# PROFILE OF SPECIFIC NEUROLOGICAL AND NEUROBEHAVIOURAL PROBLEMS IN CHILDREN WITH HIV-1 INFECTION ATTENDING DEDICATED CLINICS

**Student Name**: Rajeshree Govender
**Student Number**: GVNRAJ003

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**Supervisor: Professor Jo Wilmshurst**
**Head of Department of Paediatric Neurology**
**School of Child and Adolescent Health**
**University of Cape Town**

## DECLARATION

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Rajeshree Govender (MBChB, DcH, FCP, Certificate in Paediatric Neurology)

Departments of Paediatric Neurology, Red Cross Children's Hospital, School of Child and Adolescent Health, University of Cape Town, South Africa

**Corresponding Author: Dr Rajeshree Govender, Department of Paediatric Neurology, 5TH floor ICH, School of Child and Adolescent Health, Red Cross Children's Hospital, Rondebosch, Cape Town, 7700 SOUTH AFRICA**

**E-mail: govenderr2@ukzn.ac.za**

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**Abstract**

Aim: Neurological involvement related to HIV-1 infection is well described in the paediatric population and causes significant morbidity and mortality. This study aimed to describe specific neurological and neurobehavioural complications in this population.

Method: Children infected with HIV-1 attending infectious diseases clinics were recruited for general and neurological assessments, developmental history screening and categorization of behavioural phenotype using the Aberrant Behaviour Checklist (ABC).

Results: Eighty patients were assessed (males-44/80: females- 36/80) (median age 5 years 1 month; range: 3 months - 12 yrs). Eighteen patients (23%) were not on antiretroviral (ARV) therapy at the time of testing. The Centre for Disease Control (CDC) immune categories of the patients at the time of assessment were: Category 1- n=6/80, Category 2- n=15/80 and Category 3- n=59/80. Thirty-three percent had a history of chronic lung disease, 10% had a history of an opportunistic central nervous system infection and 12.5% had epilepsy.

Anthropometric measurements identified that 19% of the patients were microcephalic, 17% of the patients were <60% of their expected weight, 49% were 60-80% of expected weight and 45% were stunted. On neurological assessment 41% of the patients had global pyramidal tract signs, 7% had a hemiparesis, 5% had peripheral neuropathy, 16% had visual impairment, and 6% were hearing impaired. Of those who were screened for developmental deficits (patients <6years of age) 66% had gross motor delay, 75% had fine motor delay, 70% had language delay and 73% had cognitive delay. Forty one percent had HIV Encephalopathy, 81% of whom a CD4 count <15% and 48% were < 1year old.
On the aberrant behaviour checklist (ABC) scale 24/80 patients had features of hyperactivity and 22/80 patients scored in the mild-moderate range on the lethargy / social withdrawal sub-scale reflecting a correlation with the affective and adjustment disorders.

Conclusion: Diverse neurological and neurobehavioural deficits are common in children with HIV-1 infection especially those with CD4 <15%, not on ARVs, with growth impairment and <1yr of age. This study demonstrated the extent and spectrum of neurobehavioural and neurological complications in a defined HIV population. It stresses the need for early initiation of ARVs in the planning for future regimens and guidelines.

**Key for Abbreviations**

ABC Scale- Aberrant Behaviour Checklist Scale
AIDS- Acquired Immunodeficiency Syndrome
ART- Antiretroviral Therapy
CDC- Centre for Disease Control
CMV- Cytomegalovirus
CNS- Central Nervous System
CT scan- Computerised Tomography scan
DdI- Didanosine
HAART- Highly active antiretroviral therapy
HAD- HIV-Associated Dementia
HIV-1 – Human Immunodeficiency Virus 1
HIVE- HIV encephalopathy
MRI-Magnetic Resonance Imaging
NCS- Nerve conduction studies
PCR-Polymerase Chain Reaction
PI- Protease Inhibitor
PHE- Progressive HIV Encephalopathy
TB- Tuberculosis
TBM- Tuberculous Meningitis
UWFA- Under weight for age
WHO- World Health Organisation

## Introduction

At the end of 2007 an estimated 2.1 million children were infected with human immunodeficiency virus (HIV), 1.8 million (85.7%) of whom lived in sub-Saharan Africa and 280,000 (13.3%) in South Africa. At the end of 2008 275,000 children were on antiretroviral therapy (ART) in low-and middle-income countries. The number on ART in South Africa was 94,000, representing a coverage rate of 61% of all children in need of ART.[1] Global commitments to improve access to antiretroviral (ART) therapy, education campaigns and prevention of mother to child transmission of HIV has reduced the rates of paediatric HIV transmission in the developed world. However the epidemic continues to escalate in sub-Saharan Africa and parts of Asia where there is limited access to ART.

HIV-1 invades the CNS early in the course of infection. [2]
The postulated pathways by which the virus enters CNS parenchymal tissue are: [3]

1. HIV may be carried into the brain by infected macrophages-monocytes and CD4+ T lymphocytes (the “Trojan horse effect”);
2. Cell-free virus may pass from the vascular compartment into brain tissue between cerebral microvascular endothelial cells;
3. Following direct HIV infection of the endothelial cells of the blood/brain barrier, newly formed HIV viral particles may be released into the cerebral compartment;
4. Lipopolysaccharides have been implicated as markers of microbial gut translocation which lead to chronic immune activation and HIV progression.[4] Plasma endotoxins, derived from Gram-negative bacteria, undergo translocation from the gut through a “Leaky” gut barrier. These endotoxins are thought to cause immune activation in HIV infection. Elevated lipopolysaccharide levels are implicated in induction of monocyte activation and trafficking into the brain as

part of the pathogenesis of HIV- Associated Dementia (HAD).[5]

Once within the nervous system the virus infects other cell lines which include perivascular macrophages, astrocytes and microglia.[6] This inflammatory response induces apoptotic pathways causing neuronal loss. Apoptosis may be activated by viral glycoproteins gp120, tat, nef, vpr and gp41, or host derived inflammatory cytokines, free radicals and excitatory amino acids. [7]

Neurological involvement related to HIV-1 infection is well described in the paediatric population and causes significant morbidity and mortality .[8] At least 50% of HIV-1 infected children show neurological symptoms and signs during the course of the disease.[9] Involvement of the central nervous system (CNS) may be the initial manifestation of AIDS in up to 18% of children and may be the only manifestations of AIDS in 26% of these children.[10, 11]

Neurological manifestations of AIDS may be due to:

a. Direct neuronal infection by the virus and the cytokine mediated effects of the virus that lead to neurotoxicity. Perinatally infected children show early signs of HIV-1 encephalopathy. This may be because the virus influences the neuro-ontogenetic processes during early brain development.[2] Active CNS viral replication, which may co-incide with systemic HIV disease, results in progressive HIV encephalopathy (PHE). Neurological signs can occur before immune suppression.[12]

b. Immune dysregulation results in the child becoming vulnerable to other complications and sequelae including opportunistic infections, malignancies and cerebrovascular disease.

c. The side effects from drugs.

d. The effects of socio-economic problems like malnutrition, being AIDS orphans and environmental deprivation.

The central nervous system may also be a sequestered reservoir of infection.

The spectrum of neurological manifestations of the disease is diverse. Encephalopathy is the commonest manifestation and was reported as between 30-50% for progressive encephalopathy and up to 90% for static encephalopathy in the pre-treatment era. [13, 14]
Other complications include developmental delay (42%) [13], opportunistic infections (33%), [13] strokes (1.3-2.6%), [15] seizures (6-13%), [12] CNS lymphomas (2-6%)[15] and peripheral nervous system disease.[13] Behavioural problems and attention deficit hyperactivity disorder [12] are also reported to be frequent amongst these children. Anxiety and conversion disorders are described following stressors such as children's loss or separation from attachment figures.[16]

There is limited data on the prevalence of specific neurological complications in children with HIV-1 in Africa. A study of Rwandan children between 6 months and 2 years of age found that 40% of HIV-infected children had an abnormal neurodevelopmental examination at 18 months compared with only 5% of HIV-exposed uninfected children.[17] Van Rie et al[18] documented moderate to severe delay in mental, motor, and language development in the majority of HIV-infected children in Kinshasa. Another study in the Democratic Republic of Congo documented developmental impairment in both asymptomatic HIV-infected children and HIV-exposed, uninfected children supporting the theory that an environmental factor may be contributing to the developmental delay.[19] Abubakar et al in their systematic review of 6 studies in sub-Saharan Africa reported severe motor impairment and moderate cognitive impairment at 18 months of age in HIV-1 infected children. [20] Smith et al showed a significant rate of early neurocognitive, language and motor developmental disabilities in a group of HIV-infected South African children.[21]

The HIV-1 c subtype is the predominant virus causing infection in southern Africa as well as globally;[22] hence the neurological disorders described herein reflect those syndromes caused by HIV-1 subtype C.

**Aim**

This study aimed to describe the specific neurological, neurodevelopmental and behavioural complications, in a cohort of HIV positive children attending dedicated infectious disease clinics.

**Objective**

The profile obtained will identify problem areas in the current treatment regimens and will provide guidelines for the design of future holistic treatment protocols; i.e. should we start HAART earlier in children with HIV encephalopathy and should guidelines be formulated for the social, emotional and educational management of these children? The study will provide the basis for future prospective studies in the areas of neurodevelopment and psychosocial issues and will contribute towards the development of guidelines for referral to specialist centres to assist primary health care physicians.

**Methods**

Children between 1 month and 12 years of age were prospectively recruited from Infectious Disease Clinics at the Red Cross Children's Hospital and Groote Schuur Hospital (April 2006 - January 2007). Of the 30-35 patients attending each clinic, the first 6-8 patients per clinic were recruited for assessment. To reduce bias the investigator was blinded to the contents of the folders prior to recruiting the patients.

Patients underwent a full general and neurological examination by the principle investigator (a child neurologist). Patients were referred for specialist investigations as clinically indicated.

The Red Cross Children's Hospital is a paediatric tertiary centre and a referral base for patients throughout the Western Cape of South Africa. The patients seen at the Kidzpositive clinic at Groote Schuur Hospital are from local communities.

**Demographic Collation**

Group demographics and specific relevant information of children attending the Infectious Diseases Clinic at Red Cross Children's Hospital and the Kidzpositive clinic at Groote Schuur Hospital were prospectively recorded to document data including age, sex, whether or not they were on HAART, date of commencement, and regimen, CD4 counts and viral loads at diagnosis, at start of HAART and the most recent viral load. Social demographics including family structure, caregiver, congruence of home and culture, language and school details were documented. Information was recorded in Appendix 1.

Clinical assessment included developmental screening, growth parameters and neurological examination. Patients under 6 years of age were classified as either developmentally delayed or not, compared to age appropriate developmental milestones modified from the Denver II Developmental Screening Test.[23] (See Appendix 2) The Denver ll Developmental Screening Test is a screening tool to identify children (birth to 6 years) at risk for developmental problems from those who are developmentally normal. [23] This was simplified as a practical tool to identify those children who had obvious deficits. HIVE was defined as at least 1 of the following findings present for at least 2 months (with no concurrent illness to explain the findings): a) failure to attain/loss of developmental milestones, verified by standard developmental scale; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurement or neuro-imaging; c) acquired symmetric motor deficit affecting a child >1 month of age.[24] The caregiver completed the Aberrant Behaviour Checklist (ABC). (Appendix 3) The Aberrant Behaviour Checklist (ABC) [25] is a rating scale that was developed primarily to measure the effects of pharmacological intervention in individuals living in residential facilities but is widely used to monitor behaviour problems in other populations. It is a third-party informant questionnaire consisting of five subscales encompassing 58 items of observable, undesirable behaviours. It

has been validated and recommended for children and adolescents with dual diagnosis .[26] It relies on clinical observations of behaviour without regard for the underlying aetiology or function of the observed behaviour.

Interpreters were used for non-English speaking and illiterate care-givers and patients.

Children were referred for audiology, neurophysiology, neuro-imaging, formal developmental assessment and or psychiatric assessment as indicated by the clinical needs of the child. Further investigations including electroencephalogram, nerve conduction studies and neuro-imaging were directed by the clinical needs of the child.

**Ethics/consent**

Written consent (Appendix 4) was obtained from the legal guardian/parent to access the medical folder and to perform the examinations. Assent from the children was obtained where it was age appropriate. This was dictated by the child's cognitive level as interpreted from the developmental history and observation. This study followed the basic needs of all children with HIV-1 and the interventions are in line with standard practice. At the time of the study staffing levels precluded an individual dedicated to managing these patients with neurological complications. Following the study, a Neuro-HIV clinic has been established at Red Cross Children's Hospital.

Ethical approval was obtained from the University of Cape Town, Faculty of Health Sciences Research Ethics Committee (Ethics approval number: 059/2006).



**Statistical Analysis**

The data was entered into a Microsoft Excel spreadsheet and analysed using standard statistical methods in SPSS Version 10.0, SPSS Inc., Chicago USA. Pearson's correlation coefficient was used to correlate variables. A p-value of $<0.05$ was regarded as statistically significant.

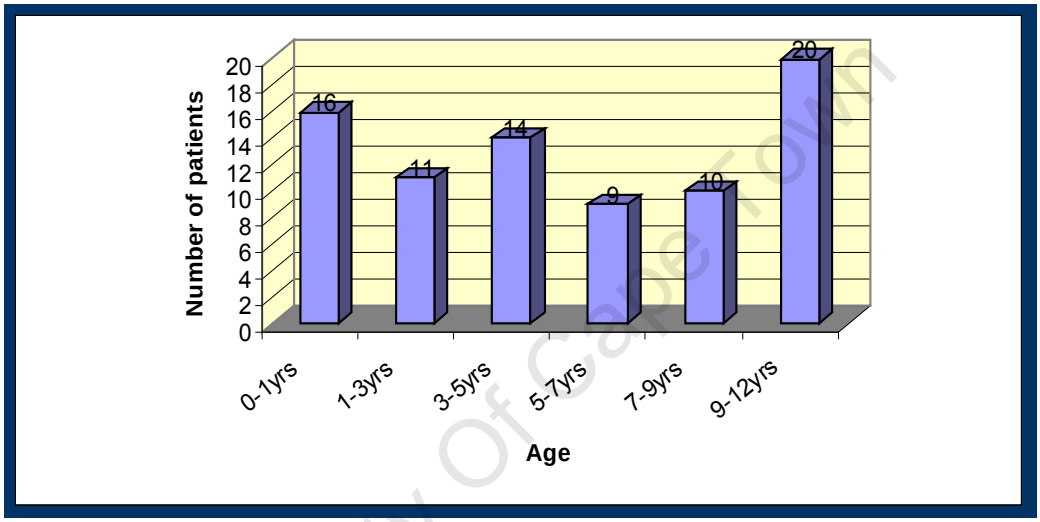
**Results**

Eighty patients were assessed (male n=44: female n=36) (African indigenous ancestry n=62; mixed ancestry n=18). Fifty patients were recruited from Red Cross Hospital and 30 from Groote Schuur Hospital. The two populations were clinically similar. Their ages ranged from 3 months to 12 years (mean: 5 years 3 months of age, median: 5 years 1 month of age).

See Figure 1.

**Figure 1**

Age Distribution of participants in Study






The parent was the primary care-giver for 50% of patients (40/80), another relative was the care-giver for 40% (32/80) and 10% of children (8/80) were institutionalised. Thirty patients were orphans. Most patients (75/80) resided in urban/peri-urban areas. Forty percent of school eligible children (18/45) were in an age-inappropriate lower grade.

Prior health complications (See Figure 2) consisted of chronic lung disease (29/80), disseminated *Cytomegalovirus* (CMV) infection (5/80) and central nervous system opportunistic infections (12/80) (Tuberculous meningitis 5/80, Pneumococcal meningitis 2/80, CMV meningoencephalitis 4/80 and Progressive Multifocal Leukoencephalopathy caused by JC Virus in 1 patient). Three patients with confirmed attention deficit hyperactivity disorder were receiving methylphenidate at the time of the assessment.

**Figure 2**

Past medical history

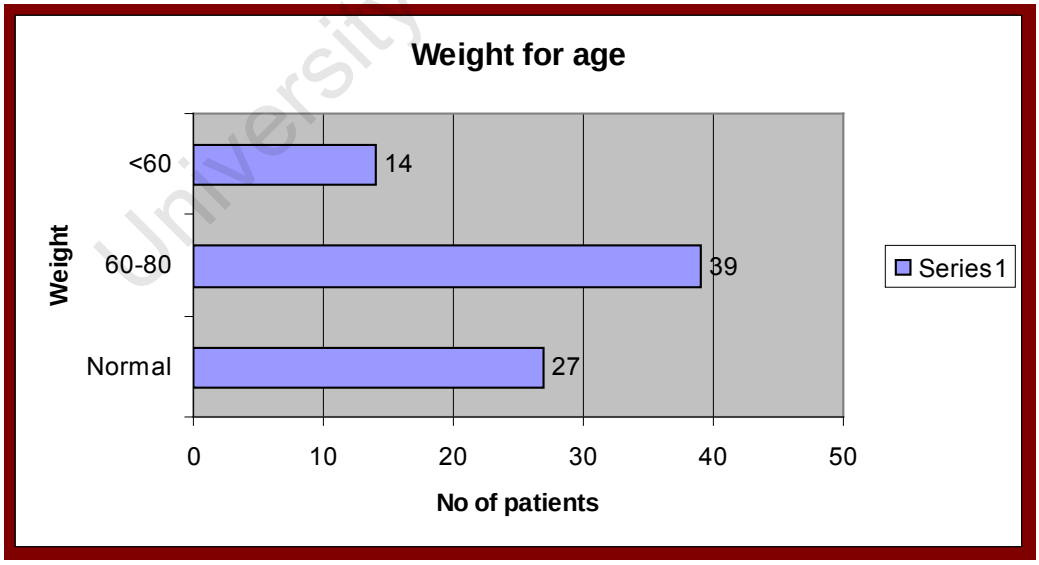
| Condition | No. of patients |
|---|---|
| Chronic Lung disease | 29 |
| *Cytomegalovirus* infection | 5 |
| CNS opportunistic infections | 12 |
| Attention Deficit Hyperactivity Disorder on therapy | 3 |

**Anthropometry**

On anthropometric assessment, 27 children had a normal weight for age, 39 children were between 60-80% of expected weight for age (under weight for age) and 14 patients were less than 60% of expected weight for age (marasmic). See Figure 3

**Figure 3**

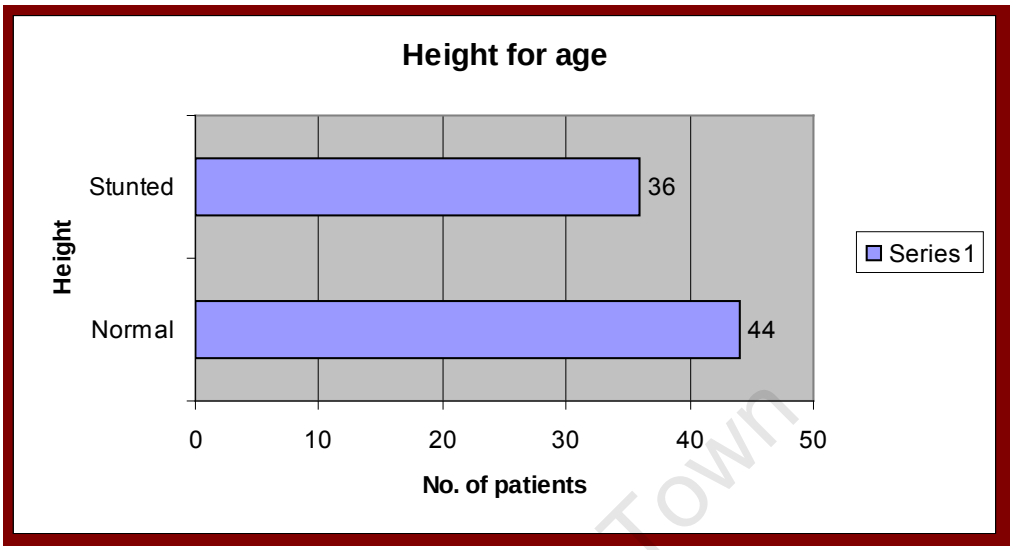
Weight for age




Stunting (height <90% of expected for age) was documented in 36 patients. See Figure 4

**Figure 4**

Height for age




Nineteen percent (15/80) of children were microcephalic.

**Immune Status**

At the time of the assessment 6 patients were in immunological category 1 (CD4 % >25%), 15 patients were in category 2 (CD4 % 15-25%) and 59 patients were in category 3 (CD4 % <15%). See Figure 5

**Figure 5**

Number of participants per immune category at assessment

| | **At testing** |
|---|---|
| **Category 1 CD4 >25%** | 6 (36%) |
| **Category 2 CD4 15-25%** | 15 (22%) |
| **Category 3 CD4 <15%** | 59 (42%) |

**Antiretroviral therapy**

Twenty three percent (18/80) of patients were not on antiretroviral therapy at the time of assessment. Eight patients did not meet current guidelines for initiation of HAART.[27] Ten remaining patients were HAART eligible but 4 had defaulted follow-up, 3 were being initiated for treatment (attending adherence counseling) and 3 had no explanation. Patients on therapy were prescribed different antiretroviral regimens reflecting changes to first line regimens.

**Developmental Screening**

Developmental screening (Figure 6) in patients < 6years of age (n=50) identified delay in gross motor skills in 66% of patients (33/50), fine motor delay in 75% (31/41), language delay in 70% (29/41), social delay in 56% (23/41) and cognitive delay in 73% (25/34) of patients (assessed by the child's ability to count, do mathematical sums, copy figures, relate a story, answering questions). Nine infants were too young to be assessed beyond their gross motor skills and 16 patients were too young to be assessed for cognitive delay. Patients under 18 months of age were not assessed for cognitive functioning.

**Figure 6**

Correlation between Immune Categories, Anthropometry, Therapy and Neurodevelopment (patients <6 years of age: n=50/80)

| | **Immune Category 1 CD4 >25% N=5** | **Category 2 CD4 15-25% N=8** | **Category 3 CD4 <15% N=37** | **Children not treated with HAART n=15** | **UWFA (n=30) +Marasmic (n=14) total n=44** | **Stunted n=30** | **Microcephaly n=15** |
|---|---|---|---|---|---|---|---|
| Gross Motor Delay | 2 | 4 | 27 | 12 (80%)* | 34 (77%)* | 23(76%)* | 14 (93%)* |
| Fine Motor Delay | 1 | 4 | 26 | 8 (53%) | 28 (63%) | 21(70%)* | 11 (73%)* |
| Language Delay | 4 | 4 | 21 | 9 (60%)* | 29 (65%) * | 21(70%)* | 10 (66%)* |
| Social Delay | 1 | 4 | 18 | 7(46%) | 23 (52%) | 18(60%)* | 7 (46%) |
| Cognitive Delay | 2 | 4 | 19 | 10 (67%)* | 31 (70%)* | 20(67%)* | 7/10 (70%)* |

Key / Definitions: * = statistically significant; UWFA = underweight for age, defined as 60-80% of expected weight; Marasmic defined as less than 60% of expected weight for age. Stunted defined as height for age <90% of expected for age.



**Aberrant Behaviour Checklist**

On the aberrant behaviour checklist (ABC) scale 24 patients had features of hyperactivity and 22 patients scored in the mild-moderate range on the lethargy / social withdrawal sub-scale consistent with a correlation with the affective and adjustment disorders. Children < 1year of age could not be assessed for stereotypies and other behaviour problems.

The results of the Aberrant Behaviour Checklist are reflected in Figure 7.

**Figure 7**

Correlation between Immune categories, anthropometry, therapy and behaviour/encephalopathy

| | Immune Category 1 CD4 >25% N=6 | Category 2 CD4 15-25% N=15 | Category 3 CD4 <15% N=59 | Children not treated with HAART n=18 | UWFA (n=39) +Marasmic (n=14) total n=53 | Stunted n=36 | Microcephaly n=15 |
|---|---|---|---|---|---|---|---|
| Irritability | 1 | 2 | 5 | 1(5%) | 6 (11%) | 4(11%) | 1/10(10%) |
| Lethargy | 3 | 5 | 14 | 5(28%) | 6 (11%) | 6(16%) | 1/10(10%) |
| Stereotypies | 1 | 1 | 6 | 3(16%) | 6 (11%) | 5(13%) | 4/11 (36%)* |
| Hyperactivity | 3 | 7 | 14 | 2(11%) | 17 (32%) | 7(19%) | 15 (100%)* |
| Encephalopathy | 2 | 4 | 27* | 11 (61%)* | 33 (62%)* | 24(66%)* | 15 (100%)* |

Key / Definitions: * = statistically significant; UWFA = underweight for age, defined as 60-80% of expected weight; Marasmic defined as less than 60% of expected weight for age. Stunted defined as height for age <90% of expected for age.



**Correlation between neurology, immune categories, therapy and anthropometry**

Encephalopathy was more common in immune category 3 (CD4 <15%) (r value= 0.198)(p=0.026) compared to Immune categories 1(CD4 >25%) and 2 (CD4 15-25%). Developmental and behavioural problems were also more common in immune category 3 than immune categories 1 and 2 but did not reach statistical significance (Figures 6 and 7).

Gross motor delay (r value=0.4) (p=0.002), language delay (r value= 0.62) (p=0.005), cognitive delay (r value=0.359) (p=0.03) assessed on the modified Denver Developmental Screening Tool II and encephalopathy

(r value=0.52) (p=0.027) had a strong correlation with patients not receiving HAART (Figures 6 and 7).

All the patients with HIV encephalopathy were < 80% of expected weight for age. Of the patients assessed on developmental screening (patients <6 years of age), gross motor delay (77%), language delay (65%), and cognitive delay (70%) had a strong correlation with an abnormal weight for age (weight <80% of expected for age). On the ABC scales irritability was documented in 6 patients (r value= 0.143)(p=0.052), lethargy in 6 patients (r value=0.182) (p=0.08), stereotypies in 6 patients (r value=0.224)(p=0.122) and hyperactivity in 17 (r value=0.012)(p=0.420) of the patients with abnormal weight for age. The children who were stunted were statistically more likely to have developmental delay in all fields and HIV encephalopathy.

All patients with microcephaly fulfilled the diagnostic criteria for HIV encephalopathy (Figure 7). In the microcephalic group assessed for developmental delay, there was statistically significant correlation with gross motor delay (14/15) (r value=0.432) (p=0.03), fine motor delay (11/15) (r value=0.08) (p=0.05), language delay (10/15) (r value=0.422)(p=0.027) and cognitive delay (7/10) (r value=1)(p=0.048). Stereotypies were documented in 4 patients with microcephaly (r value=0.212) (p=0.006), and hyperactivity (n=14 mild, n=1 moderate) in all the patients with microcephaly. There was no statistically significant correlation with irritability (r value=0.448) (p=0.107) and lethargy (r value=0.554) (p=0.264) and microcephaly.



**Neurological Deficits**

Neurological Deficits were identified in 60% of the group. (Figure 8)

Abnormal neurological findings were global pyramidal tract deficits in 41% of patients, hemiparesis in 7%, distal muscle weakness in 6%, proximal muscle weakness in 4%, cranial nerve deficits in 4%, visual impairment in 16% and hearing impairment in 6% of the cohort. Forty percent of the children had a normal neurological examination.

**Figure 8**

Neurological Findings on clinical examination

| **Neurological Deficit** | **N=80** |
|---|---|
| Global Pyramidal Tract signs | 33 |
| Hemiparesis | 6 |
| Distal Muscle weakness | 4 |
| Proximal Muscle Weakness | 3 |
| Cranial nerve deficits | 3 |
| Hearing impairment | 5 |
| Visual Impairment | 18 |
| Normal Neurological Examination | 32 |



Forty one percent of patients (33/80) fulfilled the diagnostic criteria for HIV encephalopathy. All of these patients fulfilled criteria B and/or C of the definition of HIVE (see above).Eighty one percent (27/33) of this group had a CD4 count <15%, 48% (16/33) were infants (<1year old) and 18% (6/33) were not receiving antiretroviral agents.

Eleven patients had a history of seizures (idiopathic: n=7, symptomatic: n=4). All the patients with seizures had Computerised Tomography (CT) scans of the brain performed. In the symptomatic group three were secondary to cerebrovascular events and one to CMV meningoencephalitis. Eight children had generalized seizures and three partial focal motor. Eight children underwent electroencephalogram, of whom three were abnormal (focal discharges n=2 and generalised epileptiform discharges n=1). Anticonvulsant therapy consisted of carbamazepine (n=1), sodium valproate (n=9) and lamotrigine (n=1).

Six patients (7.5%) had cerebrovascular events. Co-morbidities included CNS co-infection (2/6) (Pneumococcus n=1, Tuberculous meningitis n=1) and

thrombocytopaenia in one patient. Vasculitic and pro-thrombotic screens were negative in all these patients.

Four patients had pain and distal weakness. Their nerve conduction studies confirmed axonal peripheral neuropathies. Three of these patients were receiving stavudine (d4t) and 1 patient had a positive CMV PCR result.

**Investigations**

Because of financial constraints neuro-imaging was only performed as indicated by the clinical needs of the patient. Computerised tomography scans of the brain performed in 26 patients demonstrated cerebral atrophy in 11 patients, calcification in 5 patients (periventricular n=2 and basal ganglia n=3), cerebral infarcts in 8 children and 2 scans were normal. One patient who had JC Virus isolated on CSF underwent magnetic resonance imaging (MRI) which demonstrated white matter lesions consistent with progressive multifocal leukoencephalopathy (Figure 9). Sixteen patients underwent lumbar punctures. Four of these patients had elevated CSF protein levels (median 0.63g/l normal range- 0.15-0.45g/l) and lymphocytosis identified as part of a diagnostic work-up for developmental delay. Twelve patients underwent CSF examination for suspected opportunistic CNS infections (10 patients had raised CSF protein levels median figure= 0.72g/l, 2 had lymphocytosis and 1 had polymorph predominance). The opportunistic organisms isolated were Streptococcus Pneumonia n=2, JC Virus n=1 and CMV (confirmed via polymerase chain reaction (PCR) positive on CSF) n=4. Tuberculous Meningitis (TBM) was suspected in 4 patients based on additional supporting diagnostic tests (Mantoux skin test, Chest radiograph, and a TB contact history). Based on clinical suspicion of hearing impairment, 5 patients who had Brainstem auditory evoked responses had evidence of sensorineural hearing impairment following meningitis in two and of unknown cause in three.

**Figure 9**

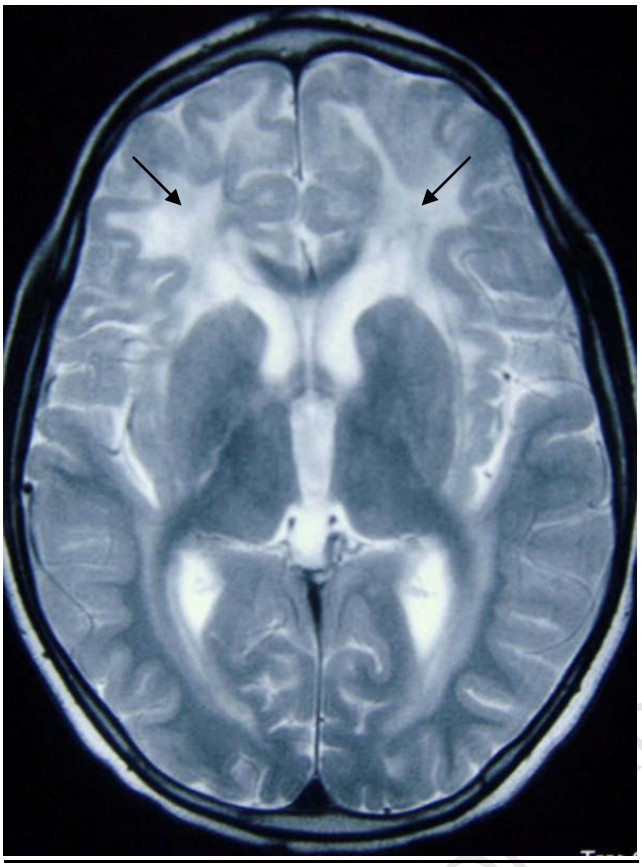


Figure 9: Axial T2 Image of patient with Progressive Multifocal Leukoencephalopathy demonstrating sub-cortical and periventricular white matter hyperintensities of predominantly the frontal lobes



**Discussion**

Sixty percent of our patients had neurological complications. This cohort was recruited from dedicated infectious diseases clinics and was representative of children from specialized and community services in South Africa. This study confirmed that neurological disease in these patients is underestimated and their care not optimized.

**HIV Encephalopathy (HIVE)** is the hallmark of developmental disabilities in HIV infected children. It is categorized as an AIDs defining condition i.e. a clinical (Category C) condition in the Centers for Disease Control and Prevention (CDC) classification system for HIV-1 infection in children less

than 13 years of age.[24] Based on the World Health Organization (WHO) clinical staging system HIVE is listed as a WHO stage 4 disorder.[28] The broad spectrum of clinical manifestations and severity of CNS disease associated with HIVE lead to the development of a classification system for HIVE, currently used at the HIV and AIDS Malignancy Branch of the National Cancer Institute of the National Institute of Health.[29]

HIVE is defined as either progressive (sub-acute or plateau), or static.[29, 30] Progressive HIV encephalopathy (PHE) is the most severe subtype often seen in children who are naïve to antiretroviral therapy. The features of this disorder are impaired brain growth, progressive motor dysfunction and loss or plateau of the acquisition of age-appropriate developmental milestones.[29, 31] The course of the plateau type of encephalopathy is more indolent with either the absence of acquisition of new skills or a slower rate of acquisition of new skills.[31] Children with static encephalopathy tend to have fixed neurodevelopmental deficits with no loss of skills.[31]

Forty one percent of our cohort (n=33/80) fulfilled the diagnostic criteria for HIVE. Forty eight percent of this group were under the age of 1yr, which is comparable with other reports.[32,33] Early onset of neurological symptoms and signs (<1yr) in HIV infected children has a different pathophysiology than those in older children.[34] When children from the French Perinatal Cohort were compared with the French SEROCO adult cohort the cumulative incidence of encephalopathy was higher in children only during the first and second years of life suggesting a pre-natal onset of brain infection in the sub-group of patients with early onset of neurological signs.[34] Children in whom signs of encephalopathy appear in the first year of life have greater severity and shorter survival than those in whom encephalopathy appears later.[35] Reflecting other studies, our patients with more severe immunosuppression had higher rates of encephalopathy.[36]

**Neurodevelopmental deficits** are evident in children with severe HIV encephalopathy. In children with severe HIV encephalopathy the effects are global i.e. in all neurodevelopmental domains. In the less advanced stages of the disease selective functions maybe differentially affected.[37] Speech and language deficits may appear early.[37] Language assessment has been suggested as a useful tool to determine the best time to initiate therapy or to monitor treatment.[38] In our cohort 70% of patients had language delay. This was similar to the rates of gross motor delay (66%), fine motor delay (75%) and cognitive delay (73%) in our patients. Motor impairment is also frequently found in HIV CNS disease.[39] The rate of gross motor deficits in our cohort was higher than described in other studies.[32] Motor deficits are also seen more frequently in children <1yr of age.[32] This is borne out in our cohort where 65% of the patients with gross motor delay were <1yr of age.
Other factors contributing to neurodevelopmental delay in this population include malnutrition, environmental deprivation, co-morbid chronic infections and prolonged hospitalisation.

**Growth failure and malnutrition** are common in HIV-1 infection due to poor caloric intake, chronic diarrhoea, oro-motor inco-ordination, and recurrent infections. [40]
Children with impaired growth may have a low weight for age (60-80% of expected weight for age: underweight for age, <60% expected weight for age: marasmic) or a low height for age (height for age <90% expected for age: stunting).[41] Stunting is an indication of slow skeletal growth and a well established child health indicator of poor socio-economic conditions, chronic or repeated infections as well as chronic malnutrition. [42]

Children who are chronically malnourished exhibit behavioural changes, including irritability, apathy, reduced social responsiveness, anxiety, and attention deficits.[43] In addition, infants and young children who have malnutrition frequently demonstrate delay in achievement of motor skills, delayed mental development, and may have permanent cognitive deficits.

Dose-dependent relationships between impaired growth and poor school performance and decreased intellectual achievement are reported. [44,45] The correlation between malnutrition and developmental delay has also been demonstrated in patients post liver transplantation.[46] Malnutrition has also been well described as a co-factor in HIV disease exacerbating the immunosuppression. [47]

We found a statistically significant correlation between children who were underweight for age (UWFA) or stunted and delayed in all developmental domains, behavioural problems and encephalopathy. Pollack et al found that HIV-1 infected infants with more pronounced growth failure had the most marked cognitive and motor delay.[48] Wiznia et al reported a correlation between poor weight for age and decreased cognitive function.[49] Missmer et al found that stunting was a strong predictor of decreased functional status.[50]

Microcephaly is one of the diagnostic criteria for HIV encephalopathy. Microcephaly is an indicator of impaired brain growth and cortical atrophy, usually secondary to HIV encephalopathy. Cortical atrophy is associated with disease progression and neuro-developmental delay.[35] In our cohort children there was a strong correlation between children with microcephaly and developmental delay and hyperactivity.
Growth parameters are important markers of disease progression in HIV infected children and may be predictive of neurodevelopmental status.[31]

**Behaviour problems** were reported in 28 patients. The high rate of patients scoring in the mild-moderate range for the sub-scale lethargy / social withdrawal (n=22) reflects a correlation with the affective and adjustment disorders but could also be a symptom of the chronic debilitating illness in this cohort. Patients who scored in the mild range on the stereotypies sub-scale (n=8) correlated with organic brain syndromes and pervasive developmental disorders. Those in the irritability sub-scale (n= 8) correlated with oppositional defiant disorder and attention deficit disorder. Children with HIV-infection are

reported to have more frequent behavioural problems and developmental delay compared to established childhood norms.[51] The key behaviour problems described were psychosomatic (28%), learning difficulties (25%), hyperactivity (20%), conduct (16%), and anxiety (8%).[51] Prevalence rates of 28.6% for attention deficit/ hyperactivity disorder (ADHD), 24.3% for anxiety disorders and 25% for depression are reported.[52-56] In our cohort 30% of patients scored in the mild–moderate hyperactivity spectrum. This percentage is higher compared to ADHD in the general population (3-5%) and to children with other chronic medical conditions associated with behavioural problems.[57] A variety of aetiologies have been proposed for these problems. These include direct effects of the HIV on the frontal cortex and basal ganglia-structures associated with regulation of behaviour, attention and concentration.[58] In addition, the children may also have other medical and environmental risk factors that may contribute to neuro-behavioral abnormalities. Environmental factors affecting families living with HIV include poverty, violence, overcrowding, nutritional status, frequent hospitalization and single-parent households.[59] In our group of patients 10% were institutionalized and 40% were not being cared for by a parent. Such factors would likely increase the risk of psychological difficulties. Maternal HIV also has an impact on children's emotional and behavioural functioning.[59]

**HAART** produces a positive and sustained effect on neuro-cognitive impairment in HIV infected patients.[60] When HAART is commenced during early infancy, the prevalence of CNS effects may be reduced to less than 2%.[61] Our patients without treatment had significantly greater rates of developmental delay and HIVE. Although HAART reverses some of the damage caused by the virus, residual features of arrested HIV encephalopathy may persist with behavioural problems, neurological and cognitive deficits[62] stressing the need for early initiation of HAART.
The public sector ART programme in South Africa commenced in April 2004, but access to therapy for children remained limited during the first few years of the programme. Therapy was often commenced in children with

established neurological disease and the impact from this delay evident in the limited reversibility of disease.

**Cerebrovascular events** have an annual incidence of 1.3% in HIV infected children; this figure is thought to be highly underestimated.[15] Strokes are the commonest cause of focal neurological deficits in children with HIV infection.[63] Strokes in HIV infection may be secondary to hemorrhage resulting from HIV related thrombocytopaenia[15] as occurred in one patient in our series. Infarct related strokes may result from pro-thrombotic states, often due to protein S deficiency[64] or a vasculopathy. Vasculopathy maybe secondary to the HIV virus which is known to cause a segmental aneurysmal dilatation of the arteries of the circle of Willis associated with destruction of the elastic lamina and focal thrombotic occlusion[15] or due to other opportunistic infections. In our group two cerebrovascular events were thought due to vasculitis secondary to a co-infection (*Streptococcus Pneumonia* n=1, Tuberculous meningitis n=1). By exclusion of other risk factors the cause of the stroke in the remaining three patients was presumed due to HIV related vasculopathy. An association between Moyamoya disease and HIV is described in adults[65]and a child.[66] Both HIV-mediated cytokine responses and HAART have been implicated in causing cerebrovascular disease and the Moyamoya phenomenon.[67]

**Neuromuscular complications,** often considered uncommon in HIV positive children may be under-estimated due to the difficulty in diagnosing neuromuscular disorders in chronically ill, non-verbal children. The aetiology of neuromuscular complications in HIV infection is multi-factorial and maybe due to the neurotoxicity of antiretroviral drugs in association with immune-mediated mechanisms triggered by HIV infection, the sequelae of chronic illness and opportunistic infections.

The prevalence of peripheral neuropathies is quoted as about 5%.[68] The mechanisms of neuropathy are secondary to immunological dysregulation from the HIV infection and exposure to ARVS especially the Nucleoside

analogues (didanosine, d4T) that inhibit reverse transcriptase. In our cohort, three of the four affected patients were on d4T. Recent evidence supports mitochondrial toxicity as a principal mechanism for didanosine and d4T-associated neuropathy. [69] Opportunistic infections like CMV and Varicella zoster virus are also implicated in a lumbo-sacral polyradiculoneuropathy. [70] One affected patient in our cohort had a CMV PCR that was positive.
In a comprehensive series described by the National Institute of Health, an axonal peripheral neuropathy was described in 12/50 HIV positive children. [71] Another series also described axonal neuropathy as the commonest sub-type in HIV associated neuropathy.[72] All the patients in our cohort with peripheral neuropathy also demonstrated an axonal degenerative pattern of injury.

**Seizure disorders** are reported in about 16% of children with HIV related CNS disease.[73] Epilepsy is usually secondary to other complications (such as opportunistic infections and febrile illnesses) rather than due to HIV CNS disease.[13] The concurrent use of anticonvulsants and antiretrovirals poses a therapeutic dilemma for the clinician caring for HIV-positive patients requiring both groups of medications. Concomitant antiretroviral-anticonvulsant use has been associated with both increases and decreases in anticonvulsant concentrations, loss of viral suppression, and decreased concentrations of antiretrovirals.[74] These drugs may interact through multiple mechanisms including competition for protein binding and enhanced or reduced liver metabolism (interactions with cytochrome P450 system). One of the patients in our group was concomitantly on carbamazepine and a protease inhibitor (PI). Because carbamazepine induces the enzymes of the P450 system concomitant use with a PI may result in sub-therapeutic ARV levels and treatment failure, as well as potential resistance to the PI class of drugs.[75] PIs may, in turn, cause toxic levels of anticonvulsants.
Our unit recommends the use of sodium valproate for HIV-infected children on ARVs. However this agent also interacts with several of the ARVs especially efavirenz, ritonavir and zidovudine via induction of CYP450 isoenzymes.[74] Margolis et al[76] found that Valproate in combination with

enfuvirtide reduces the pool CD 4 cells which are latently infected with HIV raising the possibility, in theory, of a cure for HIV. Follow-up studies have not supported this theory to be of clinical efficacy.[77,78]

**CNS opportunistic infections** occurred in 15% of our cohort.

South Africa has one of the five largest national TB epidemics in the world; the estimated incidence rate was 948 / 100,000 population / annum in 2007.[79] The TB incidence rate has increased dramatically as the HIV epidemic has worsened, with the number of TB cases more than doubling since 1996. In our cohort 4 children were previously treated for TB meningitis. Tuberculous meningitis is the commonest type of bacterial meningitis admitted to one centre in the Western Cape of South Africa.[80] HIV/ TB co-infection has implications for disease progression and management. Immunosuppression, due to HIV, predisposes the patient to dissemination of M. tuberculosis (MTB). Tuberculosis is thought to increase HIV replication and viral load.[81] The mechanisms by which these interactions are thought to occur are due to both promoter enhancement and cytokine activity playing key roles in the heightened HIV activity seen in the presence of *M. tuberculosis*.[81, 82] Tuberculosis may reactivate latent HIV in monocytes recruited to the site of the MTB infection via a stimulatory transcription factor[83] and latent HIV reservoirs are thus established at sites of MTB infection.[84] There is also evidence that TB increases systemic HIV heterogeneity[85] which has implications for resistance to antiretroviral drugs. Managing co-infection with TB is complicated by the drug-drug interactions and the interaction of both classes of drugs on the cytochrome P450 system.

Streptococcus Pneumoniae and Haemophilus Influenza Type B are pathogens which frequently cause bacterial meningitis in HIV-infected children. [86] Progressive multifocal leukoencephalopathy (affecting one patient in our series) is reported in 14% of adults with AIDS[87] but infrequently in HIV-infected children. CMV is described as the commonest opportunistic infection in HIV-infected children.[88] CMV causes both primary neurological syndromes (meningoencephalitis, peripheral neuropathy) and is a co-factor in the

activation of HIV in the brain.[88] In our series 5 patients (6%) had CMV co-infection.

None of the patients in our cohort had a CNS lymphoma, however this complication does occur in our population.[89]

**Neuroimaging** has been used as an objective measure of ongoing brain injury and of the response to ARVs.[90] Children with HIV infection may have neuro-imaging abnormalities due to HIVE (cerebral atrophy, leukoencephalopathy, basal ganglia calcification) or secondary to complications from being immunocompromised (infarcts, malignancies, infections). The prevalence of CT abnormalities of any type has varied from 63% to 86%.[91, 92] In our cohort 11 patients had evidence of cerebral atrophy on neuro-imaging. The degree of cerebral atrophy has also been correlated with scores on neuropsychological tests.[93]

Imaging abnormalities were identified in 76% of patients classified as non-encephalopathic[94] and hence could be used as a marker to initiate antiretroviral therapy early in the disease course. The commonest CT abnormalities are ventriculomegaly, cerebral atrophy, white matter changes and basal ganglia calcification, as occurred in our cohort.[94]

Of the patients who had CT scans of the brain performed 11% had evidence of basal ganglia calcification. Other series have reported 61% of patients having basal ganglia calcification.[95] Post-mortem studies[95] have shown variable degrees of calcific vasculopathy of the basal ganglia. Other studies have shown varying degrees of blood-brain-barrier disruption with associated oedema and inflammation in the basal ganglia at the time when basal ganglia calcification was documented on neuro-imaging.[96] Calcification is seen primarily in vertically infected children and may indicate a selective vulnerability of the basal ganglia of the developing brain to HIV infection. All our patients with basal ganglia calcification had HIVE. This has been reported in another series. [94]

In resource limited settings CT imaging is more accessible than MRI. Magnetic Resonance Imaging is the neuro-imaging modality of choice if there

are no financial constraints. Magnetic resonance imaging and more specifically volumetric MRI are more sensitive and specific in assessing HIV associated brain changes. Proton MRS Studies in adults with HIV infection are consistent with neuronal cell loss and inflammation some of which is shown to be reversible with antiretroviral therapy on follow-up studies.[97, 98]

This study had some **limitations.** The neurodevelopmental deficits and behaviour problems identified can not be considered as solely related to HIV infection due to the complex socio-economic profile of the participants, including orphan status, limited maternal education and malnutrition. We lack a comparison group to control for environmental factors. Peri-natal factors such as prematurity and other perinatal insults were not taken into consideration in the interpretation of the results of the neurological and developmental assessments.

The developmental screening was not performed via formalized tools but more history related and by observation and modified from the Denver II Developmental Screening test. The limitations of using this scale are that it is used as a crude screening tool to identify only severe problems; and it could only be applied to children < 6years of age. This simplified method was incorporated to recruit more patients with minimal impact to their clinic time attendance. Cognitive and fine motor assessments could not be done in infants and this is taken into account in the analysis of the data. The wide age range also limits interpretation of some of the data. As a result the developmental findings should be treated with some caution.

The use of an interpreter when administering the ABC scale, could have introduced a bias and since the care-givers had different levels of literacy their interpretation of the questions and insights may have varied. The ABC was translated verbally during the assessment by the interpreter.

The small sample in this study limits the potential to generalise the findings. The patients recruited at the Red Cross Hospital clinic may represent a biased sample as some complex patients are referred from secondary level health facilities for assessment. For the group of patients on HAART, the

duration of treatment prior to the assessment is not taken into account and this could also lead to bias.

**Conclusion**

Neurological complications of HIV are common and span a wide spectrum of disorders. The impact of HIV related CNS neurocognitive dysfunction is a challenge that is compounded by co-morbidities and the complex socio-economic problems in South Africa and other resource limited settings. Poor socio-economic status, low birth weight, anaemia, malnutrition, childhood encephalopathies such as tuberculous meningitis and other bacterial meningitides as well as the effects of maternal AIDS on the child are all confounding factors affecting the neuro-developmental and behaviour outcomes in a child afflicted with HIV. These variables pose a major challenge in determining the incidence of HIV-attributable CNS disease in children[99] and illustrate the layering effects of multiple pathologies influencing clinical phenotypes.

Although progress has been made in increasing ART access to South African children with HIV infection, many children start ART late and a sizable proportion who need ART are still not receiving therapy. Consequently, HIV related neurocognitive disability remains a significant problem because of these challenges and the limited access to regimens with the highest efficacy in penetrating the blood-brain barrier. In current practice PHE is an ARV eligibility criterion, comprehensive neurological, developmental and behavioural assessment though, is rarely performed in resource-limited settings due to a shortage of skilled staff. This compounds the delays in initiating HAART and other strategies for care of HIV-associated neurodevelopmental impairment. Socio-economic problems may prevent patients attending clinics to collect medication.

All patients with persistent developmental delay and abnormal neurological signs require timely referral. Assessment and management should be trans-disciplinary.

There is a need for further longitudinal studies on the neuro-developmental complications of HIV. Populations with access to HAART are surviving into adolescence; these groups need to be studied to understand their long-term neurological and neuropsychological complications. The impact of persistent neurodevelopmental sequelae on education, employment and social integration is of increasing importance as children treated with HAART survive into adulthood.[100] With improved understanding of the risks inherent in HIV related illnesses, effective medical and psychosocial interventions can be implemented early to improve health and quality of life of these children. In addition intervention studies are urgently needed to establish the best way to manage the complex, multi-faceted psychosocial and developmental needs of these children.

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# Appendix 1: Group demographics

| | | |
|---|---|---|
| **Date of examination** | | |
| | | |
| **Age in months** | | |
| | | |
| **Gender** | **Ancestry** | |
| | | |
| **On HAART if yes itemise** | | |
| | | |
| **Date of commencement** | | |
| | | |
| **CD4 at diagnosis (DIAG)** | **at start ART** | **most recent (date)** |
| | | |
| **Viral load DIAG** | **start of ART** | **most recent (date)** |
| | | |
| **COH at DIAG cms / centile** | **start of ART** | **most recent (date)** |
| | | |

| |
|---|
| **FAMILY COMPOSITION** |
| **Care giver e.g.: granny, biological mom, foster:** |
| **Address, i.e.: family home or institution:** |
| **Cultural Congruence of home:** |
| |
| **SCHOOL/CRECHE:** |
| Name |
| **Grade:** |
| **Grade age appropriate** |
| **Teacher's report if available** |
| **Perinatal and relevant PMH** (e.g. HIE, tuberculosis): |
| |
| **PREVIOUS INVESTIGATIONS OF RELEVANCE** (e.g. CT, EEG, audiology): |
| |
| **PREVIOUS DOCUMENTED MILESTONES** |
| **Walking:** |
| **Talking:** |
| **Other:** |
| **Any regression:** |
| **EMOTIONAL STATUS** |
| **Never documented:** |
| **Happy, sad, aggressive, labile etc:** |
| **SEIZURES** |
| **BEHAVIOURAL PROBLEMS** |
| **Date documented:** |
| **Inattentive, hyperactive, conduct disorder, distractible, disobedient etc:** |

**Clinical information**

| | |
|---|---|
| **Date** | |
| **Age in months :** | |
| **Head Circumference ( COH):** | |
| **Weight :** | |
| **Height :** | |
| **Mood: happy, sad, irritable, cross etc** | |
| **general behaviour, playful, busy, hyperactive, withdrawn etc** | |
| **MOTOR** | |
| **power UL** | R L |
| **LL** | R L |
| **Proximal VS Distal** | |
| **Tone** | Central Appendicular |
| **Deep tendon reflexes: brisk, depressed UL** | R L |
| **LL** | R L |
| **Superficial reflexes** | Plantars Abd |
| | |
| **Sensory** | |
| **Light touch** | |
| **Pain** | |
| **Posterior column** | |
| | |
| **Abnormal movements** | |
| **cerebellar signs : finger pointing, ataxia, nystagmus** | |
| **cranial nerves** | |
| **vision / fundi** | |
| **ears** | |

**Appendix 2: Norms of development (Modified from Denver 2 Developmental Screen)**

| Age in months: | Activity | present | Normal range |
|---|---|---|---|
| | Lifts chin off coach when prone | | |
| | Smiles responsively | | |
| | Stills or startles to sounds | | 2 months |
| | | | |
| | Regards own hand | | |
| | Supine lie head central | | |
| | Vocalizes | | 2- 4 months |
| | | | |
| | Turns to Voice | | |
| | No head lag when pulled to sit | | |
| | Grasps with whole hand | | |
| | Laughs | | 4-6 months |
| | | | |
| | Waves Bye-bye | | |
| | Sits securely | | |
| | Feeds self with biscuit | | |
| | Jabbers/Babbles- non-specific | | 6-8 months |
| | | | |
| | Indicates wants | | |
| | Crawls | | |
| | Points with index finger | | |
| | Babbles- specific | | 8-10 months |
| | | | |
| | | | |
| | | | |

| | | |
|---|---|---|
| | Drinks from a cup | |
| | Scribbles | |
| | Walks with support | |
| | 2-3 words with meaning | 10-12 months |
| | | |
| | Assists with removing clothes | |
| | Walks unaided at least 10 steps | |
| | Scribbles | |
| | 3-4 single words with meaning | 12-18 months |
| | | |
| | Up steps/ runs | |
| | Uses a spoon | |
| | Puts on clothes | |
| | Combines 2 words | 18-24 months |
| | | |
| | Washes hands | |
| | Jumps | |
| | Imitates vertical line | |
| | Dry during day | |
| | Sentences 3-4 words/knows name | 24-36 months |
| | | |
| | Dresses | |
| | Stands on one leg 2 seconds | |
| | Counts to four | |
| | Copies circle | |
| | Knows adjectives | 36-48 months |
| | | |
| | | |

| | | |
|---|---|---|
| | Brushes teeth | |
| | Catch a ball | |
| | Tells his age | |
| | Counts to 10 | |
| | Copies a cross | |
| | Draw a person- 3 parts | |
| | Knows 4 colours | 4-5years |
| | | |
| | Draws man 6 parts | |
| | Knows morning from pm | |
| | Copies square | |
| | Knows opposites | |
| | Heel-to-toe walks | 5-6 years |

# Appendix 3

## ABERRANT BEHAVIOR CHECKLIST-COMMUNITY

Client's Name: Rater's Name:

Client's Gender: Relationship to Client: Parent

Date of Birth: Teacher

Today's date: Trainer/ Supervisor

Other (Specify)

Where was the client observed: Home

School

Residential Unit

Workshop

Other (Specify)

If in School-Type of Class Developmentally Handicapped

Multi-handicapped

Severe Behavior Handicapped

Other

Race Group Caucasian

African- American

Hispanic

Other

CLIENT'S MEDICAL STATUS

| | | | |
|---|---|---|---|
| A. Deafness | Yes | No | Don't know |
| B. Blindness | Yes | No | Don't' know |
| C. Epilepsy | Yes | No | Don't know |
| D. Cerebral Palsy | Yes | No | Don't know |
| E. Other | Yes | No | Don't know |

CURRENT MEDICATION (Please list any medication and dosage schedule)

_____

_____

_____

_____



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INSTRUCTIONS

The ABC Community Rating Scale is designed to be used with clients living in the community. Please note that the term client is used throughout to refer to the person being rated. This may be a child of school age, an adolescent, or an adult.

Please rate the client's behavior for the last four weeks. For each item, decide whether the behavior is a problem and circle the appropriate number:

0 = not at all a problem
1= the behavior is a problem but slight in degree
2 = the behavior is moderately serious
3 = the problem is severe in degree

When judging the client's behavior please keep the following points in mind:

a. Take relative frequency into account for each behavior specified. For example if the client averages more temper outbursts than most other clients you know or most others in his/her classes, it is probably moderately serious (2) or severe (3) even if these occur only once or twice a week. Other behaviors such as non-compliance, would probably have to occur more frequently to merit an extreme rating.
b. If you have access to this information, consider the experiences of other care providers with this client. If the client has problems with others but not with you, try to take the whole picture into account.
c. Try to consider whether a given behavior interferes with his/her *development /functioning* or *relationships.* For example body rocking or social withdrawal may not disrupt other children or adults, but it almost certainly hinders individual development or functioning.

*Do not spend too much time on each item-your first reaction is usually the right one.*

| | | | | |
|---|---|---|---|---|
| 1. Excessively active at home, school, work or elsewhere | 0 | 1 | 2 | 3 |
| 2. Injures self on purpose | 0 | 1 | 2 | 3 |
| 3. Listless, sluggish, inactive | 0 | 1 | 2 | 3 |
| 4. Aggressive to other children or adults (physically or verbal) | 0 | 1 | 2 | 3 |
| 5. Seeks isolation from others | 0 | 1 | 2 | 3 |
| 6. Meaningless recurring body movements | 0 | 1 | 2 | 3 |
| 7. Boisterous (inappropriately noisy and rough) | 0 | 1 | 2 | 3 |
| 8 Screams inappropriately | 0 | 1 | 2 | 3 |
| 9. Talks excessively | 0 | 1 | 2 | 3 |
| 10. Temper tantrums/outburst | 0 | 1 | 2 | 3 |
| 11. Stereotyped behavior, abnormal, repetitive movements | 0 | 1 | 2 | 3 |
| 12. Preoccupied stares into space | 0 | 1 | 2 | 3 |
| 13. Impulsive (acts without thinking) | 0 | 1 | 2 | 3 |
| 14. Irritable and whiny | 0 | 1 | 2 | 3 |
| 15. Restless, unable to sit still | 0 | 1 | 2 | 3 |
| 16. Withdrawn prefers solitary activity | 0 | 1 | 2 | 3 |
| 17. Odd bizarre behavior | 0 | 1 | 2 | 3 |
| 18. Disobedient difficult to control | 0 | 1 | 2 | 3 |
| 19. Yells at inappropriate times | 0 | 1 | 2 | 3 |
| 20. Fixed facial expression, lacks emotional responsiveness | 0 | 1 | 2 | 3 |

| | | | | |
|---|---|---|---|---|
| 21. Disturbs others | 0 | 1 | 2 | 3 |
| 22. Repetitive speech | 0 | 1 | 2 | 3 |
| 23. Does nothing but sit and watch others | 0 | 1 | 2 | 3 |
| 24. Uncooperative | 0 | 1 | 2 | 3 |
| 25. Depressed Mood | 0 | 1 | 2 | 3 |
| 26. Resists any form of physical contact | 0 | 1 | 2 | 3 |
| 27. Moves or rolls head back and forth repetitively | 0 | 1 | 2 | 3 |
| 28. Does not pay attention to instructions | 0 | 1 | 2 | 3 |
| 29. Demands must be met immediately | 0 | 1 | 2 | 3 |
| 30. Isolates himself/herself from other children or adults | 0 | 1 | 2 | 3 |

---

| | | | | |
|---|---|---|---|---|
| 31. Disrupts group activities | 0 | 1 | 2 | 3 |
| 32. Sits or stands in one position for a long time | 0 | 1 | 2 | 3 |
| 33. Talks to self loudly | 0 | 1 | 2 | 3 |
| 34. Cries over minor annoyances and hurts | 0 | 1 | 2 | 3 |
| 35. Repetitive hand, body or head movements | 0 | 1 | 2 | 3 |
| 36. Mood changes quickly | 0 | 1 | 2 | 3 |
| 37. Unresponsive to structured activities (does not react) | 0 | 1 | 2 | 3 |
| 38. Does not stay in seat | 0 | 1 | 2 | 3 |
| 39. Will not sit still for any length of time | 0 | 1 | 2 | 3 |
| 40. Is difficult to reach, contact, or get through to | 0 | 1 | 2 | 3 |

---

| | | | | |
|---|---|---|---|---|
| 41. Cries and screams inappropriately | 0 | 1 | 2 | 3 |
| 42. Prefers to be alone | 0 | 1 | 2 | 3 |
| 43. Does not try to communicate by words or gestures | 0 | 1 | 2 | 3 |
| 44. Easily distractible | 0 | 1 | 2 | 3 |
| 45. Waves or shakes the extremities repeatedly | 0 | 1 | 2 | 3 |
| 46. Repeats a word or phrase over and over | 0 | 1 | 2 | 3 |
| 47. Stamps foot or bangs objects or slams doors | 0 | 1 | 2 | 3 |
| 48. Constantly runs or jumps around the room | 0 | 1 | 2 | 3 |
| 49. Rocks body back and forth repeatedly | 0 | 1 | 2 | 3 |
| 50. Deliberately hurts himself/herself | 0 | 1 | 2 | 3 |

---

| | | | | |
|---|---|---|---|---|
| 51. Pays no attention when spoken to | 0 | 1 | 2 | 3 |
| 52. Does physical violence to self | 0 | 1 | 2 | 3 |
| 53. Inactive, never moves spontaneously | 0 | 1 | 2 | 3 |
| 54. Tends to be excessively active | 0 | 1 | 2 | 3 |
| 55. Responds negatively to affection | 0 | 1 | 2 | 3 |
| 56. Deliberately ignores directions | 0 | 1 | 2 | 3 |
| 57. Has temper outbursts or tantrums when he /she does not get own way | 0 | 1 | 2 | 3 |
| 58. Shows few social reactions to others | 0 | 1 | 2 | 3 |

# Appendix 4

CONSENT

Parent/legal guardian:

I---------- the parent/legal guardian (delete whichever is not applicable) of ---------- give my consent for the records of this child to be used for research regarding HIV infection in children. I also consent for clinical examinations to be recorded for study purposes. I understand that confidentiality will be respected. I voluntarily give consent ---------- to participate in studies concerned with HIV infection in children. I am free to withdraw my child if I wish. The aim of this study is to improve the overall management of all children who are HIV positive

Signature

Date

Witness

Signature