3
Previously interrupted and back on ART for protocol reasons	4
ART-96W treatment status at onset of HIVE	
On ART not yet interrupted	2
On uninterrupted ART (site decision to maintain ART)	3
In protocol-defined interruption phase	0
Previously interrupted and back on ART for protocol reasons	0

ART-Def, ART was deferred.

DISCUSSION

Unlike previous descriptions of HIVE in the era of limited ART availability, we observed progressive deterioration over 6 to 12 months, followed by gradual recovery as the most common pattern seen. This is in contrast to partial or no recovery commonly seen in the early ART era. Gross motor and language development recovered over 1 to 2 years and UMN signs resolved over 2.5 to 4 years, despite unchanged ART in 16 cases; however, three had persistent spastic diplegia. We previously reported this recovery pattern in four CHER participants who developed stigmata of HIVE which then resolved on continuous ART.[11] Interestingly, 70% did not catch up with head growth and persisted on a lower growth centile.

This study shows that the natural progression of HIVE after early ART tends towards recovery. This is important for interpreting intervention studies to improve HIVE outcomes. A similar pattern was also described for lower limb muscle tone by Mann et al. when reviewing cases referred for a HIVE natural history study by reviewing medical records. Over time, 13 out of 19 children identified from a HIVE database had resolved by 2 years after the initial visit. All had initiated ART under old guidelines and before early initiation was routine.[19] In our study, neither age at ART initiation nor cumulative time with unsuppressed HIV RNA PCR viral load was significantly different in HIVE cases versus non-cases. The proportion with suppressed HIV RNA viral load at the last recorded visit was marginally lower in cases versus non-cases, which may

Table 3: Neurological deterioration and recovery among cases of human immunodeficiency virus encephalopathy (n=20)[a]

	Subgroup	Affected, n	Full recovery	Partial recovery	Minimal or no recovery	Lost to follow-up	No data
Upper motor neuron signs	Not on ART	4	3	0	1	0	0
	ART, viral load>1000c/mL	6	2	1	3	0	0
	Viral load<400c/mL	8	7	0	0	1	0
Gross motor	Not on ART	3	2	1	0	0	0
	ART, viral load>1000c/mL	7	4	3	0	0	0
	Viral load<400 c/mL	9	8	0	0	1	0
Language	Not on ART	2	2	0	0	0	0
	ART, viral load >1000c/mL	6	5	1	0	0	0
	Viral load <400c/mL	4	4	0	0	0	0
Personal social	Not on ART	1	1	0	0	0	1
	ART, viral load >1000c/mL	3	3	0	0	0	1
	Viral load <400c/mL	0	0	0	0	0	0
Fine motor	Not on ART	0	0	0	0	0	1
	ART, viral load >1000c/mL	1	1	0	0	0	1
	Viral load <400c/mL	0	0	0	0	0	0
Impaired brain growth	Not on ART (2 had imaging)	3 (1 cortical atrophy)	2 (1 cortical atrophy)	0	1 (0 cortical atrophy)	0	0
	ART, viral load >1000c/mL (3 had imaging)	4 (0 cortical atrophy)	2 (0 cortical atrophy)	0	2 (0 cortical atrophy)	0	0
	Viral load <400c/mL (all had imaging)	9 (4 cortical atrophy)	1 (1 cortical atrophy)	0	8 (3 cortical atrophy)	0	0

[a]Four cases not on ART at onset of neurological deterioration; seven cases on ART at onset but viral load >1000 copies/mL; nine cases on ART at onset with viral load <400 copies/mL. No participants had viral load between 400 and 1000 copies/mL at onset. ART, antiretroviral therapy.

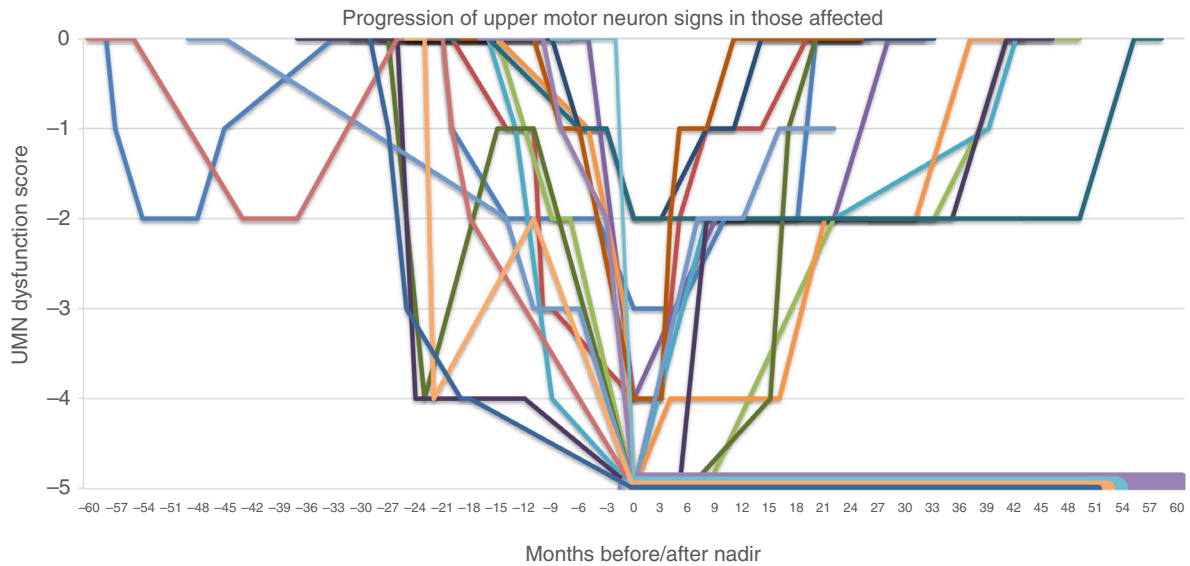

Figure 1: Progression of upper motor neuron (UMN) signs in those affected (n=18). [a]Upper motor neuron abnormalities were scored as follows: 0, normal; −1, brisk reflexes; −2, extremely brisk or spreading reflexes or increased tone; −3, crossed adductor response; −4, clonus (at least three beats) or Babinski/up-going plantar response; −5, gait disturbance related to UMN dysfunction. Each line represents an individual case. [Colour figure can be viewed at wileyonlinelibrary.com]

be related to the longer cumulative time on ART in cases because of earlier ART re-initiation after HIVE diagnosis.

The pathogenesis of HIVE in virally suppressed children remains poorly understood. Immunopathological processes may be governed by viral and host factors.[20] HIV crosses

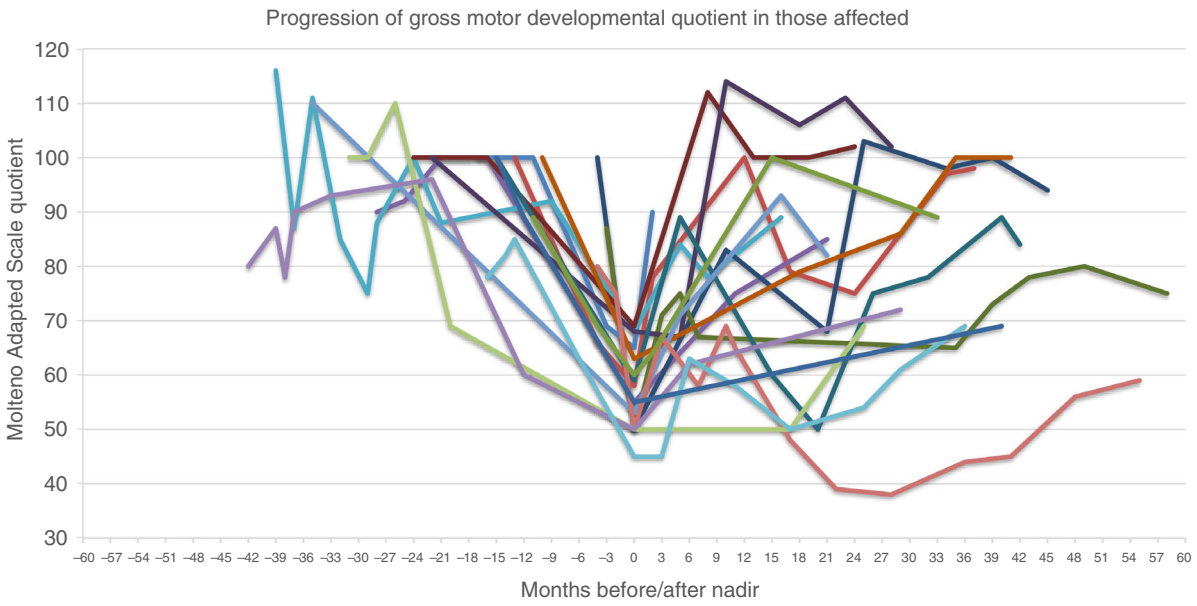

Figure 2: Progression of gross motor developmental quotient on the Molteno Adapted Scale in those affected (n=19). For those with two episodes of deterioration, the nadir of the first episode was used as time 0. [Colour figure can be viewed at wileyonlinelibrary.com]

the blood–brain barrier transported by infected monocytes/macrophages and CD4+ T-lymphocytes. Astrocytes are then infected and a host inflammatory response leads to a neurotoxic cascade that may damage the inflammation-sensitive myelin sheath. Although this may occur because of infectious virus, it may also occur in its absence. A correlation has been found between the severity of cognitive impairment and the degree of tumour necrosis factor elevation within astrocytes and microglial cells and the number of activated microglia cells in brain tissue,[21] but not with the number of HIV-infected cells or the amount of HIV in brain tissue. Evidence suggests that the pathogenesis of HIVE in children on suppressive ART may be mediated by activated microglial cells and astrocytes over-producing inflammatory cytokines in response to persisting viral proteins, particularly gp120.[2,22] Conceivably, therefore, white matter demyelination that occurs despite virological suppression may be related to disordered immune regulatory mechanisms. This may plausibly be mediated by cytokine release together with antibodies against myelin oligodendrocyte glycoprotein. Myelin oligodendrocyte glycoprotein antibodies are implicated in causing neuroinflammation and demyelination in HIV-associated neurological disorder, even after viral clearance.[23] This is consistent with the white matter hyperintensities seen on T2/FLAIR (fluid-attenuated inversion recovery) magnetic resonance imaging in participants from the CHER trial[24] (nine from the current study were included). Inflammation may have resolved over time as exposure to HIV antigens decreased.

We postulate that, in children treated early, the initial brain infection is relatively well controlled, whereas later there is a quantitative and/or qualitative breakdown of immune regulation in the central nervous system (CNS). Chronic intrathecal immune activation in HIV+ patients has been reported, even after several years of ART.[25] Markers of intrathecal inflammation include myelin oligodentrocyte glycoprotein antibodies, myelin basic protein, neopterin, β-2-microglobulin, oligoclonal bands, and immunoglobulin G index. Notably, ART intensification has no effect on intrathecal immunoactivation, a finding that argues against ongoing viral replication in the CNS. This finding raises the question of whether immunomodulatory therapy (at the time of neurological deterioration) may be of benefit; however, that spontaneous recovery occurred in most study participants (albeit at a slow rate) argues against such a need. Another possible contributing factor, that of ART neurotoxicity, is unlikely as the children improved on an unchanged regimen. Even though protease inhibitors disrupt astrocyte function at therapeutic concentrations in mouse models, our participants resolved on unchanged lopinavir/ritonavir.[26] We hypothesize that intrathecal inflammation, most likely in response to residual HIV proteins, contributes to HIVE and that resolution occurs after inflammation has resolved.

The most prevalent HIV-related neurological impairments in the study participants were impaired brain growth and pyramidal tract dysfunction (UMN signs), which are consistent with cerebral white matter (myelin) involvement, namely HIV-related leukoencephalopathy. A diffusion tensor imaging study at our site showed predominant involvement of corticospinal tracts in CHER HIV+ children at 5 years of age compared with uninfected individuals[27] (only 5 of the 17 who had neuroimaging in the current study were included in the diffusion tensor imaging study).

HIV-associated oligodentrocyte/myelin injury has been observed clinically from neuroimaging studies and brain biopsies.[28,29] Myelin injury is also associated with blood–brain barrier deregulation. The normalization of brain growth and disappearance of UMN signs in most children is probably related to cerebral white matter recovery of myelin maintenance (remyelination) during developmental maturation. Mann et al.[19] and our group[30] demonstrated locomotor recovery with time. Whatever the cause, the extent of recovery in our cases suggests that extensive neuronal loss does not occur and, despite visible demyelination, the integrity of neuronal connections is preserved. Further studies are warranted to explore this possibility. The sensitivity of standard CNS imaging for mild demyelination is poor, possibly highlighting the need for functional white matter imaging modalities (magnetic resonance spectroscopy and diffusion tensor imaging) in combination with inflammatory markers to unravel this disease process.

The CHER trial was not a neurodevelopmental trial and focussed on clinical endpoints including mortality. The initial clinical signs may have been subtle in young infants and may not have met objective criteria for a study endpoint. Most participants remained in active follow-up beyond the trial close-out (September 2011), providing additional data on progression of early neurological abnormalities detected during the trial. Unfortunately, we did not have prenatal data including information about maternal viral loads and health status. We also could not determine whether HIV infection was intra-uterine or perinatal, which may have contributed to a vulnerable CNS in the developing child.

We used stringent diagnostic criteria for HIVE, requiring two out of three signs (where Centers for Disease Control and Prevention criteria only require one), which excluded milder forms of neurocognitive disturbance. The Molteno Adapted Scale is insufficiently sensitive to detect subtle abnormalities and it is possible that a more detailed developmental assessment tool may have identified additional cases. As we did not measure cerebrospinal fluid viral load, the possibility of low-level cerebrospinal fluid viraemia (<40 copies/mL) could not be excluded. Only structural imaging was performed and, while radiological assessments of brain atrophy were performed by a single neuroradiologist, final assessments of atrophy were subjective. It is possible that volumetric measurements may have identified additional cases.

Whether high viral load or treatment interruption affects the progression of HIVE may be another avenue for further study.

We conclude that HIVE may occur despite early ART initiation and virological suppression and then resolve on unchanged ART, most likely as intrathecal inflammation subsides.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Outline of the CHER trial.

Figure S2: Origin of human immunodeficiency virus encephalopathy cases.

Figure S3: Progression of language developmental quotient on the Molteno Adapted Scale in those affected.

Appendix S1: Sources of support.

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