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**Neurocognitive outcome of HIV-
infected children on antiretroviral
therapy at Red Cross Children's
Hospital**

Thesis document submitted to the Department of Paediatrics and
Child Health of the University of Cape Town in partial fulfilment of
the requirements for the degree M Med (Paed)

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Faculty of Health Sciences

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Declaration

I, *Lara Smith* hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Lara Smith

Date

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Abbreviations

AIDS: Acquired Immuno-Deficiency Syndrome
ART: Antiretroviral therapy
ARV: Antiretroviral
CDC: Centers for Disease Control
CDG: Childhood Disability Grant
CSF: Cerebro-spinal fluid
CT scan: Computed Tomography scan
DAP: Goodenough "Draw-a-Person" test
GQ: General Quotient
HAART: Highly active antiretroviral treatment
HIV: Human Immunodeficiency Virus
MC: Motor Coordination
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
PI: Protease Inhibitors
PMTCT: Perinatal Maternal to Child transmission
TROG: Test for Reception of Grammar
VMI: Visual Motor Integration
VP: Visual Perception

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Abstract

Central nervous system involvement contributes significantly to the morbidity and mortality of paediatric HIV infection. The spectrum of CNS morbidity varies from minor developmental disabilities to severe, progressive encephalopathy. Therefore regular developmental evaluation should be regarded as an essential component of the overall care of HIV-infected children. Antiretroviral therapy may arrest or even reverse neurocognitive and motor deficits associated with HIV infection.

Method: This study examined the neurocognitive outcome of HIV-infected children on short-term antiretroviral therapy at the Infectious Diseases Clinic in Red Cross Children's War Memorial Hospital, Cape Town. 39 patients were selected, with clinical category B & C (according to Centers for Disease Control classification), or immune category 2 and 3 disease. Ages ranged from 3 months to 14 years, and 24 males and 15 females participated. Specific exclusion criteria were pre-existing cognitive disabilities due to causes other than HIV. All children received triple drug antiretroviral treatment/highly active antiretroviral therapy.

Data collection was done at baseline and 6 months after commencement of treatment and included clinical and immunological staging, neurological examination, completion of a neurobehavioral checklist and administration of neurocognitive tests with a battery of standardised tests to cover the age range of 0-13 yr.

Results: In children 4 years and older the baseline verbal, non-verbal and fine motor scores were on the 5th, 22nd and 10th centiles respectively and did not show significant change after 6 months of antiretroviral treatment. In children less than 6 years the mean baseline Griffiths Scales of Mental Development general quotient (GQ) was 73 with no statistically significant change after 6 months therapy. No behavioural abnormalities were noted at baseline and after 6 months an increase in hyperactivity was described by categories. The most commonly found neurological abnormality was hyper-reflexia (13 out of 39). There was no significant correlation between the initial CD4 count and

cognitive performance. Nine patients did not complete the study due to death in 3 patients, hospitalisation (medically unfit) in 2 patients, poor adherence in 2 patients and 2 patients being lost to follow-up at time of follow-up.

Conclusions:

The findings in this pilot study indicate that HIV infected children at baseline have varying neuro-developmental disabilities. Six-month assessments showed neither significant improvement nor deterioration in neurocognitive performance. The short duration of the study and the small number of patients in this pilot study may have been insufficient to determine potential positive changes. Conversely, in this study HAART may not have reversed established neurocognitive deficits, but may protect against further neuro-developmental degeneration. Further studies are needed to establish the extent and spectrum of developmental disabilities in HIV-infected children in sub-Saharan Africa, as well as the longer-term effects of highly active antiretroviral treatment (HAART) on neurocognitive function.

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Introduction

HIV/AIDS has become one of the major causes contributing to the burden of disease over the past few years. A third of the population is under 15 years of age in South Africa and HIV/AIDS has become one of the leading causes of death in children under five since 2000 in South Africa. It accounts for 40.3% of deaths, whereas low birth-weight, diarrhoeal disease, lower respiratory tract infections and malnutrition together accounts for 30%. The HIV prevalence amongst woman attending antenatal clinics in 2002 alone rose to 26.5% and with the help of prevention of mother-to-child transmission (PMTCT) the rise in the childhood mortality rates hope to be slowed. Unfortunately, at this time of the study, very few public hospitals were providing anti-retroviral medication for infected patients, but programmes have recently been launched to roll out anti-retroviral medication.^{1,2}

Developmental delay may be the initial central nervous system manifestation of paediatric HIV infection. Although reports emerging in the literature suggest a protective or therapeutic effect on the central nervous system of highly active antiretroviral treatment (HAART) in adults (in the form of AIDS dementia), there are only limited studies on this issue in children.^{3,4,5} Published studies have not addressed the developmental disabilities of HIV-infected children living in sub-Saharan Africa and indeed in South Africa. It can be postulated that these children may be at a greater risk for developmental problems compared to HIV-infected children living in rich countries, mainly because of unfavourable socio-economic circumstances and access to fewer service resources. The World Health Organisation recently published recommendations for treating HIV-infected individuals with antiretroviral therapy in resource-limited settings. This document emphasises the importance of clinical monitoring, including regular developmental assessment of children on antiretroviral therapy. Although regular developmental evaluation should be regarded as an essential component of the overall care of all HIV-infected children, it is precisely in developing countries that resources to undertake such evaluations are

extremely scarce.⁶ Therefore, neuro-developmental evaluation may be compromised.

The children attending the Infectious Disease clinic at Red Cross Children's War Memorial Hospital have well described HIV-infection status and are followed up on a regular basis. The neurocognitive function of HIV infected children attending the Infectious Diseases clinic has never been documented and as an antiretroviral treatment program was to be rolled out it was imperative that their baseline development be documented. Due to the unavailability of antiretroviral therapy in the public sector in South Africa, the impact of these drugs on the central nervous system has not been previously evaluated. This provided the opportunity to assess the short-term effect of HAART on the physical status and neurocognitive function of HIV-infected children.

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Literature review

Mechanisms of neuro-developmental disease

Involvement of the central nervous system contributes substantially to morbidity and mortality of HIV-infected children. Problems are caused either by a primary effect of the virus on the brain or are secondary to the effects of immune deficiency resulting in neurological disease.^{7,8,9,10} The clinical spectrum ranges from minor developmental disabilities to severe and progressive encephalopathy.¹¹ The majority of children with HIV infection acquire their infection by mother-to-child transmission. A large proportion of infants with HIV-1 infection show early and marked cognitive and motor delays or declines that may be important indicators of HIV disease progression.^{10,12} These abnormalities are not attributable to other risk factors for developmental delay (i.e. biological or environmental risk factors).¹³

The factors that trigger the progression to HIV related neurological disease and encephalopathy in children remain unknown. Even though HIV invades the central nervous system from the very beginning of infection, the timeframe between invasion, persistent infection, latency and central nervous system manifestations is variable. Central nervous system damage is caused by direct and indirect mechanisms associated with HIV infection. Indirect mechanisms, particularly neuronal attrition secondary to apoptosis is believed to be the predominant mechanism of neuronal damage. The mere presence of the virus in the central nervous system does not necessarily indicate central nervous system compromise, but may be related to speed of HIV replication, viral load and number and type of infected cells within the central nervous system.^{8,14}

Clinical Presentation of HIV related central nervous system disease

Neurological complications in HIV-infected children occur due to either primary neurological disease due to HIV (see Box 1), secondary to immunosuppression, or from complications of antiretroviral therapy.^{10,15,16}

Severe immunosuppression in HIV infected children can lead to neurological complications due to a variety of causes affecting the central nervous system. This includes central nervous system infections (due to a range of microorganisms, including *cryptococcus neoformans*, *toxoplasma gondii*, *treponema pallidum*, herpes viruses, *JC virus*, various bacteria and mycobacteria), primary central nervous system lymphoma, seizures and strokes. More than 50% of strokes are haemorrhagic and often occur in patients with thrombocytopaenia and central nervous system neoplasia and are usually only seen in children with advanced HIV disease or encephalopathy. Opportunistic infections and intracranial tumours may not occur as commonly as in adults, but as the survival rate increases among children these will be seen more frequently.^{9,15,17}

Peripheral nervous system involvement includes HIV related neuropathy and myelopathy. Peripheral nerve involvement can take several forms and may occur in up to a third of HIV-infected children, sensory distal neuropathy being the commonest. Spinal cord involvement in HIV myelopathy is a rare finding, but should be suspected in an HIV-infected child presenting with spastic paraparesis (bilateral lower limb hypertonia) without cognitive decline and requires MRI of the brain to exclude bilateral cerebral involvement mimicking spinal compromise.^{9,18}

Toxicity due to nucleoside reverse transcriptase inhibitor antiretroviral treatment may cause mitochondrial dysfunction leading to seizures and developmental regression. In-utero exposure to antiretroviral drugs may also lead to neurological disease. The most common side-effect of antiretrovirals remain peripheral neuropathy and is also thought to be on the basis of mitochondrial toxicity. Discontinuation of these drugs usually leads to resolution.^{9,19}

Box 1: Primary CNS involvement in paediatric HIV infection.^{7, 8}

- Normal neurological findings
- HIV-related CNS compromise - overall cognitive functioning within the normal range with impairments in selective neurological, developmental functions or a spectrum of neuro-developmental problems
- HIV-related encephalopathy:
 - a) Static encephalopathy
 - b) Progressive encephalopathy
 - i. Subacute progressive course - rapid regression
 - ii. Plateau course - less severe, no regression and no gain

Even though developmental compromise may be the initial central nervous system manifestation of paediatric HIV infection, the presentation may be extremely variable.^{10, 20} HIV encephalopathy is the most severe central nervous system presentation, resulting in significant neurologically based abnormalities in cognitive, motor, linguistic, psychosocial and sensory/perceptual development.

In HIV-related CNS compromise where overall cognitive functioning falls within the normal range the impairments in neurological and developmental functions can present as a wide spectrum of neuro-developmental problems. These occur in variable degrees of severity. Common abnormalities in neuro-development that have been found are summarised in box 2:^{11, 10}

Box 2 Common neurocognitive manifestations in HIV-infected children

AREA	ABNORMALITY
Cognitive deficits	Decreased intelligence levels
	Specific learning disabilities
	Attention deficits
	Visual-motor deficits
Motor deficits	Abnormal reflexes
	Abnormal muscle tone
	Impaired strength
	Delayed motor development
	Loss of motor milestones
Adaptive behaviour deficits	Delayed self-help skills
Communication deficits	Expressive language delays
	Receptive language delays
	Articulation deficits
Behavioural/social/emotional deficits	Hyperactivity
	Depression/withdrawal
	Autistic-like behaviours
	Anxiety
	Oppositional-defiant behaviour

In older children or adolescents, HIV-associated dementia may present with difficulty in concentration, slow mental responses, behavioural changes (such as apathy or loss of libido) and motor signs (such as unsteady gait, leg weakness or tremor).²¹

The extent of the developmental and cognitive impairment appears to be directly related to the extent of HIV infection in the central nervous system. Children with HIV infection may present with developmental delays at birth or remain relatively asymptomatic for a number of months or years before presenting with developmental compromise. Early HIV infection increases a child's risk for poor neurodevelopmental functioning within the first 2 years of life.²² A large proportion of HIV-infected children will acquire some form of central nervous system abnormality during the course of their lifetime, but central nervous system disease manifestations appear to be more common in younger children.²³ Up to 50% of children born with HIV infection will display a developmental abnormality within the first year of life, and approximately 90% of the children will acquire an abnormality during the course of their life.¹¹ The incidence of HIV-related encephalopathy appears to be highest during the first year of life.²⁴

HIV encephalopathy may be static or progressive. Children with static encephalopathy continue to gain new skills and abilities, but at a slower rate than expected for age. Their scores on standardised neurocognitive tests are usually below normal and remain stable over time. Children with progressive encephalopathy usually show continued global developmental impairment. The subacute, progressive form is frequently encountered during infancy and early childhood. These children tend to regress i.e. they lose previously acquired skills. Children who experience a plateau course of the progressive form fail to acquire new skills, but do not lose previously acquired milestones.^{7,8,25} (Box 1)

The majority of untreated HIV-infected children with developmental disabilities seem to experience an intermediate pattern of plateaus and deteriorations with an overall declining course.^{7,8,11}

The manifestations of progressive encephalopathy include:

1. Impaired brain growth or acquired microcephaly determined by serial head circumference measurements or brain atrophy confirmed by CT or MRI scan,
2. Decline or regression in cognitive and neuro-behavioural performance, verified by test scales, and
3. Progressive motor dysfunction or acquired symmetrical motor deficit manifested by two or more of paresis, pathological reflexes, ataxia or gait disturbances.^{7,26,27,28}

High risk groups for developmental problems

Environmental factors, poor socio-economic circumstances and health status are known to contribute to developmental problems in infants. In addition to this, infants born to HIV-infected mothers are at increased risk for a variety of other factors that can influence and adversely affect development, including low birth weight, poor antenatal care, caregiver mental health problems as well as drug and alcohol abuse and other congenital infections.^{11, 29} Poor nutrition and adverse environmental circumstances can further contribute to developmental problems, through associated factors such as prolonged hospitalisation and social isolation. Socio-economic variables that can particularly influence the child's development include parental occupation and parental education. Families who can afford to buy toys and household utensils and who therefore increase their child's exposure to stimulation can contribute to the development of manipulative and spatial-perceptual skills of their child.^{8, 30} The presence of pre-/peri-/or post-natal risk factors for neuro-developmental delay remains circumstantial evidence and does not appear to account for the full extent of developmental delays found in children with HIV.²⁹

Both the age of onset of disease and the type of clinical manifestation of the disease are important medical prognostic factors. Generally speaking the more advanced the disease, the higher the risk of developing encephalopathy. It has been found that up to 70-80% of children in the Centers for Disease Control

clinical category B or C will develop encephalopathy. Regardless of the age of presentation, progressive HIV associated encephalopathy shortens life expectancy.³ The risk is increased even further if the diagnosis of HIV is made within the first 48 hours of life.³¹ Progressive encephalopathy is an independent marker of mortality and is associated with significant immunodeficiency, high viral loads, early age of infection and shortened survival.^{22,23,27,32} Motor (both fine and gross motor) dysfunction may also predict later disease progression.³³ Advanced central nervous system involvement signals extremely poor outcome.

Early and persistent delay in motor development or regression in late infancy distinguishes many children who are HIV-infected from exposed, but uninfected children.^{27,34,35} However there is significant variability in early neurodevelopmental outcome amongst children with HIV infection. Children who are not highly symptomatic have been found to be relatively normal neurodevelopmentally.³⁶

Impact of developmental problems and HIV infection

Both HIV infection and developmental disabilities impact not only on the individual, but also on the family, community, welfare and health systems. The importance of early intervention programs as a mechanism for decreasing the impact of chronic health problems or developmental needs on children and their families is increasingly recognized.³⁷ In HIV-infected children one of the most important early interventions is anti-retroviral therapy. Cognitive disorders have an enormous societal impact. In children this significantly impacts on educational systems, requiring provision of special educational resources for learning disabilities. Learning problems in turn may lead to secondary mental health and behavioural problems and together be the cause of independent living not being achieved. Cognitive disorders, including HIV encephalopathy, require aggressive prevention, education and intervention to decrease their manifestation.^{23,38} Intellectual disability is disproportionately prevalent among lower socio-economic groups and substantial prevention efforts must focus on the biologic well-being and the early life experiences of children living in poverty. In this regard, prenatal care, regular health supervision, and family support services represent major prevention strategies.³⁷

Currently, HIV is the greatest infectious cause of paediatric intellectual disability in the United States.¹¹ The effect of HIV infection on neurodevelopment, cognitive function, school progress and ultimately adult labour skills and productivity will become a significant issue in South Africa, especially with the availability of antiretroviral treatment.

Diagnosis of neurocognitive problems

Serial neuropsychological tests are the most reliable measure of developmental delay, but the diagnosis may be based on neurological and developmental observations and parental report collectively. Standardised developmental screening checklists that include both motor and language skills may be adequate for this purpose.²⁹ As formal testing in sub-Saharan Africa is seldom possible due to insufficient funds and trained staff, a simplified screening appraisal needs to be used or developed. A thorough neurological examination is the most sensitive method of detecting neurological impairment in HIV infection. This allows for identifying abnormal findings, excluding non-HIV-related neurological illness and categorising as far as possible the course the patient seems to be following. Impaired brain growth or microcephaly may be identified by serial head circumference measurements, but measurements have been shown to indicate low sensitivity as a measure of brain atrophy.²³ A baseline neuro-developmental assessment should be obtained for all children. The frequency of follow on evaluations will be influenced by several factors, including severity of neurocognitive involvement, age of the child, value of repeated examinations in terms of available therapeutic intervention measures and the child's health status. A suggested schedule is to see children under 1 year every three months, children between 1-3 years every 6 months, children between 3 and 10 years annually and children older than 10 every 2 years, unless new deficits appear.^{8,25}

Neuro-imaging remains an important aspect of the evaluation, even if not always available in the sub-Saharan setting. Changes on neuro-imaging may precede or follow clinical manifestations.²⁷ Radiological features including

cerebral atrophy, basal ganglia calcification, calcified microangiopathy and white matter changes, may be identified with Computed Tomography (CT) or Magnetic Resonance Imaging scans.^{8,25,39} CT scan abnormalities are particularly associated with gross motor delays, and cognitive changes are especially pronounced in children with progressive brain atrophy.^{40, 41}

Only non-specific abnormalities have been found on EEG and cerebrospinal fluid (CSF). CSF analysis may be useful to exclude non-HIV causes of central nervous system involvement.^{25,42,43} Interestingly, the cerebrospinal HIV RNA concentration (or viral load) correlates with progressive neurological disease in HIV-infected children.⁴⁴ Neurological complications secondary to vascular events, neoplasms or opportunistic infections are rare, especially when compared with the adult HIV population.^{7,8,27,45}

Other causes of neuro-developmental problems in HIV infection

Before central nervous system manifestations are ascribed to HIV infection other causes of neurological dysfunction should be considered. This includes the effects of maternal substance abuse, congenital central nervous system infections such as cytomegalovirus and toxoplasmosis, as well as other causes of early static encephalopathy such as prematurity, birth trauma or genetic mechanisms.²⁷ If other factors can explain neuro-developmental problems that are detected, then the dysfunction should not be classified as HIV-related encephalopathy or compromise.⁸ Additional assessments that may be required are hearing evaluations for children with recurrent otitis media, visual assessments to exclude blindness caused by cytomegalovirus and psychological assessments if psychopathological disorders are present.³¹

The effect of anti-retroviral therapy on neurodevelopment

Highly active antiretroviral therapy (HAART) may halt or even reverse neurocognitive and motor problems.^{14, 27, 46} HAART appears to have a protective effect, but does not protect all patients, because of different pathogenic mechanisms involved.^{5, 47} The most important role of HAART is in preventing the progression to encephalopathy and should therefore be considered before it is present. There are still differences of opinion as to the exact timing of initiating therapy or the specific regime.⁴⁸ American guidelines suggest starting treatment in all children under the age of 12 months regardless of clinical, immunological or viral status, whereas WHO and South African guidelines are based on clinical, immunological and virological (if available) guidelines in this age group (children < 18 months).^{6, 26} According to current South African guidelines minor central nervous system deficits are not an absolute indication to start treatment, but clinically manifest HIV-1-associated encephalopathy is an indication for HAART treatment, irrespective of immune status.^{4, 49} The presence of subtle neurological abnormalities may indicate a poorer prognosis and hence a need for therapy and may well influence the decision to start HAART.⁵⁰ HAART may not necessarily reverse all the central nervous system manifestations and once a child has HIV encephalopathy, the response to HAART is variable. If neurological symptoms start after the second year of life, antiretroviral therapy appears to have limited benefits.^{39, 51} However, some children do improve significantly.¹⁴ In adults HAART may reduce the incidence of HIV dementia, but HIV-associated cognitive impairment remains a major clinical problem among individuals with advanced disease and the best response to HAART appears to occur within the first year of treatment.^{3, 39, 52}

HAART strategies that are effective against systemic manifestations based on certain clinical, virological or immunological markers may not provide optimal treatment for central nervous system manifestations of HIV.²³ In choosing an appropriate regime any CNS-effective treatment should be based on either Zidovudine or Stavudine (both Nucleoside Reverse Transcriptase Inhibitors), since these substances readily enter the cerebrospinal fluid; however, Non Nucleoside Reverse Transcriptase Inhibitors can also be used.^{5, 49, 53} Triple

drug therapy frequently includes a Protease Inhibitor. There is limited data about the effectiveness of protease inhibitors in children with HIV encephalopathy, but it may also provide a protective role by lowering the systemic viral burden and thus lessening the risk of central nervous system invasion.^{5, 51} Furthermore, some antiretrovirals may not inhibit viral replication adequately in central nervous system tissue because of limited CSF / CNS penetration. To achieve adequate central nervous system concentrations large dosages may be required, but the increased risk of toxicity makes this impractical.²¹ It is therefore imperative to include drugs that cross the blood-brain barrier.¹⁴ The importance of the early use of antiretroviral combination therapy to prevent neurological damage has been emphasised.^{39,51,54} HAART decreases overall mortality and prevalence of central nervous system opportunistic infections, but these therapies may be less active in preventing direct HIV effects on the brain.⁵⁵

For many children, HAART has transformed HIV infection from a terminal illness to a chronic disease. Despite the introduction of HAART resulting in a decline in the prevalence of HIV encephalopathy, prolonged survival may lead to an increased prevalence of other neurological complications, such as seizures, CNS lymphoma, and cerebrovascular accidents.^{8, 55, 56} The long-term neurological consequences of HAART remain largely unknown. The central nervous system may in fact be relatively vulnerable to neurological deterioration if antiretrovirals with limited cerebral penetration are administered. Clinical and neuropathological improvement may be transient and may be limited by the development of resistance to the antiretrovirals. Once HIV encephalopathy has been established, response to HAART is variable, but marked improvement may occur in some patients.⁵⁷ As HIV infected patients live longer, newer and more effective drugs to combat the neurological effects of HIV infection will be required.^{23, 56}

Side effects of HAART on the central and peripheral nervous system, as well as interactions with known neurological medications must be taken into account as these could contribute to further neurological deterioration.⁴⁹ Specific drug problems to be aware of include peripheral neuropathy (usually self-limiting) with the use of Stavudine and Didanosine; headaches (occurring with

Didanosine), and sleep disturbances with Efavirenz therapy (for example drowsiness and insomnia), concentration problems and unusual dreams (this tends to diminish after 2-4 weeks).⁹

Additional management of HIV disabilities

Management of cognitive disabilities in HIV infection, in addition to HAART, includes specific remediation/educational support programmes or general stimulation in day-care and school settings. The establishment of toy libraries could serve as an alternative stimulation program in resource-limited settings. This will provide many deprived children access to toys and group socialising, where parents are not able to afford crèche and pre-school fees. Additional health needs stated in the literature may include physical rehabilitation and surgery for motor and orthopaedic problems. General measures that need addressing are ensuring up to date immunisations to prevent bacterial meningitis and optimal nutritional intake. Medical problems such as seizures and central nervous system lymphoma will need appropriate management.³¹

The World Health Organisation argues that in view of the wide range of serious neurological and developmental abnormalities that are important complications of HIV infection, regular developmental evaluation should become an essential component of the overall care of all HIV-infected children.⁶

Aim of the Study

The purpose of this study was to evaluate the short-term effect of HAART on neurocognitive function in HIV-infected children.

Specific objectives

The objectives in the study were:

1. To describe the baseline neurocognitive function of HIV infected children in the Infectious diseases clinic at Red Cross Children's Hospital.
2. To describe the neurocognitive function of HIV-infected children receiving antiretroviral therapy at 6 months after commencement of treatment.
3. To correlate neurocognitive and immunological outcomes.

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Methodology

Study Design

This was a prospective descriptive pilot study.

This study formed part of a larger study looking at outcome of antiretroviral therapy naïve-children on highly active antiretroviral treatment (HAART) (Appendix 1).

Participants

The participants included children meeting the inclusion criteria for the antiretroviral treatment programme, who attended the Infectious Diseases Clinic at Red Cross Children's Hospital, during the period February 2002 to December 2003. The inclusion criteria for the antiretroviral treatment programme were: HIV-infected, with specific clinical, immunological and selective social criteria (Appendix 1).

39 patients were enrolled in this study. Ages of the participants ranged from 3 months to 14 years and

Specific exclusion criteria were:

- Pre-existing cognitive disabilities due to causes other than HIV (such as genetic abnormalities and syndromes)
- Neonatal Hypoxic ischaemic encephalopathy
- Hospitalisation at the time of baseline testing

Intervention

Highly active antiretroviral treatment (HAART) was administered to all participants as per antiretroviral therapy study schedule.

The management of children on HAART was carried out by the staff at the Infectious Disease Clinic as part of the antiretroviral treatment program (Appendix 1 and 2). All regime decisions were made as per protocol.

Table 1 HAART regimes for children on the antiretroviral treatment programme

First line antiretroviral regimens	
Stavudine & Lamivudine plus Ritonavir	Starting regimen for children < 3 years or < 10 kg, based on local cost, administration issues and potential effectiveness
Stavudine & Lamivudine plus Efavirenz	Preferred 1 st line regimen for children > 3 years or > 10 kg

Data collection

- **Demographic data:**

This included a history on social circumstances, birth background, feeding history, schooling history (of primary care-giver and patient) and previous medical history at enrolment (Appendix 4).

- **Clinical and laboratory assessment of HIV status**

Assessments were done at enrolment and following 6 months of HAART.

1. Clinical staging according to CDC classification (Appendix 2)
2. Immunological staging (using CD4 count and viral load; Appendix 2)

- **Neuro-developmental assessment**

Clinical neurological and neurodevelopmental assessment were done at enrolment and following 6 months of HAART.

The assessment included:

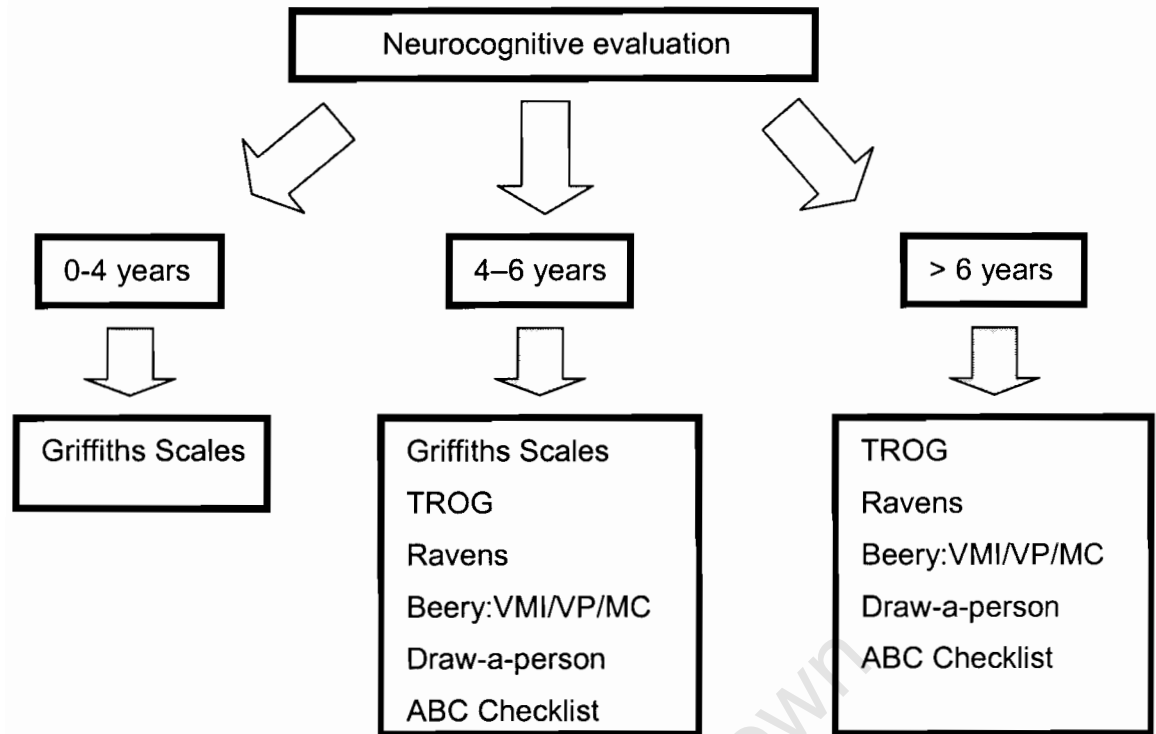
1. Neurological examination (Initial Assessment, Appendix 4 & 5)
2. Cognitive testing with a battery of standardised tests to cover the age range of 0-13 years: (Appendix 6)
3. Behavioural assessment by means of a questionnaire, the Aberrant Behaviour Checklist. (Appendix 6.5)

The history included: previous seizures, episodes of meningitis and previous neuroradiological investigations (CT scan or MRI). A schooling history was taken from children 6 and older as a guide to cognitive performance.

Neurological evaluation included examination of the cranial nerves, the cerebellum (looking especially for ataxia) and the motor system, specifically evaluating reflexes, power, tone and gait. Head circumference measurements were also taken.

Neurocognitive evaluation was done according to age, as follows:

Box 3: Summary of neurocognitive evaluation according to age



1) The Griffiths Scales of Mental Development:

The Griffiths Scales of mental development was administered. This scale is a comprehensive assessment of the different aspects of normal infant and child development that has been validated (but not yet standardised) for use in children of different language groups (English, Afrikaans and Xhosa) in South Africa. Cultural bias between different ethnic groups may remain, but all children in this study were predominately Xhosa speaking.⁵⁸

Subscales consist of the following areas:

- A. Locomotor Subscale: This evaluates the gross motor function. It observes physical development in young children and includes the ability to run fast, to bounce and catch a ball, to jump off stairs and skipping.

- B. Personal-Social Subscale: This area assesses personal and social development and includes ability to give home address and to dress/undress him/her self.
- C. Hearing and Speech: This is the most intellectual of the scales and gives opportunity for the study of the growth and development of language. Items include naming of colours, comprehension of the use of items, opposites and repetition of sentences with 6-16 syllables.
- D. Eye and Hand Co-ordination Subscale: This subscale consists of items relating to the handwork and visual ability of the child. Items include drawing and threading beads. This includes assessment of fine motor function.
- E. Performance Subscale: These tests enable the examiner to observe and measure skills in manipulation, speed of working and precision. It is done with the use of form boards and pattern making.
- F. Practical Reasoning: This looks at the earliest indications of arithmetical comprehension and the realisation of the simplest practical problems. It indicates the child's ability to benefit from formal schooling.

2) Other tests:

a) TROG (Test for Reception of Grammar, Bishop)⁵⁹

This is an individually administered, multiple-choice test designed in English to assess understanding of grammatical contrasts. The TROG may be used for a quantitative assessment of comprehension in order to discover whether or not a person's comprehension is normal for their age. The TROG may be administered as part of a battery of tests as done in this study. It may also be used for a qualitative assessment of comprehension, to successfully further explore the exact nature of the problem. The TROG has been used to detect problems in children with a range of developmental disabilities. The test consists of 80 four-choice picture items. In each item the subject is required to select from an array of pictures that corresponds to a phrase or sentence spoken by the tester and are

arranged in order of increasing difficulty. Vocabulary cards are provided to establish whether the subject knows the meaning of the individual words used. The test is appropriate for a wide age range (4 to 13 years of age) and no expressive speech is required from the subject. For this study the test was translated and back translated into Xhosa. However, the test has not been validated for this language.

b) Ravens Coloured Progressive Matrices (CPM)⁶⁰

The Ravens CPM is internationally recognised as a culture-fair test of non-verbal intelligence, designed for use with children between the ages of 5½ and 11½ years and has been extrapolated for ages 3 ½ - 5 years and 11-12 years. It consists of pattern recognition with distracters in a booklet form. The Raven's Coloured Progressive Matrices (CPM) test is used extensively across a wide variety of settings in South Africa, however more appropriate local normative data has yet to be established.

c) Beery-Buktenica Developmental test of Visual Motor Integration (VMI), Visual Perception (VP) and Motor Coordination (MC)^{61, 62}

The Beery test was designed to measure visual-motor integration, the co-ordination of visual and motor functioning, and to reflect developmental age differences in that area. It consists of a developmental sequence of geometric forms to be copied with paper and pencil and is designed for ages 3 years to adult. Researchers have found the Beery-Buktenica test to be a valuable predictor of future performance when used in combination with other measures, and has been reported to be a particularly good predictor of achievement by children from low social economic groups. It is also predictive for future literacy.

The two supplemental standardised tests, Visual Perception and Motor Coordination look at visual and motor performances on their own. If the child performs poorly on the VMI it could be because he or she has adequate visual perception and/or motor co-ordination abilities, but has not yet learned to integrate or co-ordinate these two

areas. The two supplemental tests will help to indicate possible deficiencies in the child's visual and/or motor abilities. The sequence in which these tests are administered should always be fixed with the VMI first, followed by the VP and lastly the MC. The Visual Perception consists of geometric shapes that need to be matched from a selection of other shapes and the Motor Coordination consists of shapes that need to be drawn by connecting dots.

d) Goodenough "Draw-a-Person" test.^{63, 64}

Children's drawings reflect their draughtsmanship, perceptual awareness, knowledge and understanding of the world around them and their feelings. It draws on the developing ability to translate what is felt into form, with scores achieved that bear a substantial relationship to other measures of the level of cognitive development.⁶⁵ The child is asked to draw a man, taking his/her time and to the best of his/her ability. The test is suitable for children between 3 and 10 years of age. The test is reasonably reliable, correlating well with the Stanford-Binet test, a standardised test for the measurement of intelligence.

Neurobehavioural checklist: Aberrant Behavioural Checklist

A range of behavioural abnormalities has been described in children with HIV and AIDS. It was therefore necessary to include some form of assessment on behaviour. A full psychological assessment was not possible and it was decided to use a questionnaire to obtain information about participant's behaviour.

The questionnaire consists of a 58-question checklist completed by the child's guardian and looks at the following areas of behaviour: irritability, lethargy, stereotypy, hyperactivity and inappropriate speech, and scores the behaviour as none, mildly, moderately or severely problematic. It was designed for use in community settings.

For a summary on score sheets and test charts of the tests see Appendix 6.

Administration and Interpretation of scores:

All tests were performed with standard administration in the patient's first language, or language of the child's preference, with the help of an interpreter. All test material was available in Xhosa, English and Afrikaans (translated from the original English).

Raw scores obtained for the Ravens Coloured Progressive Matrices and Test for Reception of Grammar (TROG) were converted to percentiles using the test manual guidelines (see Appendix 6 for extrapolated results of the TROG and Ravens).

The Visual Motor Integration (VMI), Visual Perception (VP), Motor Coordination (MC) raw scores were converted to standard scores and percentiles using the test manual guidelines (see Appendix 6).

The Draw-a-Person score was converted to a quotient by dividing the score obtained in months with the chronological age in months.

DAP Quotient (%) = (developmental age according to test/chronological age) x 100

A summary of each test's benefits and limitations is found in Appendix 7

Specific neuro-developmental tests are standardised tests for specific ethnic groups to the exclusion of others and there are only limited numbers of these tests available to assess pre-school children. As children develop their expected milestones change and therefore finding the appropriate developmental assessment tool is always a challenge. Several factors need to be considered when choosing from the small number of standardised test instruments available, including the age of the child, the child's level of functioning, available tests and trained staff to administer the tests.¹¹ The only standardised South African tests that are available for developmental

assessment of pre-school children, are the Junior South African Individual Scales (JSAIS) which measures I.Q., and the School Readiness Evaluation by Trained Testers (SETT). These existing assessment measures are not comprehensive, as most tests focus on specific aspects of development or only serve as a screening measure. In South Africa this need has been met by adapting a foreign test for use in this country, as has been done with the Griffiths scales.³⁰ The JSAIS and SETT tests were not used in this pilot study, as these tests may only be administered by registered psychologists (for which no funding was available) and also have a more limited age spectrum to which they can be applied. In an expanded study with more funding and participants these tests could be used.

An optimal test battery to use for the neuro-developmental assessment of HIV infected infants, children and adolescents needs to be designed to evaluate the wide range of areas known to be vulnerable to the effects of HIV. This would include general cognitive function, language (receptive and expressive), perceptual-motor skills, attention, memory, and academic skills. Tests should be selected that yield standard scores accounting for age-related changes in development and thus facilitating comparisons.⁸ The tests chosen in this study attempt to cover most of these abilities and variables.

Finding appropriate cognitive tests for Southern Africa remains a challenge, due to many cultural and socio-economic variables together with limited local research in this area. Results done on a pilot study involving 379 Xhosa speaking children using the Ravens Coloured Progressive Matrices indicated that it appeared that the norms generated revealed a tendency to be lower than those obtained by Raven during the standardisation of this instrument in the United Kingdom and America. It concluded that there is an urgent need for more appropriate South African normative data for this test and that further research into the effects of cultural and socio-economic factors on non-verbal intelligence is required when assessing African children from disadvantaged backgrounds.⁶⁶

Data analysis

Patient data was written onto case report forms (Appendix 4-6). The data was entered into a Microsoft Excel spreadsheet and analysed using standard statistical methods in SPSS Version 10.0. The Lilliefors test for normality was applied to all sets of data. Results were analysed using paired sample T-test (parametric test) for normally distributed data, set at the 95% Confidence Interval; or with the Wilcoxon Signed Ranks Test (non-parametric test) for non-normally distributed data. Analysis was done for baseline and follow-up data. Correlation coefficient using Pearsons bivariate method was used to correlate unrelated data.

Ethical considerations

The Research Ethics Committee, of the University of Cape Town approved the protocol. Written informed consent from the parent or legal guardian was obtained prior to enrolment of children to the study (Appendix 3).

Results

Participants

A total of 39 patients were enrolled. The baseline features of the cohort are presented in table 2

Table 2 Descriptive data of participants (n = 39)

Age range	4months to 173months (14years)
Mean age (\pmSD)	60 months (\pm 46)
Male : Female ratio	24 : 15 (61.5% : 38.5%)
CDC Clinical category	Category A = 0
	Category B = 17 (44%)
	Category C = 22 (56%)
Immune category	Category 1 = 0
	Category 2 = 3 (8%)
	Category 3 = 36 (92%)

Only 30 patients completed 6-month follow-up assessment (77%). Reasons for non-completion are listed in table 3.

Table 3 Reasons for non-completion of study

Outcome	n
Lost to follow-up	2
Treatment discontinued due to poor adherence	2
Died	3
Medically unfit at time of 6 month testing/hospitalised	2
TOTAL	9

Demographic data

Only 23% of families received a self-generated household income. Of the 30 participants not receiving a self-generating income, 1 participant was in foster care and therefore did not receive an income. Only 62% of the 29 families without a self-generated income received some form of grant (adult or childhood), reflecting the inadequate application rate for the child support grant. The mother was alive and the primary caregiver in more than 70% of cases. Even though the mother's health status was not recorded, family members were helping with care of the child in 20% of cases. One child was permanently placed in foster care and the whereabouts of his mother were not known and another was living in a home/institution with his legal guardian, as his mother had demised (he subsequently died).

Table 4 Demographic details: PARTICIPANTS

Housing	Formal 20 (51%)	Informal 19 (49%)
Self-generating income*	Yes 9 (23%)	No 29 (74.4%)
Grant (any form)	Yes 24 (62%)	No 14 (35.9%)
Mother*	Alive 30 (77%)	Dead 8 (21%)
Primary caregiver*	Mother 29 (74%)*	Family 8 (20%)

* 1 patient in foster care – maternal status unknown

Socio-economic variables that particularly impact on the child's development include parental employment and parental education. Almost 75% of children came from unemployed homes and only 25% of guardians had completed school or obtained further education post completion of school. (Tables 5 & 6)

Table 5 Employment guardians

	Frequency (n)	Percent %
Employed	7	17.9
Unemployed	29	74.4
Pension	2	5.1
Not applicable (foster care)	1	2.6
Total	39	100.0

Table 6 Education level of carer

Maternal/Caregiver education (grade)	Frequency (n)	% of total
< Grade 7	5	12.8
Grade 8 to 10	22	56.4
Grade 12 (matric)	8	20.5
> Grade 12	2	5.1
Unknown	2	5.1
Total	39	100.0

Of the 14 children (36% of total participants) older than 6 years, and therefore eligible for school, 30% had failed a year or had a delayed onset to starting school and 3 (21% of school age children) had not yet started school. The main reasons given were finances and poor health/recurrent illnesses.

Table 7 Education details of Participants

	Frequency (n)	Percent (%)
School	11	28.2
Crèche	5	12.8
None	22	56.4
Total	38	97.4
Missing	1	2.6
	39	100.0

The majority of participants were Xhosa speaking and almost all the children apart from one Afrikaans-speaking child had some knowledge of the Xhosa language.

Table 8 Language breakdowns of participants

Language	n
Xhosa only	34 (87.2%)
Xhosa home language in English medium school	2 (5%)
Afrikaans	1
Zulu with some Xhosa	1
Sotho with some Xhosa	1

Assessment of HIV status

Immunological Data

Baseline CD4 counts were very low and Viral Loads very high (mean of 9.25% and log of 5.5 respectively) (see table 9). The mean CD4% increased after 6 months of ARV treatment and was statistically different. (Table 10)

Table 9 CD4 % (initial and 6 months) and Viral Load Log at baseline

	Mean (\pm SD)	n
Initial CD4%	9.25 (\pm 4.68)	39
6 month CD4%	15.83 (\pm 6.57)	30
Initial Viral load Log	5.55 (\pm 0.73)	35
6 month Viral Load Log	2.66 (\pm 1,12)	21

The Lilliefors test for normality was applied on both sets of data and it was concluded that there was not enough evidence to infer that the data are non-normally distributed. In the absence of sufficient evidence of non-normality, a parametric test for quantitative data (t-test) rather than a non-parametric test was used.

Table 10 CD4 %: T-Test: Paired Samples Statistics, 95% Confidence Interval

	Baseline Mean (\pm SD)	Follow-up Mean (\pm SD)	n	p
CD4%	8.66 (\pm 4.56)	15.83 (\pm 6.57)	30	0.02
Viral load log	5.37 (\pm 0.73)	2.66 (\pm 1,12)	21	0.37

Neuro-developmental Studies

i. Neurological examination

A neurological examination was conducted initially (n=39) and repeated 6 months after ARV treatment (n=30). Neurological evaluation included examination of the cranial nerves, the cerebellum (looking especially for ataxia) and the motor system, specifically evaluating reflexes, power, tone and gait. The majority of children at baseline had a normal motor examination (66%) and the most common abnormality detected was brisk deep (knee) tendon reflexes, either in isolation or with other abnormalities, which remained stable over the 6-month period. The child who had clonus in addition to hyper-reflexia improved with no clonus after 6 months of treatment. The child with gait problems in addition to hyper-reflexia died, and another who only had brisk reflexes went on to develop gait abnormalities as well (see Table 11). Neurological evaluation of the cranial nerves and the cerebellum at baseline was normal in all cases. Subsequent to enrolment (one month after treatment started) one child presented with cerebellar signs and was diagnosed with progressive multifocal leukoencephalopathy due to JC virus (polymerase chain reaction positive on CSF) and had a MRI done. He received high dose steroids in addition to HAART and has improved, but did not fully recover.

From the history one child had experienced a single previous seizure (most likely febrile in nature), no one had a history of previous meningitis and none of the participants had neuro-radiological investigations done prior to enrolment.

Table 11 Neurological examination of the motor system (see discussion)

	Frequency Initial	Frequency 6-month	Percent % Initial	Percent % 6-month
Normal	26	19	66.7	48.7
Abnormal Reflexes	9	9	23.1	23.1
Abnormal reflexes + tone	1	1	2.6	2.6
Abnormal reflexes + gait	1	1	2.6	2.6
Abnormal reflexes + clonus	1	0	2.6	0
Abnormal reflexes, power + tone	1	0	2.6	0
Completed examination*	39	30	100.0	76.9

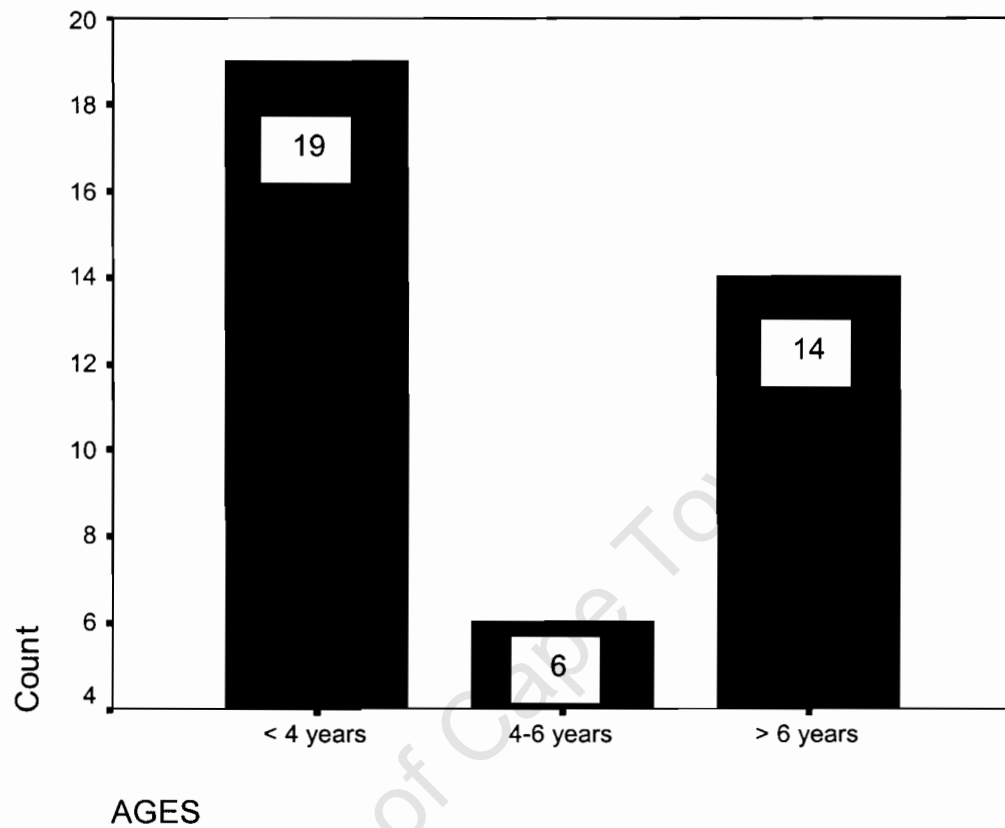
* Reasons for non-completion of study are discussed in Table 3

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ii. Developmental & Cognitive testing

As previously set out in the methodology section, participants were sub-divided into age groups for neuro-developmental tests.

Box 4 Graph of participant age groups used for neurocognitive tests



(numbers reflect total number of participants in each group)

A total of 26 Griffiths assessments were done, this included the 25 children who were due to be tested with the Griffiths Scales of Mental Developmental according to the protocol as well as 1 child who was 2 months above 6 years. Reasons for failure of follow-up assessments after 6 months have already been discussed. (Table 3)

As some children in the 4 - 6 year overlap age group (6 in total) were not able to perform some or all of the other tests the number of these tests that were administered differs. 4 of the 6 children were unable to do some of the tests, 2 of them could not perform any of the tests for children over 4, and only 2 children in the overlap group could be assessed with all the tests administered. Due to initial translation problems the behavioural checklist could only be administered to 12 patients.

Table 12 Number of tests done

TEST	BASELINE	6 MONTHS
The Griffiths Scales of Mental Development	26	17
Test for Reception of Grammar (TROG)	16	16
Ravens Coloured Progressive Matrices	17	16
Visual Motor Integration (VMI),	18	17
Visual Perception (VP)	18	17
Motor Coordination (MP)	18	17
Goodenough "Draw-a-Person" test	18	17
Neurobehavioural checklist: (ABC)	12	12

Certain groups of children, including infants born to HIV-infected mothers, have been identified as being at an increased risk of developmental delay. Attempts were made, as far as possible, to identify risk factors in this study by careful history taking and information obtained from the Road-to-Health card during the initial assessment (see Table 13). Specific exclusion criteria were used to avoid misinterpretation of results. These included pre-existing cognitive disabilities due to causes other than HIV and a history of hypoxic ischaemic

encephalopathy (HIE) during the neonatal period. Infected children who were hospitalised or sick at time of enrolment were also excluded.

Table 13 Risk factors for developmental delay identified from the history

Risk Factors	n	Reason
None	20	
Unknown	17	Reasons given included <ul style="list-style-type: none"> ▪ lost road-to-health cards and ▪ mother not the primary caregiver and therefore unable to obtain accurate history.
Possible	2	1= premature birth 1= low appgars and history of alcohol ingestion during pregnancy, but no history of HIE or clinical features of Foetal Alcohol Syndrome (FAS).

For children over the age of 4 years a battery of tests was used (see Box 3). For all tests a score was achieved in the lower range of expected at baseline as well as after 6-month follow-up. The Test for Reception of Grammar (TROG) results were well below normal.

Table 14 Test Battery results (descriptive)

Test	Initial test Mean (\pm SD)	n	Follow-up test Mean (\pm SD)	n
Ravens %	20.8 (\pm 20.1)	17	22.5 (\pm 22.3)	16
TROG %	5.2 (\pm 8.5)	16	5.4 (\pm 8.2)	16
DAP mental age (months)	79.2 (\pm 17.9)	18	83.8 (\pm 19.2)	17
VMI percentile	9.9 (\pm 11.3)	18	11.59 (\pm 11.5)	17
VP percentile	15.3 (\pm 12.7)	18	13.6 (\pm 24)	17
MC percentile	23.9 (\pm 17.6)	18	17.61 (\pm 16.5)	17

The Lilliefors test for normality was applied on all sets of data and it was concluded that there was not enough evidence to infer that the data for the Griffiths, Draw-a-person test and Motor Co-ordination are non-normally distributed. In the absence of sufficient evidence of non-normality, a parametric test for quantitative data, the t-test was used. (Table 15) However, it was concluded that there was enough evidence to infer that the data in the Test for Reception of Grammar (TROG), Visual Motor Integration and Visual Perception are non-normally distributed. Therefore with this evidence of non-normality the non-parametric Wilcoxon Signed Ranks Test, was used. (Table 15)

**Table 15 Comparison of baseline and 6-month test results
(children >4 years)**

	n	p
Ravens#	16	0.666
Draw-a-person#	17	0.270
Motor Co-ordination#	17	0.113
TROG*	18	0.233
Visual Motor Integration*	18	0.587
Visual Perception*	18	0.201

T-Test: Paired Samples, significance at 95%

Confidence Interval

* Wilcoxon Signed Ranks Test

For children under the age of 6 years the Griffiths Scales of Mental Developmental was administered. Of the 26 patients tested at baseline only 17 completed 6 month follow-up testing (therefore all 9 non completers of the study). Of the 5 children who died (3) or were hospitalised (2) subsequent to enrolment, their mean quotient (GQ) at baseline was 58.8 (62; 36; 72; 48; 76 respectively). A summary of quotients at baseline for all enrolled children vs baseline participants who completed the study is given in table 16.

Table 16 Results of Griffiths quotient and sub-quotients – all children at baseline (n=26) and children who completed follow-up (n=17)

	Mean baseline (\pm SD) n=26	Mean follow-up (\pm SD) n=17
Griffiths	71.6 (\pm 16.3)	72.7 (\pm 14.8)
A. Locomotor	67.3 (\pm 18.6)	68.1 (\pm 16.3)
B. Personal-social	80.5 (\pm 25.1)	82.8 (\pm 24.6)
C. Hearing & speech	69.1 (\pm 16.8)	70.7 (\pm 16.0)
D. Eye & hand co-ordination	74.3 (\pm 15.9)	74.9 (\pm 12.9)
E. Performance	69 (\pm 17.7)	69.8 (\pm 18.8)
F. Practical reasoning	70.8 (\pm 16.5)	71.5 (\pm 16.2)

There was no statistical significant change after 6 months of antiretroviral treatment.

Table 17 Comparison of baseline and 6 month results for Griffiths, using T-Test: Paired Samples, significance at 95% Confidence Interval, n=17

	p (two tailed)
Griffiths (GQ)	0.349
A. Locomotor	0.086
B. Personal-Social integration	0.774
C. Hearing & Speech	0.352
D. Eye & Hand Co-ordination	0.745
E. Performance	0.562
F. Practical Reasoning	0.361

When the Griffiths results are categorised into groups of normal, mild, moderate and severe disability then it can be seen that 50% of children fell in the group with mild disabilities. None of the participants fell into the severe disability category.

Table 18 Griffiths Categories

Functional ability	Frequency (n) at baseline	% of Griffiths (n=26) at baseline	Frequency (n) at 6 months	% of Griffiths (n=17) at 6 month
Normal= >75	10	38.5	9	52.9
Mild= 50-75	13	50.0	8	47.1
Mod= 35-49	3	11.5	0	0
Total	26	100.0	17	100

Percentile scores of test were related to intelligent quotient (IQ) scores using charts available for this. A normal IQ score is considered to be above 75. (see Box 6) At baseline the majority of children were functioning below normal. (Table 19)

Table 19 Summary of baseline cognitive functioning

	Number of tests (n) Baseline	% of n < 75 (n)	% of n > 75 (n)
TROG	16	81% (13)	19% (3)
Ravens	17	59% (10)	41% (7)
DAP	18	33% (6)	66% (12)
Griffiths (GQ)	26*	62% (16)	38 % (10)

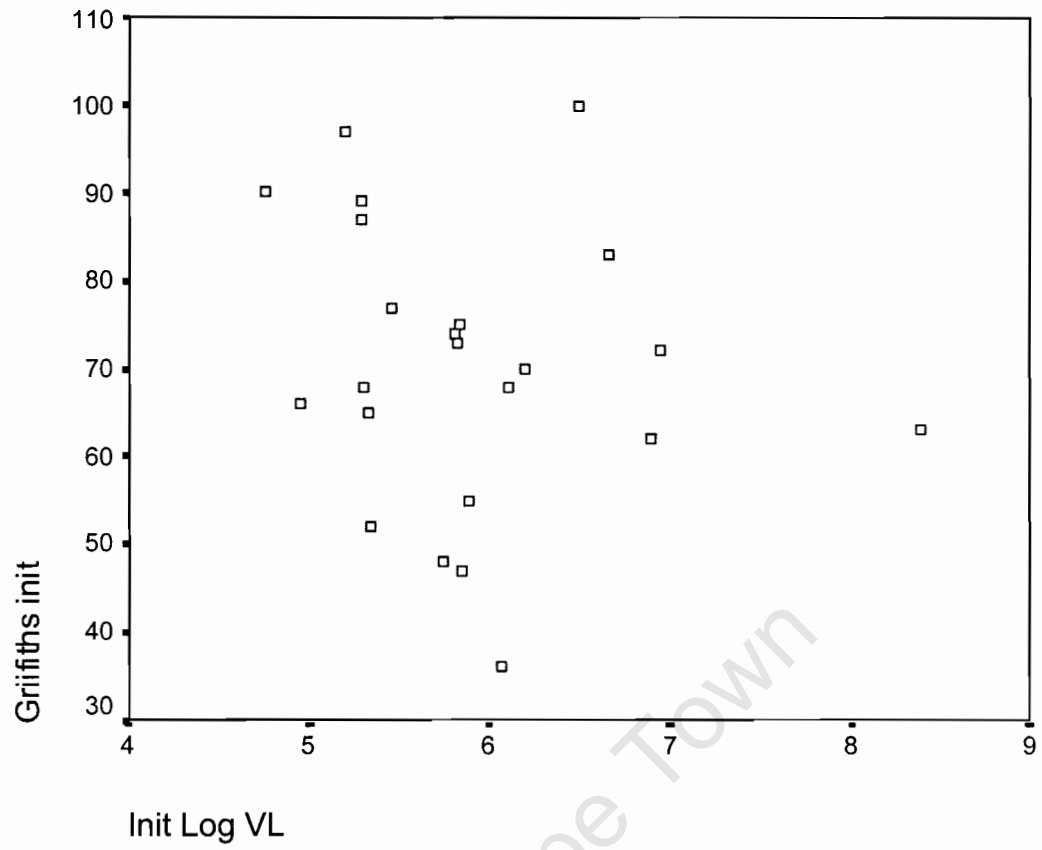
Advanced central nervous system involvement signals extremely poor outcome and it is accepted that the more advanced the disease, the higher the risk of developing encephalopathy. Two of the children who initially fell in the moderate disability group, subsequently died, and the other one improved to mild disability after 6 months of antiretroviral treatment. Even though none of the children in this study were classified as having encephalopathy, many had some form of neurocognitive abnormality. However, correlations between neurocognitive measurements and immunological outcomes (baseline viral load and CD4) were not statistically significant. (See table 20)

Table 20 Pearsons Correlations at Baseline
Correlation coefficient (p value)

	Viral Load Log	n	CD4%	n
Ravens (%)	-0.1 (0.7)	15	-0.44 (0.9)	17
TROG (%)	0.1 (0.7)	14	-0.1 (0.6)	16
DAP Q	0.1 (0.6)	16	-0.3 (0.2)	18
VMI (%)_	0.2 (0.4)	16	0.2 (0.3)	18
VP (%)	-0.02 (0.9)	16	0.2 (0.5)	18
MC (%)	-0.3 (0.3)	16	-0.2 (0.3)	18
Griffiths GQ	-0.2 (0.5)	23	-0.01 (1)	26

As indicated in the above findings, there was no correlation between the viral load and Griffiths quotient results. A wide range of results was found, with some children achieving high quotients on the Griffiths with low viral loads, and visa versa for children with relatively higher viral loads achieving low quotients. (box 5)

Box 5 Graph illustrating the Griffiths general quotient vs the initial viral load log



iii. Behavioural Evaluation

Behaviour was evaluated for all children over 4 years, by means of a neurobehavioral checklist, the Aberrant Behavioural Checklist, which was completed by the caregiver. Only 12 checklists were completed at baseline with 6-month follow up. The checklist was translated into Xhosa and the caregiver filled it in alone or with the help of an interpreter.

The areas of behaviour that were evaluated were irritability, lethargy, stereotypy, hyperactivity and inappropriate speech. Scores were categorised as nil, mild moderate or severe, and were then compared with each other.

At baseline only mild or no problems were noted. At 6 months there appeared to be an increase in perceived behavioural problems. (Table 21)

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Table 21

Results of Behaviour (ABC) categories [n (% of total ABC = 12)]

Ranges	Irritability		Lethargy		Stereotypy		Hyperactivity		Inappropriate speech	
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>
Nil	10 (83%)	8 (66%)	12 (100%)	11 (92%)	11 (92%)	11 (92%)	12 (100%)	10 (83%)	10 (83%)	10 (83%)
Mild	2 (16%)	3 (25%)			1 (8%)	1 (8%)		1 (8%)	2 (16%)	2 (16%)
Mod				1 (8%)				1 (8%)		
Severe		1 (8%)								

Pre refers to baseline data and Post refers to 6-month follow-up.

Discussion

The purpose of this study was to evaluate the short-term effect of HAART on neurocognitive function in HIV-infected children. There are numerous factors that can have an impact on development and these factors need to be taken into consideration when evaluating the response of one single factor, such as antiretroviral treatment on neuro-development. The many cultural and socio-economic variables that may have an influence on the results needed to be documented at baseline. It is for these reasons that children tested at baseline were used as their own control for follow up after 6 months of treatment

Demographic data:

Even though no major biological risk factors contributing to developmental delay due to causes other than HIV were found, other significant risk factors are often additive. The participants came from low socio-economic environments and had either HIV infected parents or parents who had demised. Environmental risk factors, such as maternal depression, violence and social isolation frequently coexist with biologic risks and these emotional problems are common causes and consequences of cognitive and language disorders.³⁷ In this small pilot study it was not possible to obtain in-depth background on all such possible risk factors. To provide information about economic background the focus was on housing, income and employment. Findings indicate an almost equal distribution between formal and informal housing, but only 23% earning a household income and a further 62% relying on grants and pensions to survive. Childhood disability grants (CDG) were not routinely applied for in all HIV infected children. Subsequent to enrolment to the study this was reviewed and applications for a disability grant were made for children in CDC clinical category C, CDC immune category III and all other children with disabilities or defects that meet the criteria set out in the grant (these include severe neurodevelopmental delay). As parental education can particularly impact on the child's development, this was also assessed and in this study only 20% of caregivers had matriculated, with a further 5% obtaining further education.

Clinical and laboratory assessment of HIV status

Even though developmental delay may be the initial central nervous system manifestation of paediatric HIV infection (even prior to other clinical manifestations), all the children enrolled in this study had signs of clinical HIV infection and the majority were already severely infected, falling in immune category 3 with a mean CD4 of 9.25% at baseline. The fact that 5 patients did not complete the study due to death (in 3 cases) and hospitalisation (in 2 cases) is also a reflection of the severity of illness.

Children were initially screened clinically according to the CDC (Centres for Disease Control) classification (see Appendix 2). If screening criteria were met, a baseline CD4 count and viral load was done to decide on qualification for enrolment to the study (see Appendix 1). Despite an almost equal proportion of children in clinical categories B and C respectively, the majority had severe immunological disease as indicated by a 92% immune category 3 (CD4% < 15%) (Refer to Appendix 2).

CD4% improved significantly after 6 months of HAART, coupled with a drop in the viral load.

Neuro-developmental assessment

i. Neurological examination

The majority of children had a normal motor examination (66%) at baseline and the most common abnormality detected was brisk reflexes (23%).

Only one patient developed a serious neurological complication subsequent to start of ARV therapy, namely progressive multifocal leukoencephalopathy (presenting with cerebellar signs) that has subsequently improved on maintenance treatment. His cognitive assessments (both verbal and non-verbal) remained stable during the 6-month period, as did his scores for Beery-Buktenica Developmental test of Visual Motor Integration (VMI) and Visual Perception (VP). However his score for Motor Coordination (MC) dropped from the 70th centile to the 23rd centile after 6 months, which is consistent with his neurological deterioration. No neurological changes in other participants were noted after the 6-month treatment period.

ii. Cognitive/developmental testing

Prior to enrolment none of the participants were considered to have severe developmental or cognitive problems, however the results indicate that most of the children fell at the lower spectrum of expected neuro-cognitive function or had a mild neuro-cognitive disability. In our opinion none of the children had encephalopathy according to the Centres for Disease Control definition (see Appendix 2). This may however not be a true reflection of the incidence of encephalopathy in this clinic as neuro-cognitive assessments and regular head circumference measures were not routinely measured at follow-up in the Infectious Diseases Clinic prior to start of the antiretroviral treatment program.

Evaluating baseline neuro-cognitive function and the outcome of short-term antiretroviral treatment, the following areas should be considered:

A. Cognitive and abstract thinking is evaluated by determining both the verbal and non-verbal scores.

a) For non-verbal cognition the Ravens, Draw-a-person (DAP) and the Griffiths general quotient is used. The DAP overlaps with motor function and visual perception, as well as giving insight into cognition.

The Ravens mean percentile fell on the 22nd centile, which is equivalent to an IQ of 81. This indicates that the majority of participants (all above 6 years) have a low normal cognitive function.

The draw-a-person mean quotient was between 80-84, again falling in the low normal functioning cognitive range.

The Griffiths Scales of Mental Developmental demonstrated the participating children had a mean general quotient (GQ) of 73-75, which is below normal (Normal>75). As the Griffiths was used in children under 6 years, this could indicate that this age group is more likely to have cognitive problems, as they are more likely to be rapid HIV infection progressors and have a poorer prognosis. The children surviving in the older age group are more likely to be slow progressors may be more likely to have a slower evolving central nervous system disease pattern.

b) A measure of verbal cognition was assessed by means of the Test for Reception of Grammar (TROG) for children above 4 years. The mean percentile fell on the 5th%, an I.Q. equivalent of 60. This indicates mild intellectual disability. However, norms for the Xhosa speaking population are not known, and in fact most tests used in South Africa are not normed for socio-economic deprivation. However, these results were lower than scores derived from other low socio-economic populations, which are usually in the low normal range.

In this study the TROG is used as a general proxy of verbal cognition. It is therefore difficult to say that a low mean TROG score empirically indicates cognitive, rather than specific grammatical problems. As the TROG specifically assesses language one must also consider that possible cultural, educational and grammatical differences may have influenced the test outcome. Translation of English grammatical constructs into Xhosa could have contributed to poor performance. As all participants repeatedly made certain errors, these aspects of language may account most for the low performance results.⁵⁹

The Griffiths Scales of Mental Developmental subscale in hearing and speech showed a mean quotient of 71-73. This is once again below normal, falling in the mild disability area.

The Griffiths Scales correlate with verbal and non-verbal sub quotients of the JSAIS IQ scales (unpublished, Lewis et al). As the intelligent quotient (IQ) is a well-known measure, it can be used to help with interpretation of results comparing it with guidelines set out for interpretation of IQ: Charts are available to relate percentile scores to IQ scores.

Box 6 IQ interpretations

N >75
Mild intellectual disability = 50-75
Moderate intellectual disability = 35-50
Severe intellectual disability <35

The results indicate that the majority of the children in this study were functioning in the mild intellectual disability range prior to HAART (refer table 19).

In the group of children under 6 years who had Griffith assessments done at baseline, 5 children (83% of this group) subsequently died (n=3) or were hospitalised (n=2). 4 of the 5 children had a general quotient (GQ) <75, of which 2 had scores below 50. Unfortunately these are small numbers for statistical analysis assessments, but it would appear that there was no correlation with baseline CD4%.

Overall there was no statistical significant change after 6 months of treatment and HAART did not appear to improve neuro-developmental function in the short-term, but may have halted further progression of cognitive problems.

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B. Visual Perception

The Beery-Buktenica Developmental test of Visual Motor Integration (VMI), Visual Perception (VP), and Motor Coordination (MC) is used to assess this area of development. The VMI & VP evaluate areas of higher functioning than MC. Motor control was the least affected.

The VMI mean scaled score was 76; with a mean percentile of 10.

The VP mean scaled score was 74; with a mean percentile of 17.

This indicates functioning in the borderline area of low normal functioning and mild developmental disability respectively.

For children younger than 6 years the Griffiths subscales, eye and hand co-ordination and performance can be used to assess visual perception.

The Eye and Hand Co-ordination Subscale showed a mean quotient of 75 and the Performance Subscale showed a mean of 70, again indicating low normal functioning and mild developmental disability respectively.

The motor co-ordination mean scaled score was 86, with a mean percentile of 22.

This assessment indicates a low normal score on older ambulant children, as opposed to hospitalised HIV infected infants where one would have expected the motor component to be low as these infants often present with delayed walking as a primary developmental problem. The Griffiths locomotor scale can be used to evaluate motor function for children less than 6 years. The mean score for this scale was 68–72, which is below normal.

There were no statistical significant changes found after 6 months of ARV therapy for any of these neuro-cognitive tests.

iii. Behaviour

In general no behavioural abnormalities were noted at baseline.

The apparent increase after 6 months of antiretroviral therapy, in hyperactivity and irritability is probably due to a combination of factors, including the small

patient numbers and children becoming much more active due to improved physical health and thus perceived as hyperactive by the caregiver.

Correlations

In summary there were no correlations found between the initial CD4 count, viral load and neuro-cognitive performance. Interpretation of these results must be treated with caution, as the study numbers were so small.

The role of other factors

A factor that needs to be considered when analysing the results includes the role of behaviour on neuro-cognitive performance. Chronically ill children with frequent hospital admissions are more likely to underscore on any cognitive test and due to prolonged bed rest may also be more likely to under perform in the area of motor development. Even though the checklist did not reveal any problems, this was a subjective questionnaire based on the caregiver's perception of the child's behaviour. As their child has always been chronically ill there was no normal baseline for them to compare behaviour against. Another factor that may have played a role was the caregivers' mental health at the time of questioning. Many of them are also HIV infected and chronically ill and may also be depressed and therefore subjective judges of their children's behaviour.

The potential effect of antiretroviral therapy on neuro-behaviour also needs to be considered. The timing and duration of the antiretroviral therapy may not have been long enough to see changes. The literature suggests starting ARV treatment early in the disease to help prevention and treatment of neuro-cognitive problems, as the response to HAART once HIV encephalopathy is established, is variable. There are no definite guidelines about the optimal time to start treatment for children with central nervous system problems, but studies suggest that treatment commenced after the second year of life in the presence of neurological symptoms has limited benefit.³⁹ Starting treatment as late as

was done in the children in this study may therefore be too late as the period for optimum effect may have been missed. The best period of intervention with cognitive therapy is during the first 6 years of life due to brain neuroplasticity in this age group. Similarly in successful cognitive therapy intervention, a response is usually evident after 18 months, but it is unclear whether this applies to other interventions such as ART. Furthermore the period required for HAART to influence the central nervous system is unknown. Choice of an antiretroviral regime for children with neuro-cognitive disabilities is not yet clear and also requires further studying. This study did not include Zidovudine as first line treatment and all the regimes included a protease inhibitor.

What is not known is the effect of low socio-economic status and environment on the cognition of this study population and whether or not this overrides the positive effects treatment may have on their neuro-cognition. Violence and poverty affect both the psychological and intellectual competence of young children. Educational factors may also contribute, as often schools in low socio-economic areas are overcrowded, with a high pupil to teacher ratio; standards in these areas may be sub-normal and transport/access to school may be a problem. Recurrent illness, poor nutrition and environmental factors that can contribute to developmental problems, may be present and further negatively influence education. Environmental precursors include dysfunctional caregiving related to parental psychopathology, extreme family disorganization, prolonged hospitalisation and social isolation or socio-economic hardship. Children who live in poverty are particularly susceptible to the cumulative burdens of both social stress and the greater biologic vulnerability related to a higher prevalence of such risk factors as perinatal complications and nutritional deficiencies. However, socio-economic factors alone, however, do not appear to account for the developmental delays found in children with HIV.

Some children can manifest severe cognitive impairment despite the absence of recognizable focal neurological findings or evidence of significant risk factors for central nervous system dysfunction. The neurobiological roots of mental handicap may be found among such diverse factors as structural malformations of the brain, metabolic abnormalities, and central nervous system deficits related to infection, malnutrition, or hypoxic-ischaemic injury. This study did not

include neuro-radiological investigations and can therefore not exclude any of these possibilities.

It is obvious that many varied factors have an influence on development and that it is not possible to identify all of these. Developmental disability reflects the complex interplay among multiple risk and protective factors. Most children in this study came from similar backgrounds and environments, but individually differences may well have had an impact on neuro-developmental assessment.

Limitations of study and future plans

Limitations of this pilot study include the short duration of the study and the small number of patients. Controls of non-treated HIV children could not be used due to ethical considerations, as it would be unethical to withhold treatment from children qualifying for HAART. Future plans would be to do follow-up after 12 to 18 months of treatment to see if a longer time span is beneficial to neuro-cognitive outcome.

Conclusions

The findings at baseline indicate that HIV infected children have varying neuro-developmental disabilities, with 6-month assessment analysis showing no significant changes in neurocognitive performance. Therefore it can be concluded that in the short-term HAART did not improve or reverse neuro-cognition, but also did not seem to have a negative or deleterious effect on the baseline function. These findings are consistent with other studies showing that HAART may halt further neuro-cognitive deterioration. None of the children in this study were considered to have encephalopathy at the start of treatment, but this may be due to poorly documented neurological and developmental status previously. Children with established encephalopathy, and possibly children over the age of two years with prolonged neuro-cognitive problems, would not be expected to respond well to HAART. Further study is needed in this field to elucidate these questions.

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Appendix 1: Selection of children

Antiretroviral therapy: guidelines for the treatment of a cohort of HIV-infected children and their infected parents at Red Cross Children's Hospital Antiretroviral therapy: guidelines for the treatment of a cohort of HIV-infected children and their infected parents at Red Cross Children's Hospital (referred to as the antiretroviral treatment program study in this protocol)

(B. Eley et al)

Clinical and immunological criteria

- Clinical stage C or immunological stage 3 (Appendix 2).²⁸
- Consider ART if clinical stage B or CD4+ count < 20% or high viral load (>10⁶ copies / mL if age < 1 year, and > 10⁵ copies / mL if age > 1 year).

Social criteria

- Parent / guardian prepared to commit to long-term antiretroviral therapy
- Parent / guardian having a permanent address in Cape Town for longer than 3 months
- Parent / guardian prepared to complete a detailed questionnaire and serial evaluations
- Parent / guardian prepared to comply with adherence monitoring
- Parent with HIV infection prepared to receive antiretroviral therapy, if indicated
- Child attending the infectious disease clinic regularly, at least the last 3 appointments
- Child taking his / her medication regularly

Exclusion criteria

- Stage N or A disease, and CD4+ count > 20%
- Child currently on antiretroviral therapy
- Parent / guardian not prepared to commit to long-term antiretroviral therapy

- Parent / guardian not having a permanent address in Cape Town for longer than 3 months
- Parent / guardian not prepared to complete a detailed questionnaire and serial evaluations
- Parent / guardian not prepared to comply with adherence monitoring
- Parent with HIV infection not prepared to receive antiretroviral therapy, if indicated
- Child not attending the infectious disease clinic regularly (evaluate at least the last 3 appointments)
- Child not taking his / her medication regularly

Approach to selecting patients

Children selected at the infectious disease clinic on the basis of their clinical staging i.e. clinical category C or B (Appendix 1).²⁸

1. Caregivers informed of programme.
2. Caregivers complete a screening questionnaire.
3. If satisfactory, an initial CD4+ count to be done.
4. All information including a summary of the medical history will be reviewed by a panel of staff members attached to the clinic
5. The decision of the panel will be discussed with the caregiver within 2 weeks.
6. If a child is accepted onto the programme further information about the programme to be given and consent for antiretroviral therapy to be taken (appendix 3).
7. The instructions in Appendix 4 should be followed. These include completing a detailed assessment and baseline bloods (appendix 5), and a neurodevelopmental assessment (Appendix 6). Further information about the programme should be given.
8. Antiretroviral therapy commenced as soon as possible.
9. Antiretroviral therapy will be managed according to established guidelines.

Appendix 2: CDC Classification

CDC Clinical and Immunological Classification for Children with HIV Infection ²⁸

Clinical classification

Category N: Not symptomatic

Children who have no symptoms or signs considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

Category A: Mildly symptomatic

Children with two or more of the following features but none of the conditions in category B or C.

Features: lymphadenopathy (at more than two sites); hepatomegaly; splenomegaly; dermatitis; parotitis; recurrent or persistent upper respiratory infection, sinusitis or otitis media

Category B: Moderately symptomatic

- Anaemia (< 8 gm/dl), neutropaenia (<1000/mm³), or thrombocytopenia (< 100 000/mm³) persisting ≥ 30 days.
- Bacterial meningitis, pneumonia, or sepsis (single episode).
- Candidiasis, oropharyngeal, persisting (> 2 months) in children > 6 mo of age.
- Cardiomyopathy.
- Cytomegalovirus infection, with onset before 1 month of age.
- Diarrhoea, recurrent or chronic.
- Hepatitis.
- Herpes simplex virus (HSV) stomatitis, recurrent (≥ episodes within 1 year).
- HSV bronchitis, pneumonitis, or oesophagitis with onset before the age of 1 year.
- Herpes zoster involving at least 2 distinct episodes or more than one dermatome.
- Leiomyosarcoma.

- Lymphoid interstitial pneumonitis or pulmonary lymphoid hyperplasia complex.
- Nephropathy.
- Nocardiosis.
- Persistent fever (lasting > 1 month).
- Toxoplasmosis, onset before 1 month of age.
- Varicella, disseminated (complicated chickenpox).

Category C: Severely symptomatic

- Serious bacterial infections, multiple or recurrent.
- Candidiasis, oesophageal or pulmonary.
- Cryptococcosis, extrapulmonary.
- Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month.
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes).
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings):
 - a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests;
 - b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or MRI;
 - c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance.
- Kaposi's sarcoma.
- Lymphoma, primary, in brain.
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype.
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary.
- *Mycobacterium avium* complex, or *Mycobacterium kansasii*, disseminated.
- *Pneumocystis carinii* pneumonia.
- Progressive multifocal leukoencephalopathy

- Salmonella (nontyphoid) septicaemia, recurrent.
- Toxoplasmosis of the brain with onset at > 1 month.
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings:
 - a) persistent weight loss > 10% of baseline OR
 - b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g. 95th, 75th, 50th, 25th, 5th) in a child \geq 1 year of age OR
 - c) < 5th percentile on weight-for-height chart on two consecutive measurements, \geq 30 days apart PLUS: a) chronic diarrhoea (i.e. at least two loose stools per day for \geq 30 days) OR b) documented fever (for \geq 30 days, intermittent or constant).

Immunological classification

Immunologic category	Age of child					
	< 12 months		1-5 years		6-12 years	
	μ L	(%)	μ L	(%)	μ L	(%)
1: No evidence of suppression	\geq 1500	(\geq 25)	\geq 1000	(\geq 25)	\geq 500	(\geq 25)
2: Evidence of moderate suppression	750-1499	(15-24)	500-999	(15-24)	200-499	(15-24)
3: Evidence of severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

Appendix 3: Consent procedure for children receiving ART

Antiretroviral therapy for HIV-infected children

Assigned registration number: _____

In rich countries antiretroviral therapy is considered routine treatment for people with HIV infection. Antiretroviral therapy has revolutionised the lives of many HIV-infected adults and children. The benefits to HIV-infected children include decreased risk for death, improved growth and fewer infections such as discharging ears, pneumonia, TB and diarrhoea. Some children who developed HIV infection soon after birth are living to beyond the age of fifteen years and remain healthy, because they are being treated with antiretroviral therapy.

Doctors at the Infectious Diseases Clinic, Red Cross Children's Hospital are involved in establishing a long-term treatment programme for HIV-infected children and their caregivers. This is not a research project but rather one of many responses to the uncontrolled HIV epidemic that has inflicted tremendous suffering on the South African population. The aim of the programme is to provide optimal medical treatment i.e. antiretroviral therapy to as many HIV-infected children and their caregivers as is possible. The success and sustainability of the programme is dependant on the ability to continue to attract local and international funds. As part of the programme we will be documenting the medical progress of the children as well as the problems of treating HIV-infected children with antiretroviral drugs in South Africa. This is important, as the information will allow us to adapt the programme to suite the treatment needs of HIV-infected South Africans. All information will be entered into a database and analysed anonymously. This information will be communicated to the academic community at conferences and via publications in peer-review journals. Blood will be collected periodically to monitor the effects of treatment, including CD4+ count, viral load and other immunological markers.

If you decide that your child should not participate in this programme, it will not affect the way we treat your child. S/he will continue to receive the same standard of care that s/he presently experiences.

Consent

I understand the above information as explained to me by: _____
and am prepared to have my child (NAME): _____
participate in this antiretroviral therapy programme. I understand that strict adherence is needed for continuation of antiretroviral therapy. The programme is dependant on financial donations and a time may come when antiretroviral therapy may be discontinued because of a lack of resources. Should antiretrovirals be discontinued my child will continue to attend the infectious diseases clinic and receive medical treatment.

NAME: _____

RELATION TO CHILD: _____

SIGNATURE: _____

DATE: / / (dd/mm/yyyy)

WITNESSES: _____

Bylae 3: Toestemmings prosedure

Anitretroviral therapy for HIV- infected children

Registrasie nommer: _____

In bevoorregte lande is ART 'n roetine behandeling vir mense wat met die HIV besmet is. ART het die lewens van kinders en grootmense hervorm. Voordele van hierdie behandeling vir kinders wat met die HI Virus besmet is sluit in vermindering van die risiko van vroeër sterfte, verbeterde groei en ontwikkeling plus vermindering van infeksies soos, oor infeksies, long ontsteking, TB en diarree. sommige kinders wat die HIV infeksie ontwikkel gou na geborge, lewe nou tot die ouderdom van 15 jaar en bly gesond omdat hulle met ART behandel is.

Geneeshere by die Besmetlikheid Siektes Kliniek by Rooi Kruis Kinder Hospitaal, is betrokke by die ontwikkeling van 'n lang termyn behandeling program vir kinders wat met HIV besmet is en hul oppassers. Hierdie is nie 'n navorsings projek nie maar een van die reaksies tot die onbeheerde HIV epidemie wat Suid Afrika op die oomblik laat ondergaan. Die doel van die program is om gunstige sorg te verskaf, d.i. om ART behandeling vir so veel moontlik HIV besmette kinders en hul oppassers toe te dien. Die sukses van die program is afhanklik van die vermoë om aanhoudend binnelands en buitelandse fondse aan te trek. As deel van hierdie program sal ons die mediese verloop van al die kinders dokumenteer asook die probleme wat hierdie kinders op die program ondervind. Dit is belangrike informasie en dit sal ons die nodige inligting gee om hierdie program te ontwikkel en die behandeling behoeftes aan te pas vir ander HIV besmette kinders in SA. Alle informasie sal op 'n databasis ingeskryf word en sal naamloos ontleed word. Hierdie informasie sal versprei word deur die akademiese gemeenskap by konferensies en inskrywings in mediese joernale. Bloed sal periodies van kinders geneem word om die uitwerking van die behandeling te monitor insluitend CD4+ tellings, virus vrag en ander immuun merker.

As u besluit dat u nie u kind in hierdie program wil inskryf nie, sal dit nie die huidige manier van sy behandeling beïnvloed nie. Hy/Sy sal nog steeds dieselfde hoe standaard van sorg kry.

Toestemming

Ek verstaan die bogenoemde informasie soos aan my verduidelik deur _____

en ek is bereid om my kind (naam) _____

in hierdie program te laat deel neem. Ek verstaan dat ek streng moet aankleef soos benodig vir aanhoudende ART behandeling. Hierdie program is afhanklik van geldelike donasies en daarvoor mag die program skielik stop omdat die donasies nie voorkomend is nie. Sou dit gebeur sal my kind nog steeds die Besmetlikheid Siektes kliniek bywoon en huidige mediese behandeling ontvang.

Naam: _____

Verwantskap tot kind: _____

Handtekening: _____

Datum: _____ (DD/MM/YY)

Getuie: _____

I-appendix 3: Indlela yokunika isivumelwano

Unyango ngamachiza alwa intsholongwane kaGawulayo (HIV) kubantwana abanayo.

Inombolo yobhaliso enikeziweyo: _____

Kumazwe atyebileyo unyango ngamachiza okulwa intsholongwane kaGawulayo luqatshelwe njengonyango olunokulandelwa ngabantu abosuleleke yile ntsholongwane. Olu nyango ngamachiza seluvuselele ubomi babantu abadala nabantwana abaninzi abosuleleke yile ntsholongwane. Inzuzo kubantwana abanentshlongwane kaGawulayo ibandakanya ukucutha amathuba okusweleka, ukukhula ngokufanelekiyo kunye nokosuleleka okumbalwa zizifo ezinjengokuphuma ubofu ngeendlebe, inyumoniya, isifo sephepha (TB) kunye norhudo. Abantwana abafunyenwe yile ntsholongwane kaGawulayo emva kokuzalwa bayaphila de bagqithe kwiminyaka elishumi elinesihlanu kwaye babe besaphile kakuhle ngokwase mpilweni, kuba benyangwa ngala machiza.

Oogqirha kwiKliniki yezifo ezosulelayo, eRed Cross Children's Hospital bazibandakanye nokumisela inkqubo ende yonyango lwabantwana abanale ntsholongwane kunye nabantu ababakhathalelayo. Olu asilophando oluzakuphela kwangoku koko yenye yeendlela zokusabela kwisihelegu sentsholongwane kaGawulayo engalawulekiyo nethe yalulwamvila lwentlupheko kuluntu lwaseMzantsi Afrika. Iinjongo zale nkqubo kukunika unyango olufikelekayo, oko kukuthi, ukunika abantwana abanale ntsholongwane nabagcini babo amachiza nonyango olufanelekileyo kangangoko. Impumelelo nokuqhubela phambili kwale nkqubo kuxhomekeke ekukwazini ukutsala abanokunikezela ngemali balapha eMzantsi Afrika nabamazwe ngamazwe. Indima yale nkqubo iyakuba kukwenza amaxwebhu olwazi ngenkqubela phambili yabantwana kunye neengxaki abathi babenazo ekunyangeni abantwana abanale ntsholongwane ngala machiza eMzantsi Afrika. Lo nto ibalulekile njengoko ulwazi luya kusivumela ukuba simisele le nkqubo ukuze unyango luhambelane neemfuno zabantu abanentsholongwane kaGawulayo eMzantsi Afrika. Lonke ulwazi luyakugcinwa kwaye luhlalutywe ngokungasebenzisi gama lamntu. Olu lwazi luyakunikwa i inzululwazi nenkcuba-buchopho ukuba zilusebenzise kwiinkomfa nakupapasho. Igazi liyakumana litsalwa ukujonga ukusebenza kwalamachiza,

okubandakanya i-CD4 count, ubuninzi bentsholongwane egazini kunye nezinye iimpawu ezilwa nosuleleko.

Ukuba ugqiba ukuba umntwana wakho angayithabathi inxaxheba kule nkqubo, lo nto ayisayi kuchaphazela indlela ebenyangwa ngayo lo mntwana wakho. Uyakuqhubeka efumana ukhathalelo olufanelekileyo alufumanayo ngoku.

Isivumelwano

Ndiyaluqonda olu lwazi lungentla njengoko lucaciswe
ngu: _____ kwaye ndikulungele ukunikezela ngomntwana wam
(IGAMA): _____

ukuba athabathe inxaxheba kolu nyango ngamachiza okulwa intsholongwane kaGawulayo. Le nkqubo ixhomekeke kwiimali ezisisipho kwaye lingafika ixesha lokungaqhubekeli phambili ngenxa yemali engekho. Ukuba angangabikho la machiza, ndiyakuqhubeka ndimsa umntwana wam kwikliniki yezifo ezosulelayo, ukuba afumane unyango.

IGAMA: _____

UZALWANO
NOMNTWANA _____

USAYINO: _____

UMHLA: ___/___/___ (umhla/inyanga/unyaka)

AMANGQINA: _____

Appendix 4: Initial Assessment

Study number: _____

Name: _____

Date of completion: ____ / ____ / ____

I. Social Profile

PRIMARY CAREGIVER

Mother

Age				
HIV status	Pos	Neg	?	
Primary caregiver	Yes	No		
Marriage status	Single	Married	Partner	
Education level				
Employment	Yes	No	Specify:
Financial assistance	Yes	No	Specify:	
Grant	Yes	No	Specify:	
Other parent	Involved	Uninvolved	Specify:	

Father

Age				
HIV status	Pos	Neg	?	
Primary caregiver	Yes	No		
Marriage status	Single	Married	Partner	
Education level				
Employment	Yes	No	Specify:
Financial assistance	Yes	No	Specify:	
Grant	Yes	No	Specify:	
Other parent	Involved	Uninvolved	Specify:	

Caregiver who is not the parent

Age				
HIV status	Pos	Neg	?	
Primary caregiver	Yes	No	Specify:	
Marriage status	Single	Married	Partner	
Education level				
Employment	Yes	No	Specify:
Financial assistance	Yes	No	Specify:	
Grant	Yes	No	Specify:	
Other parent	Involved	Uninvolved	Specify:	

HOUSING

Suburb			
Type of dwelling	Formal	Informal	Other
Amenities	Water	Electricity	
Refrigerator	Yes	No	
Ownership	Self	Rent	Other

II. Assessment of Child

Date of Birth: _____ / _____ / _____

Sex: M F

Age at registration (months): _____

Perinatal history

Birth weight			
Gestational age			
Apgar score			
Risk factors	Details		
MTCT Intervention	Yes	No	Details.....
Early infant feeding	Breast only	Formula only	Mixed

Immunization

BCG	Polio drops	DPT	Hib	Hepatitis B	Measles

Previous medical history (specifically mention meningitis at any age)

Admissions	Past 2 years		
Date	Place	Diagnosis	Duration
Previous tuberculosis	Yes	No	Site.....

Day-care / School

Care of pre child during day	Self	Family member	Crèche
School	Grade:		
	Details if failed		

Clinical Features

Growth and Nutrition

Body mass (kg):	Percentile:	Z score:
Length (cm):	Percentile:	Z score:
BMI (W/H ²):	Percentile:	Z score:
Head circum (cm):	Percentile:	

CDC Clinical Classification (Appendix 2)

--

Neurological Examination (circle/tick box)

Cranial Nerves	Normal	Abnormal	Specify.....
Motor System	Normal	Abnormal	Specify
Reflexes			
Power			
Tone			
Gait			
Cerebellum (ataxia)	Normal	Abnormal	Specify
Seizures	Yes	No	
Other			

For children on HAART

Immunological classification	
Viral load	
Viral load %	
Treatment regime	

University of Cape Town

Appendix 5: Follow-up clinical assessment

Name: _____

Date: _____

Study number: _____

Clinical Features

Growth and Nutrition

Body mass (kg):	Percentile:	Z score:
Length (cm):	Percentile:	Z score:
BMI (W/H ²):	Percentile:	Z score:
Head circum (cm):	Percentile:	

CDC Clinical Classification (Appendix 2)

--

Neurological Examination (circle/tick box)

Cranial Nerves	Normal	Abnormal	Specify.....
Motor System	Normal	Abnormal	Specify
Reflexes			
Power			
Tone			
Gait			
Cerebellum (ataxia)	Normal	Abnormal	Specify
Seizures	Yes	No	
Other			

For children on HAART

Immunological classification	
Viral load	
Viral load %	
Treatment regime	

Appendix 6 Neurodevelopmental tests

1. Griffiths Scales of Mental Development: score sheet

<u>Date of test:</u>								<u>DOB:</u>	
<u>Name:</u>								<u>Study number</u>	
M.A. Credits in Months								Summary in Months	
Scales:		A	B	C	D	E	F	Scales A to F	Months
YEARS	I						*	I	$\frac{\dots \text{ items passed}}{10} =$
	II						*	II	$\frac{\dots \text{ items passed}}{10} =$
	III							III	$\frac{\dots \text{ items passed}}{3} =$
	IV							IV	$\frac{\dots \text{ items passed}}{3} =$
	V							V	$\frac{\dots \text{ items passed}}{3} =$
	VI							VI	$\frac{\dots \text{ items passed}}{3} =$
	VII							VII	$\frac{\dots \text{ items passed}}{3} =$
	VIII							VIII	$\frac{\dots \text{ items passed}}{3} =$
	Extra Months							Extras	$\frac{\dots \text{ items passed}}{3} =$
	Total M.A.'s (months)							Total M.A. (months)	=
	C.A. (months)							C.A. (months)	=
	Sub-Quotients $\frac{\text{M.A.'s} \times 100}{\text{C.A.}}$							G.Q.	

Note: The General Quotient or G.Q. is obtained by taking the average of all the six sub-quotients.

*The average of A, B, C, D and E.

2. Ravens Coloured Progressive Matrices

Scoring Table: Percentile ranks for age

Amended norms: Coloured progressive matrices Ages 5 ½ -11 years

Extrapolated 3 ½ -5 years and 11-12 years

%	Age in years																	
	12	11.6	11	10.6	10	9.6	9	8.6	8	7.6	7	6.6	6	5.6	5	4.6	4	3.6
95			35	34	33	33	32	31	30	29	28	27	26	25	24	22	21	20
92.5						32	31	30	29				25	24	23	21	20	
90			34	33	32	31	30	29	28	28	27	26	24	23	22	20	19	17
86.25											26	25	23	22	21	19	18	
85										27								16
82.5			33	32	31	30	29	28	27		25	24	22	21	20	18	17	
80										26								15
78.75											24	23	21	20	19	17	16	
75			32	31	30	29	28	27	26	25	23	22	20	19	18	16	15	14
68.75								26	25	24	22	21	19	18	17	15	14	13
66.66			31	30	29	28	27											
62.5								25	24	23	21	20	18	17	16	14	13	12
58.3			30	29	28	27	26											
56.25								24	23	22	20	19	17	16	15	13	12	11
50			29	28	27	26	25	23	22	21	19	18	16	15	14	12	11	10
43.75					26	25	24	22	21	20	18	17	15	14	13	11	10	
41.67			28	27														
37.5					25	24	23	21	20	19	17	16	14	13	12	10	9	
33.33			27	26														
31.25					24	23	22	20	19	18	16	15	13	12	11	9	8	
25			26	25	23	22	21	19	18	17	15	14	12	11	10	8	7	
21.25				24	22	21	20	18	17	16		13		10	-	-	-	
20											14		11		-	-	-	
17.5			24	23	21	20	19	17	16	15		12		9	-	-	-	
15											13		10		-	-	-	
13.75			23	22	20	19	18	16	15	14		11		8	-	-	-	
10	25	23	22	21	19	18	17	15	14	13	12	10	9	7	-	-	-	
8.34											11							
7.5	24	22	21	20	18	17	16	14	13	12		9	-	-	-	-	-	
6.67											10							
5	23	21	20	19	17	16	15	13	12	11	9	8	-	-	-	-	-	

RAVENS COLOURED PROGRESSIVE MATRICES



Scoring Sheet: SETS A, Ab, B

Name:..... Study Number:.....

School:.....

Date of Birth:..... Age:.....

Date of Test:.....

A			Ab			B		
1			1			1		
2			2			2		
3			3			3		
4			4			4		
5			5			5		
6			6			6		
7			7			7		
8			8			8		
9			9			9		
10			10			10		
11			11			11		
12			12			12		

Total time:.....

Total Score:.....

Age Equivalent:..... Percentile:.....

Tested by:.....

3. The Beery-Buktenica Developmental test of Visual Motor Integration (VMI), Visual Perception (VP) and Motor Coordination (MC)

Refer to test and scoring manual

Raw scores are converted to age equivalents, standard scores and percentiles as per test manual

4. Goodenough "Draw-a-Person" Test

The child is asked to draw a man, taking his time and to the best of his ability.

The child receives 1 point for each of the items, which is present in his/her drawing. For each 4 points, 1 year is added to the basal age, which is 3 years.

Method of scoring

1. Head present
2. Legs present
3. Arms present
4. Trunk present
5. Length of trunk > breath
6. Shoulders indicated
7. Both arms and legs attached to trunk
8. Legs attached to trunk; arms attached to trunk at correct point
9. Neck present
10. Neck outline continuous with head, trunk or both
11. Eyes present
12. Nose present
13. Mouth present
14. Nose and mouth in 2 dimensions; 2 lips shown
15. Nostrils indicated
16. Hair shown
17. Hair non-transparent, over more than circumference
18. Clothing present
19. Two articles of clothing non-transparent

20. No transparencies, both sleeves and trousers shown
21. Four or more articles of clothing definitely indicated
22. Costume complete, without incongruities
23. Fingers shown
24. Correct number of fingers shown
25. Fingers in two dimensions, length greater than breadth
26. Opposition of thumb shown
27. Hand shown distinct from fingers or arms
28. Arm joint shown, elbow, shoulder or both
29. Leg joint shown, knee, hip, or both
30. Head in proportion
31. Arms in proportion
32. Legs in proportion
33. Feet in proportion
34. Both arms and legs in 2 dimensions
35. Heel shown
36. Firm lines without overlapping at junctions
37. Firm lines with correct joining
38. Head outline more than circle
39. Trunk outline more than circle
40. Outline of arms and legs without narrowing at junction with body
41. Features symmetrical and in correct position
42. Ears present
43. Ears in correct position and proportion
44. Eyebrows or lashes
45. Pupil of eye
46. Eye length > height
47. Eye glance directed to front in profile
48. Both chin and forehead shown
49. Projection of chin shown
50. Profile with not more than 1 error
51. Correct profile

5. Aberrant Behaviour Checklist (ABC) - community

ENGLISH FORM

Name.....

Date completed.....

Patient study number.....

Completed by.....

RATING

0 = not at all a problem

1= the behaviour is a problem but slight in degree

2 = the problem is moderately serious

3= the problem is severe in degree

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 (verbally or physically)	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/outbursts	0	1	2	3

11. Stereotyped behaviour; 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 activities	0	1	2	3
17. Odd, bizarre in behaviour	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 reacts)	0	1	2	3
38. Does not stay in seat (e.g., during lesson or training periods, meals, etc.)	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 feet 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

Aberrant Behaviour Checklist:

XHOSA TRANSLATION

Name.....

Date completed.....

Patient study number.....

Completed by.....

IMIQATHANGO

0 = asiyongxaki konke

1= isimo sokuziphatha siyingxaki kodwa hayi kangako

2 = ingxaki ithande ukuba ngamandla

3= ingxaki ingamandla ngokugqithisileyo

Musa ukuchitha ixesha elininzi kakhulu kumbuzo omnye – indlela oqale wazive ngayo zisuka yeyona ichanekileyo.

1. Usoloko egqithisile ngezendo zakhe ekhaya, esikolweni, emsebenzini, okanye nakwiyiphina indawo.	0	1	2	3
2. Uzenzakalisa ngokwakhe ngabom.	0	1	2	3
3. Akakho semoyeni, uyonqena, uhleli nje akenzi nto	0	1	2	3
4. Undlondlongo kwabanye abantwana okanye abantu abadala (ngokuthetha okanye ngokubetha)	0	1	2	3
5. Uthanda ukubayedwa angabi kunye nabanye abantu	0	1	2	3
6. Iitshukumo zomzimba wakhe azinantsingiselo kwaye zenzeka rhoqo	0	1	2	3
7. Ingxolo egqithisileyo (ukwenza ingxolo engamandla, engafanelekanga)	0	1	2	3
8. Ukutswina okungafanelekanga	0	1	2	3
9. Uthetha ngokugqithisileyo kakhulu	0	1	2	3
10. Umsindo ongamandla/ ukudubula ngumsindo	0	1	2	3

11. Imikhwa; isimo esintshukumo zingaqhelekanga, neziphindaphindwayo	0	1	2	3
12. Ubakude ngeengcinga; ukuqwalasela emoyeni ungajonge ndawo	0	1	2	3
13. Uvele enze (wenza engaqalanga wacinga)	0	1	2	3
14. Ucaphuka msinya kwaye usoloko ekhalaza	0	1	2	3
15. Akazinzanga, akakwazi ukuhlala ndawonye	0	1	2	3
16. Ulilolo, uthanda ukwenza izinto anokuzenza eyedwa	0	1	2	3
17. Isimo sokuziphatha asiqhelekanga, siphume ecaleni	0	1	2	3
18. Akaphulaphuli xa alulekwa, kunzima ukulawuleka	0	1	2	3
19. Ukhwazela phezulu ngamaxesha angafanelekanga	0	1	2	3
20. Ubuso abufundeki, akabonisi kuvakalelwa	0	1	2	3
21. Uyaphazamisa kwabanye	0	1	2	3
22. Uphindaphinda intetho enye	0	1	2	3
23. Akenzi nto kodwa uhlala abukele abanye	0	1	2	3
24. Uyala ukwenza akuyalelwayo	0	1	2	3
25. Umoya wakhe usezantsi	0	1	2	3
26. Ulandula nakuphina ukusondelelana ngokwasemzimbeni (akafuni kuphathwa)	0	1	2	3
27. Ushukumisa okanye ugeqezisa intloko eyisa ngasemva nangaphambili ekuphindaphinda oku	0	1	2	3
28. Akahoyi xa ayalelwa	0	1	2	3
29. Kufuneka azifumane kwangoko izinto azifunayo	0	1	2	3
30. Uyazikhetha kwabanye abantwana okanye abantu abakhulu	0	1	2	3

31. Uyaphazamisa eqeleni xa kusenziwa izinto	0	1	2	3
32. Uhlala okanye uma ngendlela enye ithuba elide	0	1	2	3
33. Uyazithethela eyedwa evakala	0	1	2	3
34. Ukhala msinya kukucatshukiswa nje kancinane nakukuva kabuhlungu nje kancinane	0	1	2	3
35. Uphindaphinda ukushukumisa izandla, umzimba, okanye intloko	0	1	2	3
36. Utshintsha msinya aqumbe ngoku onwabe ngoku	0	1	2	3
37. Akasabeli kwiimeko eziqingqwe zanemigaqo emayilandelwe (akenzi nto kwezo)	0	1	2	3
38. Akahlali phantsi (umz. ngelixa kufundiswa okanye kuqeqeshwa)	0	1	2	3
39. Akasayikuhlala ndaweni nye ithuba elide	0	1	2	3
40. Kunzima ukumfumana, ukuqhagamshelana naye, okanye ukufikelela kuye	0	1	2	3
41. Ukhala atswine ngendlela engafanelekanga	0	1	2	3
42. Uthanda ukuba yedwa	0	1	2	3
43. Akazami kunxibelelana ngokuthetha ngomlomo okanye ngokuthetha ngokuzibonakalisa ngokwasemzimbeni	0	1	2	3
44. Uphazamiseka lula	0	1	2	3
45. Ubulisa exhawula ngokugqithisileyo kunokuqhelekileyo uphindaphinda	0	1	2	3
46. Uyaliphindaphinda ukulibiza igama okanye amagama athile	0	1	2	3
47. Ungqisha ngeenyawo, abethekise izinto, okanye agingxize iingcango ngamandla	0	1	2	3
48. Usoloko ebaleka okanye exhumaxhuma egqiba igumbi lonke	0	1	2	3
49. Ugeqezisa umzimba ewusa ngasemva nangaphambili ephindaphinda	0	1	2	3
50. Uzonzakalisa ngenjongo	0	1	2	3

51. Akahoyi xa kuthethwa naye	0	1	2	3
52. Uwuphatha gadalala umzimba wakhe	0	1	2	3
53. Uhlala nje engenzi nto, engaze ashukume ngokuthanda kwakhe	0	1	2	3
54. Uthande ukugqithisa xa esenza izinto	0	1	2	3
55. Usabela ngendlela engentlanga xa ubonisa uthando	0	1	2	3
56. Akahoyi ngabom xa asalathiswa	0	1	2	3
57. Unomsindo okhawulezileyo, okanye umsindo ovele udubule xa engayifumani into ayifunayo	0	1	2	3
58. Ubonisa ukusabela okungabhekephi ebukhweni babanye abantu	0	1	2	3

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ABC SCORE SHEET

<i>Subscale I</i>	<i>Subscale II</i>	<i>Subscale III</i>	<i>Subscale IV</i>	<i>Subscale V</i>
<i>(Irritability)</i>	<i>(Lethargy)</i>	<i>(Stereotypy)</i>	<i>(Hyperactivity)</i>	<i>(Inappropriate Speech)</i>

2_____	3_____	6_____	1_____	9_____
4_____	5_____	11_____	7_____	22_____
8_____	12_____	17_____	13_____	33_____
10_____	16_____	27_____	15_____	46_____
14_____	20_____	35_____	18_____	
19_____	23_____	45_____	21_____	
25_____	26_____	49_____	24_____	
29_____	30_____		28_____	
34_____	32_____		31_____	
36_____	37_____		38_____	
41_____	40_____		39_____	
47_____	42_____		44_____	
50_____	43_____		48_____	
52_____	53_____		51_____	
57_____	55_____		54_____	
	58_____		56_____	

Total_____Total_____Total_____Total_____Total_____

Interpretation:

A:	0 -11	0 -12	0 -5	0-12	0 - 3
B	12-23	13-25	6-10	13-25	4 - 6
C	24-34	26-37	11-15	26-37	7 - 9
D	35-45	38-48	16-21	38-48	10-12

A= No problems

B= Mild problems

C= Moderate problems

D= Severe problems

II	1	flower		
	4	cat		
	2	drink		
	3	shoe		
	8	girl		
	7	chair		
	6	horse		
	5	ball		

III	7	dog		
	8	circle		
	4	square		
	2	boy		
	5	cup		
	6	star		
	1	wall		
	3	apple		

IV	7	food		
	1	man		
	4	bird		
	6	knife		
	5	box		
	2	cow		
	8	pencil		
	3	tree		

V	1 dropping		
	6 drinking		
	8 jumping		
	2 pushing		
	5 carrying		
	4 chasing		
	3 standing		
	7 looking		

VI	8 big (fat)		
	4 red		
	3 tall		
	6 yellow		
	2 fat (big)		
	7 brown		
	5 blue		
	1 black		

TEST

A	1 shoe		
	2 bird		
	3 comb		
	4 apple		2134

B	5 eating		
	6 picking		
	7 sitting		
	8 running		2314

C	9	long		
	10	tall		
	11	red		
	12	black		1223

D	13	the boy is running		
	14	the big cup		
	15	the dog is sitting		
	16	the red ball		3421

E	17	the boy is not running		
	18	the dog is not drinking		
	19	the girl is not jumping		
	20	the dog is not sitting		3421

F	21	the boy is jumping over the box		
	22	the girl is sitting on the table		
	23	the man is eating the apple		
	24	the woman/lady is carrying the bag		1433

G	25	they are sitting on the table		
	26	the cow is looking at them		
	27	they are jumping over the wall		
	28	the elephant is carrying them		4221

H	29	the girl is pushing the horse		
	30	the boy is chasing the sheep		
	31	the man is chasing the dog		
	32	the cow is pushing the woman/lady		4324

I	33	she is sitting on the chair		
	34	the woman/lady is carrying him		
	35	he is sitting in the tree		
	36	the horse is looking at her		4134

J 37	the cats look at the ball		
38	the boy stands on the chairs		
39	the boys pick the apples		
40	the girl drops the cups		2133

K 41	the knife is longer than the pencil		
42	the box is bigger than the cup		
43	the shoe is bigger than the bird		
44	the horse is taller than the wall		4131

L 45	the girl is chased by the horse		
46	the elephant is pushed by the boy		
47	the horse is chased by the man		
48	the cow is pushed by the man		1232

M 49	the cup is in the box		
50	the pen is on the box		
51	the circle is in the star		
52	the knife is on the shoe		3124

N 53	the boy chasing the horse is fat		
54	the pencil on the shoe is blue		
55	the cow chasing the cat is brown		
56	the circle in the star is yellow		4123

O 57	the box but not the chair is red		
58	the cat is big but not black		
59	the horse but not the boy is standing		
60	the boy is sitting but not eating		1422

P 61	the pencil is above the flower		
62	the comb is below the spoon		
63	the star is above the circle		
64	the square is below the star		4343

Q 65	not only the bird but also the flower is blue		
66	the box is not only big but also blue		
67	not only the girl but also the cat is sitting		
68	the girl has not only food but also a drink		1223

R 69	the pencil is on the book that is yellow		
70	the girl chases the dog that is big		
71	the square is in the star that is blue		
72	the dog chases the horse that is brown		1243

S 73	neither the dog nor the ball is brown		
74	the pencil is neither long nor red		
75	neither the boy nor the horse is running		
76	the boy does has neither hat nor shoes		1422

T 77	the book the pencil is on is red		
78	the cat the cow chases is black		
79	the circle the star is in is red		
80	the boy the dog chases is big		3144

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XHOSA TRANSLATION**TROG FORM A**

Name:.....

Date of birth:.....

Age:..... Sex:.....

Tester:.....

Date of test:.....

Trial number:.....

TOTAL BLOCKS PASSED

AGE EQUIVALENT

CENTILE

VOCABULARY CHECK

pointing

I

Naming

pre

post correction

7	Indlovu (elephant)			
4	Umnqwazi (hat)			
3	Isingxobo (bag)			
6	Incwadi (book)			
1	Icephe (spoon)			
5	Igusha (sheep)			
2	Umfazi/inenekazi (woman/lady)			
8	Itafile (table)			

II

1	Intyatyambo (flower)			
4	Ikati (cat)			
2	Isiselo (drink)			
3	Isihlangu (shoe)			
8	Intombi (girl)			
7	Isitulo (chair)			
6	Ihashe (horse)			

5	Ibhola (ball)			
---	---------------	--	--	--

III

7	Inja (dog)			
8	Isangqa (circle)			
4	Isikwere(square)			
2	Inkwenkwe (boy)			
5	Ikomityi (cup)			
6	Inkwenkwezi (star)			
1	Udonga (wall)			
3	i-apile (apple)			

IV:

7	Ukutya (food)			
1	Indoda (man)			
4	Intaka (bird)			
6	Imela (knife)			
5	Ityesi (box)			
2	Inkomo (cow)			
8	Ipensile (pencil)			
3	Umthi (tree)			

V

1	Ukuwisa (dropping)			
6	Ukuphunga (drinking)			
8	Ukutsiba (jumping)			
2	Ukutyhala (pushing)			
5	Ukuphatha (carrying)			
4	Ukuleqa (chasing)			
3	Ukuma (standing)			
7	Ukujonga (looking)			

VI

8	Enkulu (big)			
4	-bomvu (red)			
3	Ubude (tall)			
6	Ngebala-lubhelu (yellow)			
2	Ityebile (fat)			
7	-ntsundu (brown)			
5	Blue-blowu (blue)			
1	-mnyama (black)			

A

1	Isihlangu (shoe)			
2	Intaka (bird)			
3	Ikama (comb)			
4	i-apile (apple)			2134

B

5	Ukutya (eating)			
6	Ukukha (picking)			
7	Ukuchopha (sitting)			
8	Ukubaleka (running)			2314

C

9	Ende (long)			
10	Ubude (tall)			
11	-bomvu (red)			
12	-mnyama (black)			1223

D: (8-9 yrs start here)

13	inkwenkwe iyabaleka (:the boy is running)			
14	ikomityi enkulu (the big cup)			
15	inja iyachopha (the dog is sitting)			
16	ibhola ebomvu (the red ball)			3421

E

17	inkwenkwe ayibaleki (the boy is not running)		
18	inja ayiseli (: the dog is not drinking)		
19	intombi ayitsibi (the girl is not jumping)		
20	inja ayichophi (the dog is not sitting)		3421

F:

21	inkwenkwe itsiba phezu kwetyesi (the boy is jumping over the box)		
22	intombi ichopha etafileni (the girl is sitting on the table)		
23	indoda itya i-apile (the man is eating the apple)		
24	umfazi uphatha ingxowa (the woman is carrying the bag)		1433

G:

25	bachopha etafileni (they are sitting on the table)		
26	inkomo iyabajonga (the cow is looking at them)		
27	batsiba phezu kodonga (they are jumping over the wall)		
28	indlovu iyabaphatha (the elephant is carrying them)		4221

H: (10+ yrs start here)

29	intombi ityhala ihashe (the girl is pushing the horse)		
30	inkwenkwe ileqa igusha (the boy is chasing the sheep)		
31	indoda ileqa inja (the man is chasing the dog)		
32	inkomo ityhala umfazi (the cow is pushing the woman)		4324

I:

33	uchopha esitulweni (she is sitting on the chair)		
34	umfazi uyamphatha (the woman is carrying him)		
35	uchopha emthini (he is sitting in the tree)		
36	ihashe liyamjonga (: the horse is looking at her)		4134

J:

37	iikati zijonga ibhola (: the cats look at the ball)		
38	inkwenkwe ime ezitulweni (the boy stands on the chairs)		
39	amakhwenkwe akha ii-apile (the boys pick the apples)		
40	intombi iwisa iikomityi (the girl drops the cups)		2133

K

41	Imela inde kune pensile (the knife is longer than the pencil)		
42	Ibhokisi inde enkulu komityi (the box is bigger than the cup)		
43	Isihlangu sikhulu kune ntaka (the shoe is bigger than the bird)		
44	Ihashe lide kunodonga (the horse is taller than the wall)		4131

L

	intombi ileqwa lihashe (the girl is chased by the horse)		
	indlovu ityhalwa yinkhwenkwe (the elephant is pushed by the boy)		
	ihashe lileqwa yindoda (the horse is chased by the man)		
48	inkomo ityhalwa yindoda (the cow is pushed by the man)		1232

M:

49	ikomityi ibokisi (the cup is in the box)		
50	ipensile ibokisii (the pencil is on the box)		
51	isangqa sisenkwenkwezini (the circle is in the star)		
52	imela isesihlangwini (the knife is on the shoe)		3124

N

53	Inkwenkwe etyebileyo ityhala ihashe (the boy chasing the horse is fat)		
54	Ipensile esesihlangwini iblowu (the pencil on the shoe is blue)		
55	Inkomo ileqa ikati emdaka (ngebala) (the cow chasing the cat is brown)		
56	Isangqa esisenkwenkwezini sityheli (the circle in the star is yellow)		4123

O

57	Ibhokisi kodwa hayi isitulo ibomvu (the box but not the chair is red)		
58	Ikati inkulu kodwa ayimnyamanga (the cat is big but not black)		
59	Ihashe kodwa hayi inkwenkwe limile (the horse but not the boy is standing)		
60	Inkwenkwe ihleli kodwa ayityi (the boy is sitting but not eating)		1422

P

61	ipensile iphezulu kwentyatyambo (the pencil is above the flower)		
62	ikama isezantsi kwecephe (the comb is below the spoon)		
63	inkwenkwezi iphezulu kwesangqa (the star is above the circle)		
64	imurhu isezantsi kwenkwenkwezi (the square is below the star)		4343

Q

65	Hayi intaka qha kodwa nentyantambo iblowu (ngebala) (not only the bird but also the flower is blue)		
66	Ibhokisi ayinkulwanga qha kodwa ikwa iblowu(ngebala) (the box is not only big but also blue)		
67	Ayiyo ntombi yodwa ehleliyo ne kati ihleli (not only the girl but also the cat is sitting)		
68	Intombi ayinakutya kodwa inaso nesiselo (the girl has not only food but also a drink)		1233

R

69	Ipensile isencwadini etyheli (the pencil is on the book that is yellow)		
70	Intombazana ileqainja enkulu (the girl chases the bog that is big)		
71	Isikwere sisenkwenkwezini eblowu (ngebala) (the square is in the star that is blue)		
72	Inja ileqa lhashe elimdaka ngebala (the dog chases the horse that is brown)		1243

S

73	Asiyo nja ingeyiyo ne bhola emdaka (ngebala) (neither the dog nor the ball is brown)		
74	Ipensile ayindanga ayibomvanga (the pencil is neither long nor red)		
75	Asiyo nkwenkwe ingelilo ne hashe elibakekayo (neither the boy nor the horse is running)		
76	Inkwenkwe ayinamqwazi ayinazihlangu (the boy has neither hat nor shoes)		1422

T

77	Incwadi ipensile ephezu kwayo ibomvu (the book the pencil is on is red)		
78	Ikati eleqwa yinkomo imnyama (the cat the cow chases is black)		
79	Isangqa esinenkwenkwezi sibomvu (the circle the star is in is red)		
80	Inkwenkwe eleqwa yinja indala (the boy the dog chases is big)		3144

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6.1 Test for Reception of Grammar (TROG) extrapolated centile results:

Conversion table of scores (blocks passed) to percentile (original centiles: 1-5-10-25-50-75-90-95-99)

Age	Centile																
AGE	1	(2.33) 3 (2.67)	5	7.5	10	(15) 17.5 (20)	25	(33.33) 37.5 (41.67)	50	(58.33) 62.5 (66.67)	75	82.5	90	(91.66) 92.5 (93.66)	95	(96.33) 97 (97.67)	99
4.0-4.2	1		2		3		4	5	6	7	8	9	10	11 - 12	13	14 - 15	16
4.3-4.5	1		2		3	4	5	6	7	8 - 9	10	11	12	13	14	15 - 16	17
4.6-4.8	1		2	3	4		5	6 - 7	8	9 - 10	11	12	13		14	15 - 16	17
4.9-4.11	2		3		4	5	6	7 - 8	9	10 - 11	12		13	14	15	16	17
5.0-5.5	3		4	5	6	7	8	9 - 10	11	12	13	14	15		16		17
5.6-5.11	5		6		7	8	9	10 - 11	12	13	14		15		16		17
6.0-6.11	5	6	7	8	9	10	11	12 - 13	14	15	16		17		18		19
7.0-7.11	6	7 - 8	9		10	11-12	13	14 - 15	15	16	17		18		19		20
8.0-8.11	9	10	11		12	13	14	15	16	17	18		-		19		20
9.0-9.11	10	11-12	13		14		15	16	17		18		-		19		20
10.0-10.11	11	12	13	14	15		16	17	18		-		-		19		20
11.0-11.11	12	13	14		15		16	17	18		-		-		19		20
12.0-12.11	13	14	15		16		17		18		-		-		19		20

Appendix 7 Neurocognitive assessment tools - summary

Area assessed	Test	Age Range	Pros	Limitations
Cognitive	Griffiths	0 – 6 years	Validated for language and culture Score: Developmental-Quotient and subquotients	Unreliable under 1 yr Time consuming to administer
	Ravens (non verbal)	3 ½-11 years	Easy and rapid administration Non verbal intelligence	May be affected by prior limited exposure to picture/book material
	DAP (draw-a-person) (non verbal)	3 –15 years	Easy administration Developmental age	May be affected by prior limited exposure to picture/book material
Visual perception and motor skills	Beery	Ages 4 and up	Brief administration Easy to score	Only tests fine motor
Communication	TROG	4 – 12 years	Receptive language tested	Not expressive or articulation testing Not validated for Xhosa
Adaptive Behaviour	ABC (aberrant behaviour checklist – community)	School age child	Looks at irritability, lethargy, stereotypy, hyperactivity and inappropriate speech	Not formal psychological testing

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