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**Neuropsychiatric Profile of a Cohort of Perinatally
Infected HIV Positive Children after one year of
Antiretroviral Medication**

by

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DECLARATION

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ABSTRACT

The Highly Active Antiretroviral Therapy (HAART) era in the mid-nineties signalled a dramatic change in the long-term outcome of Human Immunodeficiency Virus (HIV). Many children have shown significant neurologic benefit, and in particular, a decline in the incidence of HIV encephalopathy. As increasing numbers of children have survived into adolescence and early adulthood new challenges have arisen, such as the detection and characterization of milder forms of HIV-associated neurocognitive deficits in children previously thought to be asymptomatic.

In order to explore the neurocognitive and neuropsychiatric aspects of HIV in children initiated late onto HAART, a clinical case series is presented of nine children who underwent psychiatric evaluations, neurological examinations, and neurocognitive tests. The children were referred to a neuropsychiatric clinic at an academic children's hospital in Cape Town, South Africa, between September 2004 and August 2005. In addition, data was collected from the medical records of the two infectious diseases clinics managing their HIV illness. Following this, with a view to (a) comparing local findings with the published literature, and (b) to consolidate the reported neurocognitive and neuropsychiatric manifestations of children infected with HIV, a systematic review of the literature was performed.

It was found that the majority of children were in the borderline to mild disability range of intellectual functioning. Neurological examinations revealed no abnormalities except for microcephaly in two children and brisk reflexes in one of the two. Electroencephalograms (EEG's) were abnormal in two of the nine children. Magnetic Resonance Imaging (MRI) brain scans were normal in two referred cases. Four of the nine children were diagnosed with ADHD. Other diagnoses included adjustment disorders (n=3), and oppositional defiant disorder (n=2). The reviewed literature reports that Central Nervous System involvement and neurocognitive deficits are common and occur early in untreated, HIV positive children. HAART has significantly reduced the incidence of severe forms of HIV-associated neurocognitive disorders, especially HIV encephalopathy, but mild to moderate problems persist. Despite improvements in scores of broad based IQ tests, children continued to present with executive functioning deficits on neuropsychological testing, as well as significant learning problems. Higher rates of psychiatric disorders (mainly ADHD, depression and anxiety), prescriptions of psychotropic

medications and hospital admissions, were evident compared to the normal (HIV negative) population.

While a considerable reduction in disease progression and deaths has occurred in children treated with HAART, behavioural and scholastic difficulties continue to negatively impact on overall functioning and quality of life of children living with HIV. While early initiation of HAART is advocated, and may reduce the risk of severe forms of neurologic and neurocognitive disease, clinicians need to be able to assess and manage the minor neurocognitive and behavioural problems, as these can exert deleterious effects on the cohort of children now surviving into adulthood.

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ABBREVIATIONS

?	Query
2 ⁰	Secondary
3TC	Lamivudine (LAM)
AIDS	Acquired Immune Deficiency Syndrome
ABC	Abacavir
ADHD	Attention Deficit Hyperactivity Disorder
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Zidovudine
BBB	Blood Brain Barrier
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
BSID	Bayley Scale of Infant Development
CBCL	The Child Behaviour Checklist
CDC	Centre for Disease Control and Prevention
CDI	Childhood Depression Inventory
CMV	Cytomegalovirus
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computer Tomography
CVA	Cerebrovascular Accident
d4T	Stavudine
DBRPC	Double blind randomised placebo controlled
ddI	Didanosine
DQ	Developmental Quotient

DSM IV	Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
EEG	Electroencephalogram
ELSEN	Education for Learners with Special Educational Needs
EPSE	Extrapyramidal side effects
FAS	Foetal Alcohol Syndrome
FIs	Fusion Inhibitors
FSIQ	Full Scale Intelligence Quotient
GCI	Global Cognitive Index
GMC	General Medical Condition
HAND	HIV Associated Neurocognitive Deficits
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HIV RNA	HIV Ribonucleic Acid
HNU	HIV Negative HIV Unexposed
IQ	Intelligence Quotient
IRIS	Immune Reconstitution Inflammatory Syndrome
JSAIS	Junior South African Individual Scale
KAL	Kaletra
LAM	Lamivudine (3TC)
LA	Long Acting
LD	Learning Disability
LDL	Lower than detectable limit
LRTI	Lower Respiratory Tract Infection
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDI	Mental developmental index

MHPs	Mental Health Problems
MPH	Methylphenidate
MRI	Magnetic Resonance Imaging
NOS	Not Otherwise Specified
NNRTI	Non-nucleotide Reverse Transcriptase Inhibitor
NRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
ODD	Oppositional Defiant Disorder
PACTG	Pediatric AIDS Clinical Trials Group
PDD	Pervasive Developmental Disorder
PDI	Psychomotor Developmental Index
PE	Progressive Encephalopathy
PHACS	Paediatric HIV/AIDS cohort Study
PHE	Progressive HIV Encephalopathy
PHEU	Perinatally HIV Exposed Uninfected
PHIV	Perinatally HIV Infected
PIQ	Performance IQ
PIs	Protease Inhibitors
PMTCT	Prevention of Mother-to-Child Transmission Therapy
PTB	Pulmonary Tuberculosis
PTSD	Post Traumatic Stress Disorder
RNA	Ribonucleic Acid
RTV	Ritonavir
SA	Short Acting
SCID	Structured Clinical Interview (based on DSM-IV)
SD	Standard Deviations
SSAIS	Senior South African Individual Scale

SSAIS-R	Senior South African Individual Scale Revised
SSRI	Selective Serotonin Reuptake Inhibitor
SUDs	Substance Use Disorders
VIQ	Verbal IQ
VL	Viral Load
WHO	World Health Organisation
WISC III	The Wechsler Intelligence Scale for Children, Third Edition
WISC IV	The Wechsler Intelligence Scale for Children, Fourth Edition
WISC-R	The Wechsler Intelligence Scale for Children, Revised Edition
ZDV	Zidovudine

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CHAPTER ONE

1.1 INTRODUCTION

This chapter describes the findings of research studies conducted prior to the Highly Active Antiretroviral Therapy (HAART) era exploring the neurocognitive, neurological and psychiatric presentations in treatment-naïve Human Immunodeficiency Virus (HIV) positive children or those on antiretroviral monotherapy. A brief description of antiretroviral agents, impact on progressive HIV encephalopathy (PHE) and potential neurotoxic side effects will be provided.

During the mid-1990s the introduction of HAART, lately referred to as Combination Antiretroviral Treatment (CART), dramatically changed the nature of AIDS from a rapidly fatal disease to that of a chronic illness. Combination therapies with Protease Inhibitors (PI) became the standard treatment regimen for children, adolescents and adults (Feingold AR *et al* 2000). The impact of CART has significantly decreased the morbidity and mortality rates of HIV/AIDS. Children are living longer and most are surviving into adolescence and some into adulthood (Thorne C *et al* 2002, Hazra R *et al* 2010). Clinical and research issues pertinent to children have likewise shifted with their increased survival, to include concerns about the long-term neurocognitive sequelae of HIV and mental health issues (Mitchel CD 2006, Van Rie A *et al* 2007).

The impact of HAART was experienced considerably later in South Africa, following the 'roll-out' of the National Antiretroviral Programme in 2003, after years of pressure on the South African Government by the Treatment Action Campaign (TAC) and other activist groups (Achmat Z *et al* 2007). One effect of this has been that more people have access to antiretroviral medication, with the possibility of more children surviving to adolescence and adulthood (Eley B *et al* 2006, Davies MA *et al* 2009). While the release of the operational plan for the '*Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*,' in November 2003, was considered to be ground-breaking and the largest in the world, it stated

that, by 2009, all HIV-infected individuals requiring ART would be able to access therapy within the public health care system (Department of Health). However, the rollout has been criticized for its slow pace as funding, human, and infrastructural obstacles have impacted on the pace of the ART scale-up. Furthermore, the disparity in access to ART among the nine provinces persists: the more affluent provinces are receiving more donor funds (Ijumba P *et al* 2003, Meyers T *et al* 2007, Ojikutu B *et al* 2007). Progress in the prevention of mother to child transmission (PMCTC) and ART rollout to children have been less than favourable, with 40% of total child deaths in South Africa still due to HIV. South African Perinatally HIV infected children (PHIV) continue to be substantially denied the benefits of ART or only access treatment years after HIV diagnosis, and therefore remain at risk from HIV, both in terms of survival and poor long-term neurocognitive outcomes (Geddes R *et al* 2011).

1.1.1 Impact of HIV on neurocognitive development in untreated HIV infected children

A review of early studies examining the nature and impact of HIV on the neurocognitive development of PHIV children reveals that neurocognitive impairment occurs early, and progresses over time, in untreated perinatally HIV-infected (PHIV) children, or children on mono-therapy (Aylward EH *et al* 1992, Mellins CA *et al* 1994, Chace C *et al* 1995, Gay CL *et al* 1995, Fundaro C *et al* 1998). The pathophysiology of neurodevelopmental impairments may involve pro-inflammatory dysfunction of microvascular processes that interplay with immune mechanisms at the synaptic level of the brain (Mekmulluka J *et al* 2009, Kapetanovic s *et al* 2010).

The reported prevalence rates of neurocognitive impairment ranges from 8-60% in PHIV children. Generally, neurocognitive performance is poorer in HIV positive children than Perinatally Exposed Uninfected Children (PHEU) and HIV negative HIV Unexposed (HNU) children. In the infected group, intellectual function ranges from above average to intellectually disabled. Neurocognitive scores, however, tend to cluster in the low average to borderline range of intellectual functioning (Levenson J *et al* Mellins CA 1992).

Studies where cohorts underwent neuropsychological testing revealed that executive functioning deficits might be an early indicator of neurocognitive problems

in HIV positive children. These problems were identified in children where neurocognitive deficits were not identified on broad IQ tests. Testing identified deficits in mental processing, sequential processing, comprehension, memory, visuospatial, and time orientation tasks (Tardieu M *et al* 1995). Other studies revealed deficits suggestive of frontal lobe dysfunction, such as in sustained attention, processing speed, motor speed and visuomotor integration (Fundaro C *et al* 1998, Fishkin PE *et al* 2000). Deficits in fine motor performance were related to CD4 count, suggesting that this could be used as a behavioural marker of immune system compromise (Blanchette N *et al* 2002, Foster C *et al* 2006).

A few studies attempted to identify whether HIV is an independent risk factor for neurocognitive deficits (Chase C *et al* 2000, Mc Grath N *et al* 2006). The results were equivocal, with some studies supporting the hypothesis that HIV had an independent and substantial impact on the neurocognitive performance of HIV-infected children (Chase C *et al* 2000, Blanchette N *et al* 2001). The negative studies however suggested that risk factors other than HIV may be the main 'drivers' of developmental deficits observed, including exposure to illicit drugs pre-natally, poverty and poor nutrition. A number of studies did reveal that poor neurocognitive performance was associated with more severe disease, higher baseline viral loads and more severe immune compromise (Nozyce M *et al* 1994, Pollack H *et al* 1996, Pearson DA *et al* 2000). These studies found that the more severe the immune compromise, the more severe the neurocognitive deficits, regardless of HIV status. The conclusion reached was that immunosuppression is a unique predictor of overall neurocognitive functioning, in infected or uninfected children (Henry R *et al* 1996, Brouwers P *et al* 1995).

There appears to be an association between the degree of developmental delay and the timing of HIV infection. Children, who test HIV positive at birth, have a 14.9 times increased rate of developmental delay during the first three years of life compared to those who tested positive at a later age. Studies also suggest that early infection is not only associated with a worse neurocognitive outcome, but also a poorer prognosis for overall HIV disease (Smith R *et al* 2000, Mc Grath N *et al* 2006).

Studies that explored the impact of environmental factors on neurocognitive outcomes in HIV infected children were the most challenging and failed to definitively establish the independent neurocognitive effects of HIV compared to low socio-economic status, intrauterine exposure to illicit drugs, and other adverse environmental risk factors (Boivin MJ *et al* 1995, Kullgren K *et al* 2004). However, a few studies demonstrated that the cumulative impact of adverse environmental stressors in addition to HIV positive status conferred a worse neurocognitive outcome (Mellins CA *et al* 1994). A few studies identified protective factors against the adverse neurocognitive impact of poverty, irrespective of HIV status. These factors were the quality of the caregiver-child interactions, the caregiver-child ratio, parenting skills and provision of stimulation such as toys and reading material (Coscia JM *et al* 2001, Kullgren KA *et al* 2004).

1.1.2 Studies conducted on the African continent (other than in South Africa)

Six studies were conducted in Rwanda, The Democratic Republic of Congo (DRC), Uganda and Tanzania between 1993 and 2006 (Msellati P *et al* 1993, Boivin MJ *et al* 1995, Boivin MJ *et al* 1995, Drotar D *et al* 1997, Bagenda D *et al* 2006, Peterson NJ *et al* 2001, Mc Grath N *et al* 2006). These studies are important as the samples were naïve to Antiretroviral Treatment (ART) and born to mothers who did not abuse drugs. In contrast, most studies in the developed world were conducted in urban, poverty stricken settings, with children born to drug abusing mothers. Likewise, a study conducted in South Africa (Smith L *et al* 2008) was conducted in a peri-urban setting where the likelihood of prenatal exposure to illicit drugs was high. That study was therefore excluded from this analysis. Prior to the HAART era, it was rare to find cohorts that were entirely ART naïve as they were often treated with one or two drugs. The African studies therefore, may have more clearly identified the negative neurocognitive factors related to the virus, rather than those related to environmental factors such as perinatal exposure to drugs or treatment effects. The results of the six studies conducted in Africa were surprisingly similar, in that PHIV children continued to perform more poorly than PHEU and HIV negative unexposed (HNU) children do. Older children, however, demonstrated similar performance to PHEU children and HNU controls suggesting that these treatment naïve children may have represented a group of 'survivors' infected by a less virulent strain of HIV. This unique group of slow performers present later by progressing to an AIDS diagnosis. This is related to transmission of low fitness viruses by the mother as well as efficacious Group Antigen (Gag) specific CD8 T cell responses in the

immune recipient (infant). This facilitates immune control and reduces replicative capacity (Ferrand R *et al* 2009, Thobakgale C *et al* 2009, Prado J *et al* 2009). Neuropsychological testing in this group of African children likewise produced a similar profile to those studies conducted in the USA, with language, spatial and memory deficits evident. These studies, therefore, may confirm an independent negative neurocognitive effect of HIV. However, the low number of studies and small sample sizes remain mitigating factors in definitively establishing an independent adverse neurocognitive effect of HIV.

1.1.3 Neurological manifestations of HIV in children and adolescents

Prior to the advent of HAART, PHIV children presented at an early age and commonly with progressive neurological disease, compared to adults. Early estimates were that 80-90% of PHIV children would develop Central Nervous System (CNS) and neurocognitive dysfunction (Ultrmann M *et al* 1987, Belman A *et al* 1988, Habibi P *et al* 1989, Diamond GW *et al* 1989, Tardieu M *et al* 1994, Belman A *et al* 1994). HIV therefore invades the developing CNS earlier and with greater severity than observed in adults, with a more rapid progression to death (Schwartz L *et al* 2006). HIV causes neuronal damage in the brain by being both directly neurotoxic and causing an indirect neuro-inflammatory response. It crosses the Blood-Brain Barrier (BBB) via a 'Trojan-horse-type' mechanism, by infecting macrophages. Once in the brain, it invades and activates microglial cells, and produces neurotoxins that lead to inflammatory processes, neuronal damage, and cell death. It is thought that the severity of these clinical and neurological deficits is linked to the extent of this damage (Dube B *et al* 2005, Crawford JR *et al* 2010). The presence of neurological complications, particularly abnormalities on imaging are associated with poorer neurocognitive outcomes and poorer overall prognosis compared to neurologically asymptomatic children.

Common reported neurological sequelae of HIV in children are microcephaly, encephalopathy, myelopathy and peripheral neuropathy. Primary lymphoma of the CNS and metastasis of systemic lymphoma are common types of CNS tumours in HIV infected children (Kieck J *et al* 2004). Cerebrovascular Accidents (CVA's) appear either as a result of HIV or secondary to AIDS associated illness, for example, cardiomyopathy, thrombosis or embolism. The most severe neurological manifestation of HIV in children is progressive HIV encephalopathy (PHE) which presents clinically as a triad of neurocognitive, motor and behavioural deficits

(Wilmshurst J *et al* 2006, Chiriboga CA *et al* 2005). Psychomotor slowing and apathy are early manifestations of neurocognitive impairment and early dementia in infected children. In young children, there can be a loss of, or a failure to acquire, new developmental milestones, and, in older children, a deterioration in school performance. Psychometric tests often show a decline in composite IQ scores. Speech and language difficulties present with predominantly expressive but also receptive language difficulties. Some children develop microcephaly because of both cortical and sub cortical atrophy. Memory impairment may be a manifestation of HIV related central nervous system disease, with deficits in visuospatial memory, verbal learning and rote recall. Disturbances of motor functioning are the most frequent neurological manifestation and presents initially with changes in gait and toe-walking, because of hyperreflexia and increased tone. Other early presentations are gross and fine motor deficits with clumsiness, low muscle tone, and poor pencil grip. With further deterioration, there is a progression to spastic paresis, rigidity or muscle weakness, dystonic posturing, ataxia, tremor, and seizures (Tardieu M *et al* 1999). The third manifestation of the encephalopathy triad is behavioural aberration, with typical symptoms being apathy, uncooperativeness, and aggression. Disturbances of affect (emotional lability) and problems with hyperactivity and inattentiveness have also been noted. In the absence of significant social stressors, behavioural problems tend to escalate as the disease becomes more advanced (Wachsler-Felder JL *et al* 2008).

The neuropathological finding most commonly associated with developmental and motor deficits is myelinopathy. Myelination of the frontal and parietal regions continues through adolescence to early adulthood. Deficits in higher cortical functioning such as language, sequencing and sensory integration may, therefore, be expected in infected children. Advanced developmental skills, such as, visual motor- integration, processing speed, sequential processing and verbal memory only develop in later childhood, so will not be detected early or with broad based neurocognitive tests.

Two relatively distinct clinical courses have been identified, the more devastating and severe rapidly progressive encephalopathy of childhood, and the more benign slowly progressive course. Age of onset of the rapid PHE is usually under one year and appears to be related to the occurrence of pathological events during the late prenatal period and high maternal viral load (Ojukwu IC *et al* 2007, Tardieu M *et al*

2000). Slowly progressive encephalopathy is a much less severe neurological syndrome and commonly presents with hypotonia, marked delays in motor milestones, neurocognitive delay, and language delay (both expressive and receptive) (Ojukwu IC *et al* 2007). Radiological examination (CT and MRI) usually reveals cortical atrophy and ventricular dilatation. Calcifications of the basal ganglia and white matter subcortical changes have been found to be consistent features. There appears to be a direct correlation between progression and severity of encephalopathy and Computer Tomography (CT) scan findings. Cerebrospinal fluid (CSF) viral loads are higher in patients who present with neuropsychological impairments. In most instances, viral titres decrease after initiation of HAART, but in some patients they remain high (Mitchell CD 2006, Tardieu M *et al* 1999, Van Rie A *et al* 2007).

1.1.4 Neuropsychiatric presentations in HIV infected children and adolescents

Pre-HAART studies, reviews and reports specifically exploring the psychiatric manifestations of HIV in children and adolescents are limited and suggest that Attention Deficit Hyperactivity Disorder (ADHD), depression and anxiety disorders are common (Havens JF *et al* 1994, Tardieu M *et al* 1995, Moss H *et al* 1998, Lwin R *et al* 2001). Studies specifically exploring psychiatric disorders in HIV positive adolescents revealed very high lifetime prevalence of psychiatric disorders, particularly depression, substance abuse and conduct disturbances (Brown LK *et al* 2001, Pao M *et al* 2000, Williams PL *et al* 2010). Higher rates of psychiatric hospitalisation and psychotropic drug use were evident in this psychiatrically 'at-risk' population (Gaughan DM *et al* 2004, Wiener L *et al* 2006, Donenberg GR *et al* 2005). Recent reviews by Sharko and Roa described a limited literature with small samples, inconsistent measurements, and wide age ranges. A review of existing research by Sharko *et al* yielded eight studies, between 1993 and 2004. However, participants were not all perinatally infected and it was unclear whether participants in later studies were on ART regimens. Outcomes concurred with other studies, with higher rates of ADHD, depression, and anxiety disorders (including PTSD) being reported (Sharko *et al* 2006). The review by Rao similarly revealed few studies on psychiatric disorders, with low rates of psychosis and mania in children and adolescents compared to HIV positive adults (Rao *et al* 2007). Studies were not able to ascribe those aetiological factors related to the virus and those due to stressful family and social environments (Mellins CA *et al* 2003, Wiener L *et al*

2006). However, some studies demonstrated an equal male: female ratio in the incidence of ADHD (Nozyce M *et al* 2006). This is in contrast to the common gender distribution of ADHD, which has a male preponderance among HIV negative children (Pliszka S *et al* 2007). This discrepancy may suggest a partial viral aetiology in the presentation of ADHD in HIV positive children. Another finding suggestive of a possible viral aetiology is that the presence of depressive symptoms appeared to be associated with disease progression and a poorer prognosis (Misdrahi D *et al* 2004).

1.1.5 Antiretroviral medication in children and adolescents

There are five main classes of antiretroviral drugs: Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non Nucleotide Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), and Fusion Inhibitors (FIs). Newer classes of drugs are Entry Inhibitor CCR5 co-receptor antagonists, and HIV Integrase Strand Transfer Inhibitors (INSTIs) (Penazzato M *et al* 2010, Cysique LA *et al* 2009). There are two main mechanisms of action of ART, namely inhibition of viral replication (NRTIs, NNRTIs and PI's) and inhibition of viral entry into the target cell (FIs) (Bartlett J *et al* 2004). FIs are administered via subcutaneous injection that makes it a less favourable option for use in children. Long-term use of the antiretroviral agents has raised a number of concerns, particularly in relation to the neurocognitive impact of these drugs. Problematic issues are the penetrance of the Blood Brain Barrier (BBB), neurotoxic and psychiatric side effects, and drug–drug interactions between antiretroviral and psychotropic medications.

Antiretroviral medications are not equal in their ability to penetrate the BBB. The issue of brain penetrance is an important one with regards to effective management of neuropsychiatric manifestations. Lack of brain penetrance means that despite systemic improvements and decreased viral loads, the brain potentially can remain a sanctuary site for the virus, resulting in compartmentalisation. This would ensure viral persistence (and in some cases, genotypic divergence) and continued viral replication in the CNS, higher Cerebrospinal Fluid (CSF) viral loads and a potential source of therapy resistant strains (Patel K *et al* 2009). The NRTIs AZT, Stavudine (d4T), Lamivudine (3TC) and Abacavir (ABC) and the NNRTI, Nevirapine (NVP), penetrate the BBB effectively. Efavirenz, however, is highly protein bound and studies show that only a minimal percentage of plasma concentration reaches the

CSF (Chen L *et al* 2007, Patel K *et al* 2009). In spite of this, it has still been shown to achieve a sufficient concentration to inhibit replication of HIV. The Protease Inhibitors, with the exception of Indinavir have relatively poor BBB penetration, which has generated concern that PI based HAART, would not effectively treat CNS disease. Studies have shown, however, that PIs effectively reduce CSF viral loads to undetectable levels. MRI scans have also shown reversal of white matter lesions and metabolic improvements on Proton Magnetic Resonance Spectroscopy (Garvey L *et al* 2011). A number of cross-sectional and longitudinal studies have documented benefits for the full range of HIV associated neurocognitive symptoms with particular improvements in neurocognitive speed in children on PI-based HAART regimens (Raskino C *et al* 1999, Letendre S *et al* 2008, Sanchez-Ramon S *et al* 2003).

Agents used to treat HIV infection have been identified as a potential cause of neurological and psychological side effects. ART that penetrates the CNS may in some cases cause delirium, psychiatric presentations, neurocognitive impairment and seizures. For example, Efavirenz and AZT both have good CNS penetration, but are themselves associated with potentially significant neuropsychiatric complications. The CNS side effects of Efavirenz such as dizziness, vivid dreams, headaches, confusion and perceptual disturbances have been reported in adult studies. A case study by Louwenhaupt reported psychosis in a twelve year old girl, with an increased serum level of Efavirenz (Lowenhaupt EA *et al* 2007), and another study by Ciccarelli *et al* reported neurocognitive disorders associated with Efavirenz use in a group of otherwise asymptomatic HIV positive adults, suggesting potential neurotoxicity of this drug (Ciccarelli N *et al* 2011). Side effects sometimes associated with AZT therapy are confusion, agitation, insomnia, mania, depression, myalgia, and headache (Bhana N *et al* 2002). Reports of potential neurotoxic side effects of ART are from adult studies, with no longitudinal prospective follow up studies exploring long-term adverse CNS effects of ART in the paediatric population (Langford TD *et al* 2002, Barlett J *et al* 2004, Nath A *et al* 1998).

The potential for drug-drug interactions between psychotropic and antiretroviral medications is related to the cytochrome P450 enzymes of the liver, which metabolises antidepressants such as the Selective Serotonin Reuptake Inhibitors (SSRIs) and atypical neuroleptic agents. They include P450, 2D6, 1A2, 2C18 and 3A4, all of which are involved in the metabolism of the antiretroviral agents,

especially the PIs. There is, thus, a potential for competition by these medications resulting in raised or toxic levels of either or all classes of drugs (Gonzalez A *et al* 1998, Chen LF *et al* 2007). A further complication is that a number of SSRIs and PIs potentially inhibit these enzymes (Thompson A *et al* 2006).

Other adverse reactions associated with ART may indirectly affect the neurodevelopmental status of infected children such as adherence, tolerability, drug resistance and Immune Reconstitution Inflammatory Syndrome (IRIS), which may manifest as a neurological complication, so called 'neuroIRIS' (Smith K *et al* 2009). Rigorous adherence to complex medication regimes is important, as inconsistent use leads to the development of viral resistance (Sethi AK *et al* 2003). Children are dependent on adults (parents and teachers) to receive their medication. Therefore, an evaluation of caregivers, the home and the educational environment is an essential aspect of the management of children on antiretroviral medication. Adherence may be negatively impacted upon by the child's level of neurocognitive functioning (older children who self-administer medication), stigma, shame and secrecy (Brown LK *et al* 2000).

Clinical response to ART may differ in children compared to adults as they tend to have higher baseline HIV Ribonucleic Acid (HIV RNA) levels, which places them at higher risk of treatment failure or poor response to treatment. Viral loads also tend to decrease more slowly after initiation of treatment. In some children, an aggressive therapeutic approach, using multiple drug regimens (4 or 5 drugs), at high doses, is necessary to ensure treatment success ('mega HAART'). This strategy, though possibly virologically successful, increases the risk of increased toxicity and the use of large quantities of tablets (King JR *et al* 2003).

Finally, studies have demonstrated that the pharmacokinetics of ART can vary dramatically by age in the paediatric population. The cytochrome P450 system (which metabolises the PIs) is not fully developed in children. Drug distribution, metabolism and clearance may also be very different to adults, which may impact on paediatric dosages prescribed and responses to treatment. Decreased metabolism increases the risk of elevated plasma concentrations of the drug and increases the risk of drug toxicity. There are few studies, which evaluate the pharmacokinetics of these drugs in the paediatric populations. This may impact negatively on decisions about dosages, which often occur without adequate data (King JR *et al* 2002).

1.1.6 Access to ART and the implications for long-term neuropsychiatric outcomes

The decline in HIV encephalopathy has been one of the most dramatic effects of HAART, with reductions in prevalence in PHIV children from 35-50%, to less than 2% (Roberson KR *et al* 2007, Chiriboga CA *et al* 2005, Hazra R *et al* 2007). During the pre-HAART era it was the most devastating manifestation of HIV in children, resulting in severe global neurocognitive deficits. However, as children survive into adolescence subtler neurocognitive deficits may be evident, despite long-term treatment with HAART. These may have a significantly negative impact on youth as they survive into adulthood.

Causes of the persistence of the milder forms of HIV Associated Neurocognitive Deficits (HAND) in the HAART era are multiple. Possible explanations include late initiation of ART (with irreversible brain injury prior to initiating treatment), incomplete viral suppression in the CNS due to poor CNS penetration of certain drugs and the presence of drug-resistant viral strains. Another possibility suggested is that prolonged exposure to inflammatory responses and neurotoxic viral proteins could result in neural injury or dysfunction (Cysique L *et al* 2009, Joska JA *et al* 2010, Heaton RK *et al* 2011). Neurobehavioral disorders have been reported since the pre HAART era, with improvements demonstrated after initiation of mono- or dual therapy. However, children on HAART have shown minimal further improvements, with recent studies demonstrating high rates of psychiatric disorders in PHIV youth as they enter adolescence.

Early initiation of ART, before the age of 6 months, is associated with decreased mortality and superior clinical outcomes (Purchase SE *et al* 2011, Violari A *et al* 2008). A study by Faye *et al* revealed that in infants initiated on treatment before age six months, none presented with encephalopathy or opportunistic infections by age two. However, 6 out of 40 infants initiated on ART after 6 months presented with 7 AIDS defining events, 3 of which were encephalopathy (Faye A *et al* 2004). A study conducted in South Africa, the CHER study (Children with HIV Early Antiretroviral Treatment), demonstrated a 76% reduction in infant mortality among infants initiated on ART before age 12 weeks (Violari A *et al* 2008). Furthermore, superior neurodevelopmental scores were achieved at 11 months, compared to infants who were initiated on treatment later (Laughton B *et al* 2009). On the basis

of this strong evidence, initiation of HAART is recommended in the first year of life in the developed world and resource limited settings (Horwood C *et al* 2009, Jaspan H *et al* 2011).

Within the context of what has been elaborated in this chapter, it is important to define the neuropsychiatric profile of South African HIV positive children. Most school age children have not benefitted from early initiation of ART and may therefore present with significant residual neurocognitive and behavioural problems because of late initiation of treatment. The following chapter describes a clinical cohort of nine South African children referred to a neuropsychiatric clinic one year after initiation of HAART and who presented with behavioural problems and declining academic performance.

University of Cape Town

CHAPTER TWO

This chapter describes the findings of a clinical case series of a cohort of perinatally HIV infected children, referred to a neuropsychiatric clinic, at a children's hospital.

2.1 MOTIVATION FOR THE STUDY

The Division of Child and Adolescent Psychiatry of the Red Cross Children's Hospital has provided a consulting service to a religiously affiliated children's home, which accommodates HIV positive children. The children's home is situated in the city of Cape Town. It accommodates children from infancy to the age of thirteen years. Some children have been accommodated till the age of eighteen because of placement difficulties. It is one of the few children's homes that have accommodated HIV positive children. Over the years they have striven to provide the necessary care for chronically ill and dying children. The children are raised in the Catholic faith and cared for by an order of nuns and childcare workers. The children live in a relatively protected environment and appear to be shielded from the (often severe) psychosocial stressors experienced by infected children living in the community.

Clinicians from the Child and Adolescent Psychiatry service undertook monthly consultations to staff. Assessments of children with emotional and behavioural problems were undertaken. Common problem behaviours were discussed at these consultations. The children were referred to the hospital when they experienced peer group difficulties, aggression, and hyperactivity. Other issues like coping with illness, frequent hospitalizations, and deaths were explored with both the staff and the children. It was noticed that as the children approached adolescence (ten to twelve years old), they tended to become concerned about physical appearance (as they were usually smaller in stature than their peers), the impact of the disclosure of their HIV status, and leaving the institution when they turned thirteen years old. A number of the children had to cope with the emotionally fraught experience of being reunited and placed with estranged biological parents and families on reaching the age of thirteen when they would be discharged from the children's home.

A substantial number of the children placed at the particular children's home benefited from an externally funded ARV programme. This was spearheaded by a paediatrician at a local general hospital (Groote Schuur), prior to the rollout of the national ARV programme in late 2003 and early 2004. There was a dramatic improvement in the physical health of the children with a significant reduction in the number of deaths on receiving ART. Overall academic performance, however, did not improve and either remained the same or deteriorated to the extent that some of the children were removed from mainstream schools and placed in special schools termed ELSEN schools. ELSEN is an acronym for "Education for Learners with Special Education Needs". These are schools which provide a full package of remedial services, by a multidisciplinary team, to learners with learning difficulties or who may experience other barriers to learning. Problem behaviours also appeared to escalate within the first year after ART was started. Since the middle of 2004, there were requests to assess a group of children who were presenting with the following pattern of behaviour: disturbed and at times bizarre behaviour (episodes of aggression, perceptual disturbances and confusion), as well as a neurocognitive decline, with the impression of a deterioration of academic ability (in reading and writing), and in social skills. This raised a concern about the cause of this presentation, as it was unclear whether it was due to psychosocial stressors, side effects of the ART, or because of a poor response to the ARV medications.

There is a substantial literature describing the impact of institutional rearing on children. Earlier studies consistently report more negative outcomes socially, academically and emotionally for children raised in institutions and more favourable outcomes for children placed in foster care. Outcomes are reported to be even more favourable when children are placed in the care of biologically related families (Rutter M 2000, Zeanah CH *et al* 2000, Smyke AT *et al* 2007, Van Ijzendoorn MH *et al* 2008). Institutionalized children are exposed to multiple carers, as opposed to one or two parents in foster homes. They often display indiscriminate attachments, and poor interpersonal boundaries (Smyke AT *et al* 2002). Furthermore, there is an increased risk of abuse, peer relational problems and psychiatric disorders, particularly Attention Deficit Hyperactivity Disorder (ADHD), depression and substance abuse (Roy P *et al* 2004). Loss of contact with biological families tends to confer a worse outcome. More successful family reconstitution is associated with positive outcomes (Rutter M 2000). A study by Taussig *et al*, however, reported the

opposite, with more negative outcomes (delinquency, risk behaviours, suspensions and externalizing behaviours) in youth reunified with biological families (Taussig H *et al* 2001).

Recent reviews and selective meta-analyses on residential care in developed countries suggest that outcomes may be more favourable than previously assumed. Positive outcomes are demonstrated where behavioural and therapeutic methods focusing on family involvement are employed (Knorth E *et al* 2008). It is not clear whether one can generalize these outcomes to institutionalized HIV positive children or AIDS orphans living in developing countries.

Such environments are compromised by a lack of economic resources, therapeutic and supportive services, which may severely compromise biological families' capacity to provide adequate care for orphaned relatives (Richter L *et al* 2004, Madhavan S *et al* 2004). Studies conducted in Africa, focused on AIDS orphans, suggest that institutionalized care in adverse environments may provide a degree of stability and quality of care which is arguably superior to community based care (Kimani C *et al* 2009, Beard J *et al* 2005). Recent studies such as 'The Positive Outcomes for Orphans Study', conducted a survey in six sites across five 'less wealthy' countries and reported that physical growth, cognitive and emotional functioning were no worse for institution-reared than community based children. The hypothesis that institutional care is systematically associated with poorer outcomes was therefore not supported by this study (Whettan *et al* 2009).

As the treating clinician and visiting consultant to the children's home, it became evident to me that the children were possibly experiencing a number of stressors, which could explain their clinical presentations. The motivation for this study was therefore provided by the need to clearly identify the multiple factors (biological, psychological and social), which appeared to contribute to the children's clinical presentation.

2.2 PURPOSE OF THE STUDY

The purpose of the study is to describe the medical and neuropsychiatric presentations of a sample of PHIV children who have been treated with antiretroviral medications for more than one year.

2.3 THE SPECIFIC OBJECTIVES OF THIS STUDY

The specific objectives are to identify, with reference to the literature on paediatric HIV and ART, possible reasons for the clinical presentations in the sample of children. This will be done in order to inform the hypotheses for a larger study by describing the factors related to the human immunodeficiency virus, those related to treatments administered and those related to the broader psychosocial factors impacting on the children.

2.4 METHODOLOGY

2.4.1 Study Design

This descriptive study consists of the clinical cases manifest by the first HIV positive children referred to a newly established neuropsychiatric clinic at the Red Cross Children's Hospital and who underwent assessment and follow up. Case files and medical records were evaluated and analysed. Medical records of the same children were also examined at another treating hospital involved with the children's care (Groote Schuur Hospital). Inclusion criteria were children thirteen years and younger, with a documented history of vertical/perinatal HIV infection, who had been initiated on ART for at least one year at the point of first evaluation at the clinic. The children were a sample of institutionalised children, referred to the neuropsychiatric clinic with behavioural problems, over a course of one year (Mid 2004-mid 2005). Other children referred during that period were living in the community in the care of family. Children resident in the community were likely to have experienced different home circumstances and psychosocial stressors compared to institutionalized children and were less likely to have been on ART for a period of one year. In order

to control for various confounding factors the following children were therefore excluded from the sample: non-institutionalized children, age fourteen years and above, transfusion-infected children, those who were not vertically/perinatally infected (history of sexual molestation, or where the history was unclear) and children not initiated on ART. Clinical notes were reviewed and collated at various points over a one-year period.

2.4.2 Study population and sampling

The study sample consisted of nine perinatally infected, institutionalized children aged from five to thirteen years and six months referred to a neuropsychiatric clinic at the Red Cross Children's Hospital between September 2004 and August 2005. All the children had been on ART for more than one year. The children were referred for a neuropsychiatric assessment, as there were concerns about behavioural difficulties, new onset of psychiatric symptomatology and deteriorating academic performance and behaviour despite initiation of ART. There were four girls and five boys in the sample. The age range at the time of referral was five to thirteen years old. Seven of the nine children were ten years and older. Other clinicians within the child and adolescent mental health service, having been previously assessed and managed for behavioural and emotional problems, previously evaluated three of the children. The three children were therefore internally referred to the neuropsychiatric clinic, because of a further deterioration in behaviour, appearance of new symptoms and to exclude an organic cause for the clinical presentation. All, but one, of the children attended school regularly. This child was registered at a mainstream school, but had not attended during that year due to ill health. All the children were on ART for more than one year and had been adherent to treatment regimens. Three children were on a second regimen of ART, because of adverse side effects to prior treatment.

2.4.3 Measurements

The children were psychiatrically evaluated by a child and adolescent psychiatrist, (myself) and then referred to a paediatric neurologist for neurological examination. Children were referred to a clinical psychologist for neurocognitive testing. Psychometric assessments were deemed valuable in order to establish the cognitive functioning of the children at baseline, but also to establish whether cognitive

functioning had deteriorated or remained stable, in those previously tested. Patient demographics, such as the name, age, gender, address, contact telephone number, and hospital folder number, were obtained from the hospital folders. Clinical case notes of all clinic visits including the visits to the infectious diseases and the neuropsychiatric clinics were reviewed. The case notes provided information about compliance with visits and medical treatment, the child's current physical health status (including a history of recent hospitalizations), and their current clinical HIV staging. The records also provided information about the current ART regime and a list of other medications that were prescribed for the child. Results of CD4 counts and viral loads provided information about the current staging of the disease and the response to treatment (for example, a rise in CD4 count since initiation of ART). Other tests such as liver function, renal function, and full blood count (FBC) provided additional information about the child's health status and gave clues about possible toxic side effects to the medication. Information documenting the children's health status (particularly relating to HIV disease) was important as their medical status, disease stage and treatments received would have some impact on the psychiatric presentation and management plan, as well as overall prognosis and outcome.

The outcome of the neurological evaluation and results of neuroimaging tests, such as CT and MRI scans, were examined in order to obtain information about the patients' neurological status. Results of Electroencephalogram (EEG) tests conducted on all the children were documented. The results of psychometric tests administered were recorded. Tests administered were the Junior South African Individual Scale (JSAIS), that was used to test children under eight years old and the Senior South African Individual Scale Revised (SSAIS-R) for the older children.

Information obtained from the medical records was summarized and together with summaries of the case notes of the psychiatric, neurological and neurocognitive evaluation, formed the basis of the clinical case series.

2.4.4 Ethical and legal considerations

A number of ethical and legal issues have been taken into consideration. Informed consent was obtained from the legal guardians, to present the clinical material as a case series for a research study. Consent was obtained to access and summarize the medical records at the Red Cross Children's' hospital and Groote Schuur

Hospital. Clear information was provided with regard to the goals of the study and the guardian was informed of potential risks, as well as benefits of participating in the study. Where possible (depending on the child's neurocognitive ability), the child was informed about the study and assent was obtained. Access to the medical records was limited to the clinicians involved in the clinical assessment. Children participating in the study were not mentioned by name and data was kept in a safe and secure environment. The investigator was the only person able to link clinical data to the child's name. Psychometric assessments were not conducted at the hospital. Children were tested in a pleasant 'child-friendly' environment.

The study is deemed to benefit the participants in a number of ways; for example, the routine psychometric assessments have informed whether the children are placed in the correct academic environment. As such it has assisted in making decisions about transfer from a mainstream school to an ELSEN school or training centre. The benefit of psychiatric and neurological evaluation is to contribute to the knowledge of the psychiatric course of HIV in children on ART. There was also regular liaison with the treating clinicians at the Infectious Diseases Clinics. Because of this contact, problems with the children's health requiring their attention were timeously discussed. No costs were incurred for the clinic visits, investigations and psychometric assessments, as committed children (Act 74) are treated free of charge under the current state hospital fees structure. Consent to conduct the study was obtained from the Human Research Ethics Committee of the University of Cape Town.

2.5 RESULTS

The following is a brief description of the children evaluated. Before the cases are discussed I will describe the procedure followed. I, a Child and Adolescent Psychiatrist, conducted the initial psychiatric evaluations and follow up visits. A history for each child was compiled by interviewing the child, the caregiver, and the Social Worker from the children's home. Collateral information was gathered from the teacher and treating clinician at the Infectious Diseases Unit (Groote Schuur Hospital). The initial clinical interview was conducted with the child and the caregiver. Psychiatric diagnoses were obtained via unstructured clinical interviews and were confirmed following a number of subsequent consultations. The

Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV) classification system was used to evaluate the presence of psychiatric disorders. The children were all referred to the neurologist on the team, who conducted a neurological examination and referred for neuroimaging, when indicated. All children were referred for EEG testing. A clinical psychologist on the team conducted Neurocognitive testing. The children were subsequently followed up by myself, at the clinic and, in addition, referred within the child psychiatry service for further therapeutic interventions. I conducted monthly meetings at the children's home, where I met with the caregivers and the social worker based at the children's home.

Case 1 (5 years, 1 month)

Case 1 was admitted as an infant after his mother died, with no further contact with his biological family. Date and age of HIV diagnosis was not recorded. He was initiated on ART at the age of three years, as part of a research study. CD4 counts pre and post treatment were 699 and 821. The treatment regime was AZT, 3TC, and NVP. There were five hospitalizations prior to initiation of ART, for gastroenteritis, pneumonia, and a severe skin rash.

He was five years old at the time of the referral to the neuropsychiatric clinic and was one of twelve children living in a house on the premises of the children's home. Eight of the children had been placed in the community over a short period (within less than two months, most were alternately placed) as a decision had been made to establish a hospice for adults on the premises. During this time, he became withdrawn, mute, sucked his thumb, and insisted on being fed baby food. He displayed disorganized behaviour in that he pulled down the curtains, cut his clothes, and became fearful and restless at night. He would settle when pacified and taken into the room of his caregiver for the night. During a home visit, it was evident that he was reacting with anxiety to the departure of the children and the fact that the house was clearly being vacated. One of the caregivers was clearly distressed and struggled herself to come to terms with the speed with which the children were being placed. However, some staff members appeared to be emotionally disconnected from the children and did not appear to empathize or recognize that the situation could be emotionally distressing to them. They appeared to be more involved in general housekeeping and instrumental care of the

children, rather than fulfilling a parental role. School reported a quiet, inhibited child who was inattentive and hyperactive.

Mental state examination revealed an inhibited, anxious child who struggled to play or express himself. Neurological examination and EEG were normal. Neurocognitive testing (done when he had settled) revealed an intelligence quotient (IQ) in the average range. Intervention consisted of alternative placement in a smaller environment and with caregivers that are more regular. He was placed in one of the community cottages (along with six other boys) and attached positively to one of the caregivers, after which most of the anxiety symptoms dissipated and he settled rapidly. However, the ADHD symptoms persisted and a trial of Methylphenidate was initiated, with good response, at low dosages (he was of low weight, so dosage not increased).

Case 2 (7 years, 1 month)

This seven year old boy was admitted to the children's home as an infant and diagnosed HIV positive at the age of three months. He was admitted to hospital 8 times prior to initiation of ART, for the management of pneumonia, gastroenteritis, and severe fungal rashes. His CD4 count before treatment was 505 and 715 one year after treatment. He was initiated on ART at the age of five as a subject of a research study. The treatment regime was AZT, NVP, and 3TC. There were no adverse effects to the medication and his health improved dramatically, with no further hospitalisations. He was referred to the neuropsychiatric clinic with a one year history of hyperactivity, poor concentration, and severe aggression. His caregiver was concerned that he barely completed homework tasks and was reading less fluently than in the past.

There was a marked deterioration in the child's behaviour (increased aggression), after he was transferred from the children's home to a community home in a local township, requiring a change of school and adjustment to a social environment of a predominantly Xhosa speaking community. He presented with disruptive behaviour characterized by severe aggression, mood lability, tearfulness, and agitation. After several weeks, he failed to settle in his new environment and he was then transferred back to the children's home. From there, he was transferred yet again to another community home nearby and placed back at his previous school. Aggressive outbursts, however, persisted and his behaviour at school remained

challenging with symptoms of restlessness and inattentiveness, which settled after he received stimulant medication. However, he displayed markedly disturbed behaviour in relation to a particular caregiver, characterized by ambivalent interactions, at times intense to the point of possessiveness, and at other times hostile and overtly aggressive. The caregiver's reaction to this was equally ambivalent, inconsistent and overtly hostile. His behaviour was reported to be significantly more manageable, when the other caregiver (his primary caregiver), was on duty. His mother is alive but she has maintained only erratic contact, which further distressed the child.

Diagnoses of ADHD and an Adjustment Disorder were made. Short-acting Methylphenidate was initiated at 5mg daily and increased to 20mg daily in divided doses, to which there was a positive response. At this dosage, the formulation was changed to a long acting formulation. A second medication, the antipsychotic agent Risperidone, was added after three months because of the persistence of severe aggressive outbursts (dose range 0,5mg - 1mg daily). Subsequently his caregiver and his teacher both reported a positive response. Risperidone was stopped after 6 months, owing to excessive drowsiness and because his level of aggression had declined. The child was seen regularly for individual counselling and home visits conducted to provide parenting input to both care workers. His behaviour settled in the care of an alternative caregiver who interacted with him empathically and consistently.

Case 3 (8 years, 3 months)

Case 3, an 8 year old girl, was diagnosed HIV positive aged eleven months. Her mother was alive but abused alcohol and provided erratic care. She was removed and placed at the children's home as a toddler. Her maternal grandmother maintained contact. She presented with failure to thrive, persistent fever, coughing and generalized lymphadenopathy at the age of eleven months. She was diagnosed with marasmic kwashiorkor and tested HIV positive. There were four hospital admissions prior to initiation of ART, for the treatment of severe skin infections (molluscum contagiosum, candidiasis and abscesses) and gastroenteritis. Treatment was initiated at the age of six years, at Red Cross Children's Hospital, with d4T, 3TC, and Kaletra. Her CD4 count was 411 at initiation and 1259 a year later. The child was referred for a psychiatric assessment as she presented with regressed behaviour following placement with her biological grandmother. There

were also complaints of being inattentive and unfocused in the classroom, with poor academic performance. She fulfilled criteria for a diagnosis of ADHD, inattentive type and was initiated on a trial of short acting Methylphenidate, with good response. Because of her low weight and poor appetite the dosage was maintained at 15mg daily. She settled well in her grandmother's care and continued to attend clinic visits.

Case 4 (10 years, 8 months)

Case 4 was orphaned and placed at the children's home as an infant. Date of HIV diagnosis was not recorded in the hospital records. She was a healthy infant and child with no hospitalizations or illnesses. She was admitted on to the ARV study at Groote Schuur Hospital and commenced on ART, aged nine. The treatment regime was AZT, 3TC, and Nevirapine (NVP). She was hospitalized after she developed a toxic skin rash in reaction to NVP and she was changed to Kaletra (KAL). CD4 count before Art was 319 and 755 one year later.

She was ten years old at the time of the assessment and presented with three episodes of possible visual hallucinations. She saw a woman in her room at night, but this resolved when the furniture was rearranged in the bedroom. There were no other emotional symptoms and she functioned well socially and coped academically at a mainstream school, except for problems with arithmetic. Neurological examination revealed microcephaly and generalized brisk reflexes (no focal signs) and there was no EEG abnormality. She continued to function well and was adopted by her host family and immigrated with them to the United Kingdom.

Case 5 (11 years, 1 month)

Case 5 was an eleven year old girl who was admitted to the children's home as an infant, after her mother died. She was born and diagnosed HIV positive at Somerset Hospital. She was hospitalized three times during early childhood for severe otitis media and gastroenteritis. She was initiated on ART aged eleven as part of the research study. Her CD4 count before treatment was 328 and 889 one year after treatment started. Viral load was undetectable one year post treatment. The initial treatment regime was AZT, KAL, and 3TC.

She was referred to the Neuropsychiatric Clinic as she had experienced several episodes of visual hallucinations over a period of six to eight months associated with severe behavioural disturbances such as undressing herself, severe aggression, confusion and uncooperativeness. There were no other psychotic symptoms present and no observed alterations in level of consciousness or drowsiness following the episodes. She also displayed challenging behaviour such as disruptiveness and uncooperativeness (towards caregivers and teachers), in addition to severe restlessness and inattention for years prior to the current presentation.

Her caregiver reported that she was intermittently not orientated to the day and date and that her reading had deteriorated prior to the referral to the clinic. There was a scholastic decline to the extent that she was transferred to an ELSEN school. However, once there it was felt that she should be transferred back to the mainstream school. She made minimal progress academically in mainstream school, requiring yet another transfer back to the ELSEN School. She was referred for a neurological assessment to exclude complex partial seizures. An EEG (electroencephalogram) test was abnormal and showed left frontal and left centrotemporal foci. CT Brain and MRI (done later due to persistence of symptoms and an impression of neurocognitive decline) were normal. In addition, she presented with symptoms compatible with a diagnosis of ADHD. She was commenced on a course of the anti-epileptic, Sodium Valproate (800mg daily in divided dosages). The episodes of visual hallucinations abated but there were ongoing problems of severe restlessness, inattention, and aggression. A second medication, Methylphenidate was added after six months, to which there was a partial response (starting dosage 10mg, to maximum of 30mg daily). At this dosage, the formulation was changed to a long acting preparation. She continued to display behavioural difficulties and intermittently appeared to be confused. A lumbar puncture was therefore performed in order to establish the CSF viral load, which was undetectable. Neurological examination was normal. The neurologist added a diagnosis of a seizure disorder (complex partial seizures). The impression at this stage was that the clinical picture might have indicated early HIV encephalopathy (she fulfilled two of the three criteria of neurocognitive, behavioural and motor abnormalities). She was later placed at an alternative children's home due to her unmanageable behaviour.

Case 6 (11 years 8 months)

Case 6 was removed from his mother's care due to neglect, as an infant and placed at the children's home. He was diagnosed HIV positive as an infant. There were 13 admissions prior to initiation of ART for numerous illnesses such as diarrhoea, pneumonia, and severe infections (candida infections, episode of septicaemia). He was started on treatment as part of the research study and initiated on AZT, 3TC, and NVP. The NVP was stopped (and changed to KAL) after he developed drug induced hepatitis. His CD4 count before treatment was 538 and 825 one year later, post ART. Response to ART was positive with no further illnesses and hospitalisations.

He was initially assessed, age ten months, by the neurodevelopmental service at Red Cross Hospital and scored within the range of mild global delay. He was followed up by the neurodevelopmental service and diagnosed with ADHD at the age of five. He was referred to the psychiatric service in 2001 at the age of eight, because of aggression, oppositional behaviour, and a poor response to stimulant medication (Methylphenidate). He was diagnosed with Oppositional Defiant Disorder. He was assessed at the Neuropsychiatric Clinic at the age of twelve because of worsening of aggressive outbursts, oppositional behaviour, defiance, and verbal abuse. Behaviour problems appear to have escalated after visits to his biological father broke down and contact was made with his biological mother, with whom he had a poor relationship. He presented with increasing aggression, verbal abuse, and oppositional behaviour. The current deterioration in his behaviour was again precipitated by his distress at being placed in the care of his aunt. His biological mother lived with the aunt as well, was HIV positive and abused alcohol. His relationship with his mother (who denied her own and his HIV status) was distant and ambivalent. He struggled to adjust to the changed economic circumstances and different religion of his family of origin (Muslim faith), as he had been raised as Catholic at the children's home.

He was diagnosed with an Adjustment Disorder, in addition to a previous diagnosis of Oppositional Defiant Disorder. Neurological examination and EEG were normal. He was commenced on the neuroleptic medication, Risperidone (dose range 0,5mg - 1,5mg daily), for the management of severe aggression prior to the assessment at the Neuropsychiatric Clinic. It was elected to continue with the medication at the

same dosage of 1,5mg daily. He was referred to a social skills group. The level of aggression abated but he continued to display compositionality, verbal aggression and disregard for the adults at the time of his placement with his family. He underwent neurocognitive testing in 2001 at the age of 7 years and 9 months. There were concerns about his fluctuating academic performance, which was possibly driven by anxiety and attention/concentration difficulties. It was felt that a baseline level of neurocognitive functioning would better inform decisions about school placement and further management. The test administered was the JSAIS, which revealed an intelligence quotient in the lower limits of the low average range (IQ 80-89). Repeat neurocognitive testing at the age of twelve revealed intellectual functioning in the mild to moderate range of intellectual functioning, representing a decline over time. He was placed at an ELSEN school and subsequently permanently placed with his aunt and lost to follow up.

Case 7 (12 years, 4 months)

Case 7 was referred for placement to the children's home as a child, for terminal care. She was diagnosed HIV positive at the age of two and presented early on with numerous illnesses (pneumonia, wasting syndrome, tuberculosis, seizures and urinary tract infections), resulting in eight hospitalizations prior to initiation of ART. ART (a regime of 3TC, AZT and Efavirenz) was started at the age of ten during a period of hospitalization. The CD4 count pre and post ART were 180 and 310 respectively.

She was ten years old at the time of referral to the Neuropsychiatric Clinic. She presented with episodic vomiting, suspected to be emotionally based, as the impression was that she was trying to achieve hospitalization via self-induced vomiting. Neurological examination and EEG were normal. She struggled to cope with neurocognitive testing, as she was ill at the time, and scored below 50 for full scale IQ, which was felt to be an inaccurate reflection of her intellectual ability. The vomiting turned out to be a symptom of a gastrointestinal condition, which resulted in her becoming seriously ill. The outcome of the psychiatric assessment was that the symptoms were related to her medical condition. She was followed up for six months and improved steadily and was able to return to school.

Case 8 (13 years, 0 months)

Case 8 was born prematurely and diagnosed as an infant with congenital syphilis and Foetal Alcohol Syndrome (FAS). He was abandoned at a local hospital in the Northern Cape. His mother died soon afterwards. There is no known history of mental illness in the family. He was diagnosed HIV positive at the age of two. This was after a stormy first two years of life, with admissions for meningitis, gastroenteritis, and severe skin infections. His CD4 count before starting ART was 286. He was admitted to the research study and initiated on treatment at the age of eleven years (with a regimen of AZT, 3TC and NVP). The NVP was stopped as he developed abnormal liver functions and KAL initiated. His CD4 count one year after ART was 441, with further admissions for meningitis and a severe skin abscess. His health improved subsequently with no further admissions.

He was referred for a psychiatric evaluation initially at the age of seven years for problems of aggression, mood lability, and oppositional behaviour and a trial of Methylphenidate was initiated with poor response. He was re-referred, aged thirteen, to the Neuropsychiatric Clinic. At the time, he was attending a special school. Eighteen months prior to the recent clinical presentation, he was reunited with his family and made visits to the Northern Cape, accompanied by his caregiver, during the school holidays. The plan was that this would eventually become a permanent placement. He struggled, however, to adjust to the visits and became distressed if left alone without his caregiver. The current referral was precipitated by a sudden deterioration in mood (depressive symptoms), suicidal ideation, and two suicide attempts (suffocation, electrocution). The precipitating event was that he was informed two months prior to the presentation that he would be leaving the children's home permanently and that he would be placed with extended family. The mental state examination done during his initial visit described a shy, reticent boy. He was mildly anxious and appeared depressed. He reported depressed mood and suicidal ideation. There were no psychotic symptoms. Neurological examination was normal except for microcephaly, but the EEG was abnormal and showed right hemispheric spike and wave discharges. There was no history of observed seizures. MRI scan of the brain was normal. He was initially commenced on Sodium Valproate (a dosage of 600mg daily, in divided dosages). After initiation of the anticonvulsant, he became more contained with no further episodes of suicidal behaviour. However, his mood continued to be depressed, despite regular

counselling sessions. A course of the antidepressant, Fluoxetine, was added after three months. This was stopped after he presented with an episode of mania, two months later. Medication management consisted of a combination of Sodium Valproate and Risperidone (dose range 1-3mg daily), with a resolution of symptoms. He subsequently presented with a manic episode a year later, despite compliance with medication. In between relapses, he was contained but reported episodes of 'funny feelings' and fleeting visual hallucinations, which was accompanied by observed periods of an altered level of consciousness and postictal drowsiness. The episodes resolved after the medication dosage was increased to 1000mg daily (in divided doses). Episodes were interpreted as being epileptic in nature. Subtle neurocognitive problems also became evident during follow up: he had problems with short term memory and basic arithmetic. His CSF viral load was undetectable.

His neurocognitive ability was assessed at fifty six and eighty months respectively, while not receiving ART. He was referred for a developmental assessment because of suspected global delay, as well as problem behaviours such as aggression, defiance, and poor sleep. The test used was the Griffiths Developmental Test. The result of the test done at fifty six months indicated that he was functioning at the level of forty eight months for gross motor, fine motor, and language skills, and forty two months for personal/social development, indicating borderline developmental delay. The test was repeated at eighty months with scores of sixty six months for gross motor skills (Developmental Quotient (DQ) 82%), sixty months for fine motor (DQ 75%) and fifty four months for language (DQ 85%) and thirty six months for personal/ social development. On the basis of the test result an application was made to a special school for learners with moderate intellectual disability.

Case 8 was subsequently tested again at the age of thirteen years and scored in the mild to moderate range of intellectual ability, demonstrating a decline in neurocognitive functioning.

Case 9 (13 years, 6 months)

Case 9 was admitted to the children's home as an infant in a severely malnourished state and with a maggot infestation of the testes. His mother had abandoned him at Somerset Hospital. His mother subsequently died and contact was lost with his biological family for a number of years. His early years were characterized by nine admissions to hospital, where he presented with illnesses such as tuberculosis,

meningitis, pneumonia, gastroenteritis, shingles, and chickenpox. He presented at the age of three years with meningococcal meningitis. He was subsequently diagnosed with HIV encephalopathy. A CT scan of the brain performed at the time showed two areas of white matter hypodensity in the right frontal region. He was referred for neuropsychological testing to establish his baseline level of neurocognitive functioning in 2002, at the age of 10 years and 8 months. At the time he was not on ART. He presented with behavioural difficulties such as aggressive outbursts, was reported to be rebellious and disobedient, and had begun to struggle with numeracy and reasoning tasks. He had lost a significant amount of weight during the previous year. Neurologically, he suffered a mild speech impediment and walked with a spastic gait. The neuropsychological battery included tests of motor functioning, attention, language, visuographic ability, and memory. In addition an SSAIS was administered. The neuropsychological tests revealed problems with fine and gross motor functions, motor slowing affecting speed of visual tracking and speed of output of tasks. His vocabulary, verbal reasoning skills, auditory memory, and planning were good, but his visuospatial abilities were assessed as low average. The result of the SSAIS showed an intelligence quotient in the average range.

He was initiated on ART (AZT, NVP and 3TC) at the age of eleven as part of the research study. His CD4 count before ART was 432 and 776 one year after initiation of treatment. His health improved dramatically with no further admissions. He was thirteen years old at the time of referral to the neuropsychiatric clinic, having been initially referred to psychiatric services, aged nine, for social/communication difficulties, mood lability, aggression, restricted interests and flights into a fantasy world. On interview, he was aloof and displayed a pedantic, rigid cognitive and conversational style suggestive of Asperger's disorder. However, full criteria for Asperger's Disorder were not met. He was subsequently diagnosed with Pervasive Developmental Disorder, not otherwise specified (PDD-NOS). He was re-referred because of increasing mood lability and aggression. The precipitating event was the disclosure to the patient that he would not be adopted by his host parents and that he would continue to be resident at the children's home. An additional stressor was that the children's home made contact with his biological family and arranged weekend visits, which he found very difficult. A visit was arranged to the Eastern Cape to meet his grandfather and visit his mother's grave, both of which he experienced as traumatic, refusing subsequent contact with an aunt who lived

locally. Instead, he insisted on being adopted by his host parents, who unfortunately were not able to do so, as they planned to emigrate. Furthermore, they feared, as an older couple, that his increasingly challenging behaviour would become unmanageable. He denied his HIV status and that he was black, stating that only black people were HIV positive. He would take flight into a fantasy world as a character in 'Peter Pan'. He refused subsequent contact with family and persistently and at times coercively insisted on contact with the host parents. There were no behavioural problems at school, but he was described as 'odd and aloof', with no meaningful friendships with peers. There were no academic problems reported. He was initially diagnosed with an Adjustment Disorder and the diagnosis of PDD-nos was upheld. However, his mood deteriorated over the next few months at which point he fulfilled criteria for a Major depressive Episode (MDE). There was a poor response to Fluoxetine (which was increased to a maximum dose of 20mg daily) with ongoing irritability, aggression, and mood lability. There were no features to suggest a manic episode or symptoms suggestive of a psychosis. A trial of Sodium Valproate (700mg daily in divided doses) was initiated after the Fluoxetine was stopped, with an improvement in mood.

Subsequent testing at the Neuropsychiatric Clinic, once again demonstrated an average level of neurocognitive functioning and resolution of his neurological symptoms suggesting a positive impact of ART on the HIV encephalopathy. However, he continued to display aggressive outbursts, oppositionality, and extreme egocentricity during challenging interpersonal situations, necessitating a trial of Risperidone (up to a maximum dose of 3mg daily), with only a partial response. A brief trial of Haloperidol was equally ineffective. Subsequent to this alternative placement was sought and he was placed at another children's home, where the problems persisted, necessitating yet another placement. His host parents remained in contact.

The following section provides further details of the neuropsychiatric assessments and follow-up of the children. Relevant information obtained from the medical records will be described. The chapter will conclude with a brief summary, which will collate findings from the clinical case series, with information extracted from the medical records.

2.5.1 Psychiatric Evaluation

2.5.1.1 History of presenting complaints

The primary reason for referral to the Neuropsychiatric Clinic was for the assessment and management of emotional and behavioural difficulties that had emerged during the period following initiation of ART. The majority of children were referred for problems of aggression, hyperactivity/inattention, and mood disturbances, including mood swings, irritability, depression with suicidal ideation and intent. Two children presented with visual hallucinations (see table 1). There were also concerns about the children's academic progress: a number of caregivers felt that the children were not able to produce homework of a standard expected of them and were generally not achieving basic numeracy and literacy skills. The difficulties around homework were compounded by attention difficulties as well as uncooperative behaviour, particularly from the boys. Some of the children were felt to have lost reading and writing skills previously acquired. There was a further concern that some of the children's disruptive behaviour in the classroom was compounded by their academic difficulties.

Caregivers believed that the academic demands and standards at mainstream schools exceeded the children's ability, further compounding the stress experienced in the school environment. There were fewer concerns about the academic progress of children placed at ELSEN schools and fewer reports of challenging behaviour by their teachers. There was a consensus that all the children, except one, struggled with numeracy. Three children underwent neurocognitive assessments at a younger age, prior to referral (see table 5). All three were boys and were tested more than two years prior to referral to the neuropsychiatric clinic. Tests used were the JSAIS, SSAIS, and the Griffiths Developmental Test. One child, subsequently diagnosed with HIV encephalopathy, underwent a neuropsychological battery as he had begun to struggle with numeracy and reasoning tasks. He had also demonstrated problems with expressive language and he had acquired a spastic gait.

Table 1: History of Presenting Complaints

Cases	1	2	3	4	5	6	7	8	9
Age at Referral	5 years	7 years	8 years	10 years	11 years	11 years	12 years	13 years	13 years
Presenting Complaint									
Overall Behaviour	Regressed behaviour: crying, bedwetting, 'baby talk', wants to sleep with an adult	Severe aggression, hyperactive, inattentive	Regressed behaviour: thumb sucking, 'baby talk', 'attention seeking', 'dreamy', inattentive	Visual hallucinations, 'dreamy', inattentive	Aggression, defiant, oppositional, hyperactive, inattentive, Visual hallucinations	Aggression, Oppositional, Defiant, Swearing, Sexually inappropriate behaviour	? Self-induced vomiting to obtain hospitalization	Aggression, depressed mood, Suicidal ideation, Suicide attempts, Sexualized behaviour	Aggression, Social difficulties, Oppositional, Mood swings
Academic Progress	Struggles with drawing, basic letters and numbers	Struggles with numeracy and phonics	Lost the ability to read, struggles with numeracy	Struggles with numeracy	Struggling in all aspects	No problems reported	Recently returned to school after long-term absence due to ill health	No problems reported	Coping
Classroom Behaviour	Emotionally immature, Poor concentration	Hyperactive, Inattentive, fails to complete tasks	Dreamy, inattentive	No problem behaviours	Aggressive, defiant, disruptive	No problem behaviours	Withdrawn, quiet, no problem behaviours	No Problem behaviours	Socially aloof, egocentric
Educational and Residential Placement									
School	Preschool	Mainstream	Mainstream	Mainstream	Mainstream	ELSEN	Mainstream	ELSEN	Mainstream
Residence	Children's Home	Community Cottage	Community Cottage	Community Cottage	Children's Home	Children's Home	Community Cottage (in local township)	Children's Home	Community Cottage

2.5.1.2 Collateral information obtained from educators

Information was obtained from educators via regular questionnaires. Face to face interviews were conducted where school visits were undertaken. The questionnaires included questions about classroom behaviour (level of activity, inattention, aggression, social interaction, anxiety/mood) and academic progress. Information obtained revealed concerns mostly about problem behaviours such as restlessness, poor concentration, aggression, social and interpersonal difficulties. There was an impression that the children were immature and struggled to maintain peer relationships with children of similar age. Questionnaires revealed that all the children, except one (case 9) were not performing academically on a par with peers and required remedial input or additional input for all areas of work. There were particular concerns about three children, (cases 2, 5 and 8) who presented with more marked behavioural disturbances in the classroom environment. This included behaviour such as aggression, uncooperativeness, hyperactivity and inattention. The schools responded with frequent letters to the guardians and requests for interviews with the caregivers. None of the children were excluded from the study because of unacceptable behaviour.

2.5.1.3 Common themes that emerged following interviews with the children and caregivers

a) Leaving the children's home

A number of children had been reunited with either their biological parent/s or families. Some of them had been permanently placed or were being prepared for placement. Those who could not be placed were subsequently accommodated at a community home run by the institution. The reasons why children could not be placed back with their biological families is that some of the parents were deceased, extended family members were not able to care for a child or no ARV's were available at the local clinic or hospital in more remote rural areas. The process of placement evoked anxiety about leaving the familiar environment of the children's home and particularly familiar adults and attachment figures. One child (case 8) threatened to kill himself rather than leave the children's home and later attempted suicide by suffocation and electrocution.

b) Cultural and language issues

All the children had been raised in an English-speaking environment; because of this, they had not acquired the use of any indigenous language or Afrikaans. Some of the children, therefore, found it extremely difficult to communicate with Xhosa speaking families when they visited over weekends and holidays. They had also become alienated from the religion and cultural norms of their families as they were raised in a westernized, Christian (Catholic) environment. These issues further complicated the transition to life in the community and they have contributed to the children's experience of alienation from the new environments to which they have been exposed.

c) Economic issues

Families of origin lived in economically disadvantaged circumstances, significantly less privileged than the lifestyles the children had become accustomed to at the children's home and via volunteer host families. Some of them struggled to adjust to this. Some of the biological family members unfortunately placed the children and the home under pressure to provide money or goods that were not affordable, as a condition of contact. This cast doubt upon the motivation for receiving the children back and fuelled concerns about whether the placement would be sustained, once financial or material support ceased.

d) Developmental phase of adolescence

Three of the children were entering adolescence (aged twelve and thirteen). Anxiety was expressed about having to leave the children's home when they turned thirteen years old. A wish to "stay small like Peter Pan" was expressed by one of the children (Case 9). There was a growing awareness of their relatively small stature and delayed puberty compared to peers and a more realistic sense of the implications of being HIV positive. Concerns were expressed about the stigma of HIV and issues of confidentiality. One of the boys, for example, became reluctant to be transported in the bus belonging to the children's home, as he believed that people would associate the home with AIDS, knowing that the broader organization

provided AIDS hospice services. Sexual acting out and curiosity was more prevalent in this older group.

e) HIV

All of the children had been informed about their HIV positive status from a young age (under five years old). The younger children rarely expressed their opinion about this and appeared to adjust easily to the frequent hospital visits and medication with little outward expression of distress. However, the older children appeared to be more aware of the implications of their HIV status and would either express concerns that they might become ill and die (case 8) or deny their HIV status. Denial of HIV commonly was linked with a denial of their race, claiming that they themselves belonged to another racial group and that HIV was a condition exclusively suffered by black people.

f) Interpersonal/relational problems

Some of the children struggled to maintain positive relationships with peers and adults. The relationships with some of the caregivers were intense and ambivalent. Interactions were sometimes described as being contained, but at other times, provocative, hostile, and overtly aggressive to the extent of committing physical attacks on the caregivers. Likewise, a number of the interactions between the children were equally volatile, with frequent arguments and aggressive outbursts. This was in stark contrast to the rest of the children in the home (HIV positive, non-referred group) who were able to sustain more positive relationships with adults and peers.

g) Behaviour Management

Most of the caregivers were concerned about their ability to contain difficult behaviour in the children, and to set consistent limits and boundaries. The adults' management of the children was inconsistent and there was not enough effective communication across shifts. Consensus about the imposition of more consistent rules, limit setting, and boundaries was difficult to achieve. It was strongly felt that the children were managed differently on different shifts and by different adults, leading to confusion and manipulative behaviour on the part of the children who

appeared to deliberately play one adult up against the other. This was confirmed in that the children's behaviour was particularly difficult on certain shifts and when in the care of certain caregivers. One of the caregivers expressed extreme emotional distress about being attacked (bitten, hit, scratched) by a child (case 2), and struggled to manage his difficult behaviour in an emotionally detached manner. Caregivers who felt more confident about their parenting skills, reported fewer behavioural problems by the children in their care and generally believed themselves to be more successful in managing difficult behaviours. All the caregivers expressed the need for regular parenting input and the need for more coherent and consistent strategies for managing problem behaviours. Some caregivers were of the opinion that there was an inappropriate reliance on medication to contain the behaviour rather than addressing inconsistent parenting practices, which they believed, drove some of the behaviour.

2.5.1.4 Psychiatric Diagnoses following psychiatric evaluation

The following diagnoses were obtained following psychiatric evaluation of the children referred:

1. Attention Deficit Hyperactivity Disorder (ADHD) n=4. Two children presented with the combined type ADHD, and another two with predominantly inattentive type ADHD. One boy and one girl were diagnosed in each group.
2. Mood Disorder due to a General Medical Condition (GMC) n=1. The underlying medical condition was a possible seizure disorder associated with early HIV encephalopathy: the child presented with two of the three criteria of behavioural, neurocognitive and motor impairments needed for diagnosis.
3. Mental Disorder not otherwise specified (NOS) due to a GMC n=1. The patient presented with episodes of disturbed behaviour, visual hallucinations, and confusion. While a definite history of observed seizures was not provided, a seizure disorder was a possible diagnosis on the basis of the general history and positive response to an anticonvulsant. The aetiology was unclear but may have been an early HIV encephalopathy (the child fulfilled two of the three criteria of behavioural, neurocognitive and motor impairments needed for diagnosis).

4. Adjustment Disorder n=3. Adjustment Disorder diagnoses was made in three of the children as they presented with significant emotional and behavioural difficulty in reaction to a proposed plan to change their placement. In the case of two of the children, it was to place them with their biological families and in one of them; a plan by the host family to adopt him was reconsidered.
5. Pervasive Developmental Disorder, not otherwise specified (PDD NOS) n=1.
6. Oppositional Defiant Disorder (ODD) n=2
7. Major Depressive Episode (MDE) n=1. A diagnosis of MDE was made in a thirteen year old boy who had been previously diagnosed with PDD NOS. There was a longstanding history of mood lability, tearfulness, and irritability, but he presented with additional symptoms of depressed mood, social withdrawal, loss of interest in usual activities and suicidal ideation.

Two children did not receive psychiatric diagnoses. One of them presented with a history of being 'dreamy', poor concentration, and having seen 'visions' which resolved spontaneously. There were no symptoms of anxiety and no seizures were observed. Neurological examination and investigations were normal. A diagnosis of ADHD, inattentive type, was considered but she did not meet the full criteria at the time. The other child presented with a history of possible self-induced vomiting and regressed behaviour, in the absence of other emotional symptoms. Evaluation revealed no psychological reason for the vomiting in this seriously physically ill child. The clinical presentation was then assessed as being related to her medical condition.

2.5.1.5 Other Diagnoses Considered

1. Schizophrenia/Psychotic disorder: The two children who presented with visual hallucinations did not display other psychotic symptoms such as delusions, thought disorder or other perceptual disturbances.
2. Bipolar Disorder: A number of children presented with significant mood disturbances such as severe irritability, mood swings, tearfulness, and

depressed mood. Case 8 presented with manic symptoms, an elevated mood, euphoria, decreased sleep, increased appetite, and hyper-sexuality. A diagnosis of Bipolar Disorder was considered but as this child had an abnormal EEG (temporal lobe focus), a diagnosis Mood Disorder secondary to a GMC was made.

3. Anxiety disorders: A number of children presented with significant anxiety symptoms and expressed distress about a number of issues such as leaving Nazareth House, growing older and their HIV status. The aggression and 'acting out' behaviour appear to have been driven by underlying anxiety as the children struggled to articulate their concerns that were expressed via their negative behaviour. Several of the children presented with anxiety symptoms such as excessive worry, irritability, and fears of abandonment. None of the presentations, however, fulfilled criteria for the DSM IV diagnosis of a Generalized Anxiety Disorder that requires additional symptoms such as restlessness, fatigue, poor concentration, muscle tension and sleep disturbances.
4. Attachment Disorders: Disturbances of attachment were felt to drive some of the behaviours observed. For example, the entire cohort displayed indiscriminate friendliness and lack of boundaries towards unfamiliar adults, commonly observed among institutionalized children. Except for case 5, the girls appeared to be more securely attached and seemed to have relationships that are more positive with their caregivers and related to adults in a more consistent manner. The boys, however, tended to relate in a more ambivalent manner, vacillating between positive interactions and volatile, provocative behaviour.

2.5.1.6 Clinical management

All the children attended a monthly follow up clinic visit. They were seen individually and with their caregivers. Behaviour-based interventions were implemented and explained to the individual child and caregiver. Monthly case discussions were also held with caregivers, Social Workers and the treating Paediatrician at the children's home. These home visits were conducted at the main house and the cottages of the children's home. The children could thus be observed in their home

environment and the quality of their relationships could be assessed. A further aspect of the home visits was that parenting input could be given to the staff members who were struggling with managing the children's behaviour, but who were not able to attend the clinic visits.

Table 2: The Diagnoses and Biopsychosocial Management of the Children Assessed.

Case	Diagnosis	Psychological Management	Medication management, maximum dosages and notes
1	ADHD (inattentive type)	Parental guidance Home visits Monthly clinic visits	*Methylphenidate (MPH) short acting (SA) 15mg Two divided dosages of 10mg at 7.30am and 5mg at 11am Medication initiated 6 months after initial assessment, due to young age
2	ADHD	Parental guidance Home visits Monthly clinic visits	MPH (SA) 5-20mg Divided dosages (7.30am, 11am, 2pm) *MPH Long acting (LA) 20mg morning Risperidone 0,5-1mg Risperidone stopped after one year
3	ADHD (inattentive type)	Monthly clinic visits	*MPH SA 15mg daily Two divided dosages of 10mg at 7.30 am and 5mg at 11am
4	No diagnosis	Monthly clinic visits	Followed up for six months
5	Mental disorder 2° GMC ADHD	Parental guidance Monthly clinic visits	*Sodium Valproate 400mg 2x daily MPH (SA) 10-20mg daily MPH SA stopped and LA commenced *MPH (LA) 30mg morning
6	Oppositional Defiant Disorder ? ADHD	Social skills group Parental guidance	Risperidone 0,5-1mg daily Lost to follow up
7	No diagnosis	No diagnosis	
8	Mood disorder 2° GMC	Social skills group Supportive counselling Parental guidance Home visits	Fluoxetine 20mg daily Manic episode precipitated after six weeks. Stopped *Sodium Valproate 400mg am/600mg pm *Risperidone 1-3 mg daily Dosage of Risperidone reduced to 1mg when stable
9	PDD NOS MDE	Social skills group Supportive counselling Parental guidance Home visits	Fluoxetine 20mg daily Poor response to Fluoxetine, so stopped after twelve weeks Haloperidol 0,5-1 mg night Poor response and Extrapiramidal side effects (EPSE) on Haloperidol, so stopped after one month *Sodium Valproate 300mg/400mg *Risperidone 1-3 mg

Note: * denotes final prescription

a) Psychotherapeutic Interventions

- i. Individual supportive counselling: Two children, both males, were referred to a nurse therapist for fortnightly psychotherapy/counselling sessions within the service.
- ii. Social skills group for preadolescents: Three children (cases 6,8 and 9), all males, were referred to a social skills group. Indications for referral were that all three boys struggled to relate to peers, had difficulties managing their anger and could not resolve conflict in a pro-social manner. The pre-adolescent group consists of twelve weekly sessions attended by about eight mixed gender children. Children receive social skills training, life skills, anger management, and understanding of feelings. Those who attended coped well and related to other members of the group. However, all three chose not to disclose in the group that they lived in a children's home and that they were HIV positive.
- iii. Parental guidance: the case manager provided Parental guidance to caregivers on an individual basis during the clinic and the home visits. Intervention that is more intensive was provided by the Clinical Social Worker employed by the children's home by means of regular support groups for caregivers.

b) Medication Management

Four children (three males, one female) were commenced on psychotropic medication shortly after the initial psychiatric assessment. Another three children were initiated on medication on later follow up, within the first year after assessment. Indications for medication were for the management of severe aggression, for depression, which was unresponsive to psychotherapy, and for ADHD symptoms. Medications prescribed were stimulants (n= 4), atypical antipsychotics (n= 4), typical antipsychotics (n=1), and antidepressant medication (n=2). Two children were medicated with anti-epileptic medication (Sodium Valproate), after EEG tests were found to be abnormal and, in addition, to treat a manic episode. The lowest effective dosages were prescribed, particularly in the case of a five year old child, and in two patients with low body weight. Standard dosages were achieved in most instances and were well tolerated, with very few adverse side effects (only one child became very drowsy on Risperidone 0,5mg daily). Generally, the response to

stimulant medication was favourable, with few adverse side effects. Academic performance, however, did not improve substantially after the initiation of stimulant medication. Response to being medicated with Risperidone for the treatment of aggression was partial, with persistence of aggressive behaviours. Response to Sodium Valproate was positive with cessation of visual hallucinations and episodes of confusion in one patient and the reduction and control of manic symptoms in another. Treatment with a SSRI, Fluoxetine, appeared to have precipitated a manic episode in the latter patient and failed to achieve amelioration in depressive symptoms in another (despite an adequate trial of twelve weeks).

2.5.2 Neurocognitive assessments

All the children were referred to a Clinical Psychologist for cognitive assessments as part of the evaluation at the Neuropsychiatric Clinic. Tests used were the Junior South African Individual Scale (JSAIS) and the Senior South African Individual Scale-Revised (SSAIS-R). Intelligence Quotients (IQ) were obtained via Verbal IQ (VIQ) and Performance IQ (PIQ) scales to reach a Full Scale IQ score (FSIQ) to reflect the child's performance.

Description of cognitive tests:

- a) The JSAIS was developed in 1979. It is a standardized test to assess the cognitive abilities as well as the functional strengths and weaknesses of South African Children, during the first year of school. The test is generally utilized for children aged six to eight years. There are twenty two subtests, which can be combined to form a verbal, performance and full scale intelligence quotient (Tlali T 2004).
- b) The SSAIS-R is a test to measure general intellectual ability of children aged seven to sixteen years. It consists of five verbal and four non-verbal subtests, the composites of which provide scores for verbal, performance and full scale IQ. A 'Socio-economic Disadvantage Scale' (SED Questionnaire), is added when disadvantage is suspected (Tlali T 2004).

Test Scores:

Three children scored in the average range, one in the borderline, and four in the mild intellectual disability range (two mild to moderate) and one in the moderate disability range. Unfortunately, most of the children were not previously tested so it was not possible to compare results with previous tests. Of those children previously tested, there was a decline in case six's score from the low average to mild intellectual disability range. Case eight's score also fell from borderline intellectual ability at 56 months to mild intellectual disability at thirteen years of age. Case nine appeared to have maintained intellectual functioning in the average range and subjectively showed improvements in motor functioning.

Management of academic problems:

Two children attended an ELSEN school prior to the evaluation. An application was made on behalf of four children for placement in a special school. Reasons for referral were poor academic performance in the mainstream school, attention problems, hyperactivity, and negative behaviours (cases 2, 5, 6, 9). Three children continue to attend a mainstream school and only one has continued to perform academically on a par with peers. A request was made for remedial input at the mainstream schools and the Social Worker initiated supervised homework sessions.

Table 3: The neurocognitive Profile of the Children Tested

Case	1	2	3	4	5	6	7	8	9
School/grade	Preschool	Mainstream	Mainstream Grade Two	Mainstream Grade Five	Mainstream	ELSEN	Mainstream	ELSEN	Mainstream Grade Seven
Age at assessment	5 years 1 month	7 years 1 month	8 years 3 months	10 years 8 months	11 years 1 month	11 years 8 months	12 years 4 months	13 years 0 months	13 years 6 months
Test	JSAIS	JSAIS	SSAIS-R	SSAIS-R	SSAIS-R	SSAIS-R	SSAIS-R	SSAIS-R	SSAIS-R
VIQ	80	68	65	86	61	58	50	55	107
PIQ	90	70	72	97	71	65	50	72	105
FSIQ	87 Average to low average ability	70 Borderline intellectual ability	64 Mild intellectual disability	90 Average intellectual ability	61 Mild intellectual disability	57 Mild to moderate intellectual disability	50 Moderate to severe intellectual disability	58 Mild to moderate intellectual disability	107 Average intellectual ability
Age at prior assessment	N/A	N/A	N/A	N/A	N/A	10 months 7 years 9 months	N/A	4 years 8 months 6 years 8 months	10 years 8 months
Test name and result of previous assessment						Griffiths: Mild Global delay JSAIS: low average to borderline ability		Griffiths Developmental Test: Borderline intellectual ability	SSAIS-R: Average intellectual ability Neuropsychological battery: fine and gross motor problems, motor slowing affecting speed of visual tracking and speed of output of tasks. Good vocabulary, verbal reasoning skills, auditory memory, and planning. Below average visuospatial ability.

2.5.3 Neurological assessment

A Paediatric Neurologist on referral to the Neuropsychiatric Clinic assessed all the children. The children were initially assessed by the psychiatric team, then referred to the Neurologist for an assessment and EEG tests. Further neurological investigations such as neuroimaging, or lumbar puncture were undertaken when clinically indicated.

Eight out of the nine children appeared to be asymptomatic from a neurological perspective. One child (case 9) presented with motor coordination deficits, visuospatial difficulties and a spastic gait, which appeared to have resolved after ART was started. Another child (case 5) presented with episodes of markedly disturbed behaviour characterized by visual hallucinations, aggression, and bizarre symptoms such as undressing herself and throwing herself to the ground. Caregivers did not observe any alterations in her level of consciousness, nor confusion, and the episodes were not followed by a period of drowsiness. It was not possible to ascertain reliably whether there was a period of amnesia for the episodes. Case 8 presented with a sudden onset of depressed mood associated with suicidal ideation and two suicide attempts (by electrocution and hanging).

CNS examination was normal in the majority of the children with no focal neurological signs elicited in any of them. One child displayed brisk reflexes and was noted to be microcephalic. Another child bore facial features compatible with Foetal Alcohol Syndrome (FAS) and was noted to be microcephalic.

All the children underwent an awake EEG examination. The EEG was normal in seven of the nine children. Tests were abnormal in two cases: Case 5 displayed left frontal and left centrotemporal foci with generalized discharges and case 8 showed right hemispheric spike and wave discharges. These two children (case 5 and 8) were then referred for neuroimaging tests (CT x1, MRI x2, which were normal, with no evidence of mass lesions or cortical atrophy. lumbar punctures were also performed in these two children in order to determine the CSF viral loads, which were undetectable. CSF cultures were also negative.

Two of the children obtained a diagnosis of a seizure disorder, of which one was diagnosed with HIV encephalopathy subsequent to the neuropsychiatric assessment.

2.5.4 Review of the medical records of the children assessed at the neuropsychiatric clinic

2.5.4.1 Tracking the records

Information was obtained from the medical records of the two treating hospitals, Groote Schuur Hospital (GSH) and Red Cross Children's Hospital. From the medical records, it appears that the children in the cohort were initially under the care of Red Cross Children's Hospital and then were transferred to the care of a paediatrician at GSH when funding became available for ART. From the records, it appears that the children were still mostly managed at the Children's Hospital when they became ill and required hospitalization and they would attend the clinic at GSH for ART. They also participated in the research study conducted at GSH. Later on, the children were transferred and managed exclusively at GSH. Currently all of the children attend the GSH Infectious Diseases Clinic but also attend specialized services (Psychiatry, Neurology, Dermatology, ENT, Occupational Therapy and Speech Therapy) at Red Cross Children's Hospital. A multidisciplinary service to HIV positive children does not exist resulting in numerous attendances to different clinics at the two hospitals with numerous absences from school.

2.5.4.2 First onset of medical illness

Seven out of the nine children presented with a medical illness before the age of one year and eight out of the nine by the age of eighteen months. Only one child was well until the age of three years and three months when she developed a skin condition (impetigo). All the children presented with infections: 3 had chest infections, one had meningitis, 4 had skin infections and one, gastroenteritis. Case 7 presented with a pneumonia and kwashiorkor. Skin infections tended to be more severe with extensive staphylococcus skin infections, impetigo, chicken pox, and ringworm. Chest infections were the second most common, with pneumonias, tuberculosis, and protracted episodes of bronchiolitis and wheezing. Case 8 was diagnosed with congenital syphilis and FAS prior to the onset of his first HIV related illness. Four of the children became ill after the HIV diagnosis was made and presented within one to five months after diagnosis.

Table 4: The initial medical presentation of the children, prior to the diagnosis of HIV.

Case	DOB	Onset of first illness	Diagnosis	Date of HIV diagnosis	Onset of ART
1	5/07/2000	22/03/01 Age: 9 months	Ringworm Eczema	Not recorded	15/03/03
2	5/07/98	8/01/99 Age: 6 months	Lower Respiratory Tract Infection (LRTI) Bronchiolitis	07/10/98	06/03/03
3	24/04/97	15/02/98 Age: 10 months	Gastroenteritis	05/08/97	26/02/04
4	27/11/94	18/02/98 Age: 3 years 3 months	Impetigo	Not recorded	4/04/03
5	10/06/94	04/09/95 Age: 15 months	Pulmonary Tuberculosis (PTB)	Not recorded	14/02/03
6	11/12/93	17/12/94 Age: 3 months	Pneumonia	14/01/94	06/03/03
7	18/04/93	22/10/93 Age: 6 months	Pneumonia Kwashiorkor	28/10/95	22/12/03
8	31/07/92	13/11/92 Age: 5 months	PTB Staphylococcus skin infection	19/01/94	14/02/03
9	22/02/92	04/08/92 Age: 6 months	Meningitis	Not recorded	14/ 02/03

2.5.4.3 Subsequent medical presentations

All of the children, except for case 4, presented with frequent episodes of illness. Case 4 was in good health bar one episode of an upper respiratory tract infection, a skin rash (Impetigo), and a middle ear infection (Otitis Media). Infections with well-known bacterial and viral organisms were the most frequent clinical presentation, but they tended to be more severe and had a more protracted course. Skin infections were the most common, followed by gastroenteritis and respiratory tract infections (Pulmonary Tuberculosis, Pneumonias). None of the children developed severe infections with opportunistic organisms, or neoplastic conditions. Two children presented with meningitis and one with generalized seizures. Case 7 presented at the age of nine and eleven (pre-ART) with grand mal seizures, both secondary to severe electrolyte disturbances associated with gastroenteritis. Case 9 presented at the age of three years with meningococcal meningitis and case 8 with an episode of viral meningitis at the age of twelve years. Three children presented with ENT problems. Case 4 presented with chronic ear infections, case 5 with otorrhoea, and case 9 with otitis media. All of the children's growth parameters were below the mean for their age. Height and weight indices generally fell between the third and twenty fifth percentiles on standard growth charts with the exception of case 7 who presented with severe failure to thrive and wasting. She was diagnosed with kwashiorkor (a severe form of protein-energy malnutrition) at the age of five. Case 3 was also diagnosed with marasmic kwashiorkor at the age of ten months.

2.5.4.4 HIV Status

All of the children had been perinatally exposed to HIV. The date of diagnosis was obtained from the medical records of five of the nine children. However, no record was found indicating the date of positive serology in the rest of the children (cases 1, 4, 5 and 9). The reason for this could be that the diagnoses were made at another hospital or that the records were lost. Of those children in whom the diagnosis date was documented, three tested positive between one and three months old (cases 2, 3 and 6). The last two children were diagnosed at the age of eighteen months (cases 7 and 8).

Table 5: Profile of the children with regard to their HIV status.

HIV Status	1	2	3	4	5	6	7	8	9
CD4 Count: Pre ART	699	505	411	319	328	538	180	286	432
CD4 Count: Post ART	821	715	1259	755	889	825	310	441	776
Viral Load: Pre ART	–	–	–	287000	–	217000	–	–	394000
Viral Load: Post ART	LDL	LDL	LDL	LDL	LDL	LDL	LDL	LDL	LDL
Hospitalisations: Pre ART	5	8	4	0	3	16	8	4	9
Hospitalisations: Post ART	0	0	0	1	0	0	4	2	0
ART: date started	15/3/03	6/3/03	26/2/03	4/4/03	14/2/03	6/3/03	22/12/03	14/2/03	14/02/03
ART at time of neuropsychiatric referral	AZT 3TC NVP	AZT NVP 3TC	d4T 3TC KAL	AZT 3TC KAL	AZT 3TC NVP	AZT 3TC KAL	AZT 3TC EFV	AZT LAM (3TC) KAL	AZT NVP 3TC
Previous Regime	–	–	–	AZT 3TC NVP	–	AZT 3TC NVP	–	AZT LAM (3TC) NVP	–
Adverse Reaction/s	–	–	–	Abnormal liver functions NVP stopped	–	Abnormal liver functions NVP Stopped	–	Abnormal liver functions NVP Stopped	–

Table 5 describes the clinical profile of the children with regard to their HIV status. The CD4 counts and viral loads pre ART were values ascertained at tests just prior to initiating treatment (within one month of initiation of treatment). Values post ART, were values ascertained at tests done two years later (between May and August 2005).

2.5.4.5 Indications for initiation of ART

Seven of the children were started on ART because of recruitment onto a clinical trial. This was an open label multicentre trial to evaluate the pharmacokinetic efficacy and safety parameters of NVP, when administered in combination with AZT and 3TC for a period of forty eight weeks. The children continued on this regime on cessation of the trial via continued funding by the pharmaceutical company. The other two children were initiated on ART because of a clinical deterioration: case 7 presented over a period of three months with persistent vomiting and diarrhoea (CMV Enteritis), wasting syndrome, severe electrolyte disturbances and pneumonia. Her CD4 count at the time was 180. Case 3 presented with failure to thrive, persistent fever, coughing and generalized lymphadenopathy. Her CD4 count was 411. She was started on ART at Red Cross Children's Hospital.

2.5.4.6 Disease stage at initiation of ART

Five of the nine children had CD4 counts below 500 (between 319 and 432). One child (case 7) had a CD4 count below 200 (180). Three of the children had CD4 counts above 500 (between 505 and 699). The records do not indicate whether the children were formally clinically staged. However, based on the clinical staging system of the World Health Organisation (WHO), one of the children qualified for WHO Clinical stage I (case 4) as she was asymptomatic. Four of the children would have been classified as WHO clinical stage II (cases 1, 2, 3 and 6) and four subjects (cases 5, 7, 8 and 9) would have qualified for Clinical stage III. Case 7 presented with an AIDS defining opportunistic infection, severe failure to thrive, and loss of developmental milestones (see Modified WHO Staging System, table 1). Case 8 presented with severe failure to thrive coupled with clinical evidence of microcephaly. Case 5 presented with a possible encephalopathy with an impression of deterioration in intellectual functioning and case 9 was previously diagnosed with an encephalopathy on the basis of a spastic gait and

motor slowing as well as neurocognitive problems and behavioural disturbances (see Table 5).

Clinicians likewise did not document immunological staging. Based on the Centre for Disease Control and Prevention (CDC) Classification system, seven of the children would have been classified as Category 2 (moderate suppression), one child Category 1 (no suppression, case 4) and one Category 3 (severe suppression, case 7).

2.5.4.7 Age at onset of ART

Six of the children were between nine and eleven years old when ART was initiated. The rest were three (case 1), five (case 2) and six years old (case 3). This represents an average time of eight years from birth to initiation of antiretroviral medications.

2.5.4.8 Medication regimes

The majority of the children were recruited into the research study so were initiated on triple therapy consisting of the NNRTI NVP, and two NRTI's AZT and 3TC. Two children were started on medication at Red Cross Children's Hospital and were not subjects of the research study. Case 7 was started, aged ten, on the NRTI's AZT and 3TC and NNRTI Efavirenz. Case 3 was initiated on two NRTI's 3TC and d4T, and the PI, KAL. She was six years old at the time. All treatment regimes (including those used in the research study) are based on standard protocols for first line treatments in HIV positive children.

2.5.4.9 Side effects and tolerance

There was a change of treatment regimen in three of the children, all due to the adverse effects of NVP. Case 4 developed a skin rash within a month of starting the medication, necessitating an admission. She was diagnosed with a grade 3 skin toxicity secondary to NVP, which was stopped and replaced with the PI, KAL. Cases 6 and 8 both developed abnormal liver functions (three and six months post treatment initiation respectively) assessed to be secondary to NVP, which was replaced by KAL. Except for the above, the medications were well tolerated with no further documented reports of side effects. There were no direct links between behavioural manifestations and particular antiretroviral medications used.

2.5.4.10 Response to ART

There was a dramatic reduction in the number of admissions after initiation of ART, with the average number of admissions down from 5 to 0,6 per child. Admissions were reduced to zero in five of the nine children. The maximum number of admissions post initiation of ART were four (case 7), followed by two in case 8, and one in case 4. Case 7 presented with progressive disease despite ART. She was re-admitted during the subsequent year for recurrent vomiting, persistently abnormal liver functions, gastroenteritis, PTB, and seizures secondary to metabolic disturbances. Her last admission was in January 2005, after which her health steadily improved. She was medically stable one year after initiation of the study. Case 4 was the only child who remained well prior to starting ART, with no admissions until she had an adverse drug reaction. She developed hepatitis in response to NVP. She recovered fully after the medication was changed. Case 8 was admitted (one year after starting ART) with an acute appendicitis and then a year later with viral meningitis. There have been no admissions in any of the children since January 2005.

The overall health status of the children has improved dramatically. There has been a steady increase in weight but generally, 'catch-up' growth in height has not occurred, with all of the children's growth parameters remaining between the third and twenty-fifth percentiles. Despite the fact that baseline (pre-HAART) neurocognitive profiles were not done in the majority of children, a comparable improvement in overall intellectual functioning based on scholastic performance was not observed. Similarly, there was a trend toward an increase in the rate of referrals for psychiatric evaluations subsequent to initiation of HAART. Medical status of the children, one year after the study was that 100% of the children remained virally suppressed (viral loads lower than detectable limits), and CD4 counts have increased in all of them. There have been only modest increases in CD4 counts in two children (cases 7 and 8) with counts remaining below 500 (CDC category II). This represents an improvement from category III to II in case 7. Case 8's immunological staging has remained at Clinical Stage II. The rest of the children's counts are between 700 and 1300, placing them in Clinical Stage I (no suppression).

2.5.5 a summary of the clinical case series correlated with information extracted from the medical records.

This group of PHIV children were initiated on HAART one year prior to referral for a neuropsychiatric assessment. They presented with behavioural problems and poor or declining academic performance, in the context of significant improvements in their overall health status. None of them was initiated on ART during infancy, with an average time of eight years from birth to initiation of treatment. WHO clinical stages at initiation of ART were that one of the children was rated as Clinical Stage I, four were Stage II and four were Stage III. Quantification of viral loads one year after the initial assessment revealed that 100% of the children were virally suppressed. CD4 percentages ranged between 28-45%.

The outcome of the psychiatric assessment was that seven of the nine children were diagnosed with psychiatric disorders. The majority (n=5) had diagnoses of ADHD, followed by mood disorders (n=2). This outcome was similar to prevalence figures cited in the literature, which reports a prevalence of ADHD as high as 50% and a 30-40% prevalence of mood disorders. Two children were diagnosed with psychiatric conditions that were possibly related to the direct effects of the virus on the brain, or due to the neurotoxic effects of ART: Delirium, and Mood disorder due to GMC. One child was diagnosed with an Autistic Spectrum Disorder (PDD-NOS). Responses to psychotropic medication were generally favourable with no severe adverse effects experienced. Therapeutic interventions consisted of parental guidance, behaviour modification, social skills groups, and individual counselling. The underlying causes for or aetiology of the psychiatric presentations were possibly a combination of factors related to the HIV disease and ART, as well as, those due to psychosocial stressors experienced by the children at the time.

CNS examination was normal in all but two of the children, who were noted to be microcephalic, with hyperreflexia in one of the two. All the children underwent EEG examinations, which were abnormal in two of them. Neuroimaging tests were normal in those referred for scans. Lumbar punctures were performed in two children, in order to determine CSF viral loads, which were undetectable in both instances. None of the children received diagnoses of HIV encephalopathy, which requires a triad of motor, neurocognitive, and behavioural problems, as none of them presented with significant

motor deficits. However, adult studies suggest that abnormal EEG's could be an early indication of HIV encephalopathy in otherwise neurologically asymptomatic HIV positive patients.

The results of neurocognitive testing indicated that the majority of the children achieved IQ scores between borderline and moderate intellectual ability, with only two children functioning in the average range of intellectual ability. It was not possible to determine whether the scores represented a decline in neurocognitive functioning, as most of the children were not previously tested. However, in the three children previously tested, scores indicate a significant decline in two of the three. The result of testing in the third child, who was previously diagnosed with PHE, showed an improvement in overall IQ score since last tested three years earlier.

The children with the lowest neurocognitive scores (with the exception of one child) were the oldest (11-13 years). These older children represent the group in whom there was the longest period before initiation of ART. These older children did not, as a group, fare better on IQ testing, in contrast to early (pre-HAART) studies which suggest that older children may represent a group of 'slow progressers', possibly infected by a less virulent strain of HIV (Koekkoek *et al* 2008, Thomaidis L *et al* 2010). The older group (n=4) were all classified as WHO stage 3 and with the exception of one, tended to score in the lower IQ ranges. The children with the three lowest IQ scores had the lowest pre-treatment CD4 counts and all were classified WHO stage III. The child with the highest CD4 count and who was clinically classified WHO stage I, achieved a neurocognitive score in the average range and continues to attend a mainstream school. Multiple aetiological factors contributed to the neurocognitive profile and poor academic performance, such as prenatal or perinatal insults to the brain, factors related to HIV (such as disease stage or degree of immune-compromise and baseline viral loads), presence of neurological deficits, possible executive functioning deficits, the impact of chronic illness and factors in the environment (such as a low caregiver-child ratio, inappropriate school placement, and a lack of remedial input).

It was not possible to determine whether initiation of ART positively impacted on neurocognitive functioning, considering that the children were not routinely neurocognitively assessed pre and post treatment. In spite of this, there was an impression that the impact on neurocognitive functioning was less favourable, with a

persistence of academic problems and a trend towards placement in special schools in the years following initiation of ART. Problems with memory, basic calculation, and concentration difficulties had been evident in follow-up sessions, suggestive of executive functioning deficits. The results, therefore, could indicate that neurocognitive problems persist in perinatally infected children with late initiation of ART.

Emerging from the clinical assessments, a number of questions were left unanswered: What is the impact of HAART on the neurocognitive functioning of children? Do the neuropsychological deficits observed in HAART-naïve children persist on initiation of HAART? Have the directly neurotoxic effects of some antiretroviral agents been explored in the paediatric population, and how may this impact on the neurocognitive functioning and behavioural profile of such a group? What is the nature and prevalence of psychiatric presentations in PHIV children, and how does this differ from the general population? To what extent are the psychiatric presentations virally or psychosocially related and what is the impact of HAART on the psychiatric morbidity of infected children? In order to answer some of these questions, the literature was explored via a systematic literature review that explored the impact of HAART on the neurodevelopmental functioning of HIV infected children, the psychiatric manifestations of HIV in children and adolescents and possible treatment related effects on psychiatric presentations and outcomes.

CHAPTER THREE

This chapter reports on the findings of a systematic review of studies exploring the neurobehavioural presentations of youth receiving HAART. This has important clinical implications as we attempt to define the psychopathology associated with HIV clearly, the long-term impact of the virus on neurocognitive functioning, and the potential for HAART to arrest or reverse neuropsychiatric sequelae.

The first report documenting a positive response of progressive HIV encephalopathy to ART was published, over 20 years ago, in a study by Pizzo *et al* (Pizzo PA *et al* 1988). Subsequent studies demonstrated that continuous intravenous infusion of AZT monotherapy resulted in improved neurodevelopmental functioning in PHIV children (Brouwers P *et al* 1990). By 2002, Mc Coig *et al* noted that combination therapies (dual therapies) were superior to monotherapy and that neurocognitive improvements were associated with decreased detectible CSF viral loads (Mc Coig C *et al* 2002).

Research studies exploring psychosocial aspects of paediatric HIV have mainly focused on issues such as orphanhood, disclosure and adherence with very few studies and a limited body of literature exploring the nature and incidence of psychiatric disorders in PHIV children. A review by Roa (Roa DR 2007) noted the limited literature related to psychiatric disorders. Studies tended to report on symptoms rather than psychiatric syndromes.

A few earlier studies (during the pre HAART era), which explored psychiatric presentations in younger children, do report high rates of anxiety, depression, and poor academic achievement (Bose S *et al* 1994, Mellins CA *et al* 2006). In contrast, Mellins *al* failed to demonstrate an association between HIV illness, perinatal illicit drug exposure, and behaviour problems (Mellins CA *et al* 2003). Similarly, Havens *et al* found no statistical difference in psychopathology between two groups of children (HIV exposed and non exposed), who were both exposed to perinatal illicit drugs (Havens JF *et al* 1994).

In this review, I aimed to specifically explore the literature covering the psychopathology associated with HIV, in order to define the nature and prevalence of psychiatric disorders in children and adolescents receiving HAART. A second aim is to establish the relationship between psychiatric presentations and neurocognitive, medical (disease stage, immune status and viral load) and CNS variables. A further aim would be to identify studies exploring the possible neurotoxic side effects of antiretroviral medications in children and adolescents.

3.1 METHODS

A review of empirical studies examining the neurobehavioural status of vertically infected HIV positive children and adolescents on HAART was conducted:

- Data bases used were PubMed and PsychINFO. Search terms used were 'HIV', 'child', 'paediatric', 'adolescent', 'psychiatric', 'behavioural', 'psychotropic', 'antiretroviral', 'HAART', neurocognitive, encephalopathy, 'neurotoxic' and 'side effects'.
- Relevant articles were searched for in reference sections of journal articles obtained.
- Studies were reviewed and information documented in tables with the following headings: Author, Type of study, Sample, Methodology, Results, and Conclusions.

3.2 INCLUSION AND EXCLUSION CRITERIA

Criteria for studies to be included in the review, were for the children to be vertically infected and on HAART therapy, for them to have undergone a psychiatric and/or neurological assessment (including neuroimaging), and lastly, to have undergone neurocognitive and/or neuropsychological testing. Studies were limited to those

published between 1997 and September 2011. The rationale for limiting studies to those published during and after 1997 is that HAART became the standard of care after 1997. Studies where the majority of samples consisted of children not vertically infected (transfusion infected, via sexual transmission), or where ART was not specifically mentioned, were excluded. The reason for this is that earlier studies using mixed samples of vertically and transfusion infected children consistently demonstrated differences in neurocognitive function between the two groups (ref). Studies conducted after 1997, but in which treatment with HAART was not indicated, were excluded.

3.3 RESULTS

3.3.1 Nature of studies:

31 studies were identified, most of them conducted in the USA, the rest in the United Kingdom (UK1), Greece (1), Thailand (1), The Democratic Republic of the Congo (DRC, 1), the Netherlands (1), Brazil (1) and South Africa (2). A number of USA studies were sub studies of large collaborative multi-site biomedical cohort studies, the Paediatric AIDS Clinical Trials group (PACTG studies 152, 219/219c, 338, 337 (Katz DG *et al* 2002), the Woman and Infant Transmission Study (WITS), (Diaz C *et al* 1998), and the Pediatric HIV/AIDS Cohort (PHACS) Study (Van Dyke R *et al* 2008). Eighteen studies examined the neurocognitive status and the rest, behavioural and psychiatric presentations in children and adolescents. Types of studies were retrospective record reviews (n=6), prospective studies (n=9), and 16 cross sectional studies. Study periods for prospective studies ranged from six months to 3 years.

Table 6: a quick reference to the research articles reviewed

Author	Type of study	Sample size	Aim/method	Results	Conclusions
Mc Coig C <i>et al</i> , 2002	Prospective Cohort study	23 PHIV children on HAART. Age range 7months-10 years. 2 groups: 1) 13 children on ABC, 3TC, ZDV 2) 10 placebo/3TC/ZDV. 20 children completed study.	To test effectiveness of combination NRTI treatment on CSF viral load and clinical signs of encephalopathy. Plasma and CSF viral loads and plasma CD4 counts performed. CSF obtained at 8, 16 and 48 weeks. Merrill palmer Scale of mental tests (<35 months), WISC III for children 6 years and older. Neuroimaging (CT) at baseline	Significant CNS involvement, in 80% of total sample (46% group 1 and 70% group 2). PHE diagnosed in 61% group 1 and 80% group 2. By week 48, 70% group 1 and 60% group 2 had normal neurological examinations. No diagnoses of PHE at completion of study. Decline in CSF HIV RNA in both groups (measurable viral loads decreased from 83% to 10% by 48 weeks). Median levels decreased below detectable levels in both groups by week 8 and 16. All undetectable levels by week 48. By week 48, emergence of different genotypic mutations in CSF and plasma, associated with viral resistance to ZDV, d4T and DDI. Most common genotype to emerge was those resistant to 3TC. 42% IQ scores in average range at baseline. Increased to 55% and 50% at week 48.	Clinical improvements in neurological status as well as CSF viral loads are associated with ART. Different genotypic mutations in CSF and plasma suggesting discordant viral evolution. Agents with high CNS penetration should be included in regimens.
Sanchez-Ramon S <i>et al</i> 2003	Retrospective recorded review	58 of 189 children who developed progressive encephalopathy (PE). 2 groups: 1 non ART (n10) and ART (HAART, mono-,	To assess impact of ART on development of PE. Medical records reviewed of children who developed PE. CD4 and CD8 counts	Similar immune and virological markers in the 2 groups. Onset of medication average 1.22 years. PE the first AIDS defining illness in 100% of group 1 vs. 44% group 2. Significantly higher mortality rates in children who developed PE (60% vs. 44%). 90%	Dramatic decline in incidence of PE since 1997 and significant decline in deaths. Starting ART prior to development of PE conferred neuroprotection

		dual therapy) before onset of PE (n27)	documented. Children followed up between 1994 and 2000.	deaths in group 1. 6.2x faster progression to PE in group 1, with median age of onset 0.6 years in group 1 vs. 2.5 years in group 2. Highest degree of clinical improvement in children on HAART (compared to no treatment, monotherapy or 2 agents). Dramatic decline in incidence in PE after 1997 (5.6% 1997, 0.0% 1998, 1.5% 1999 and 0.0% 2000)	with slower progression to PE. Greatest neurological improvements were experienced in children on combination therapies. ART therefore alters the natural history and neurological outcome of HIV.
Toledo M <i>et al</i> 2003	Retrospective record review	4 of 107 children met inclusion criteria. Ages 2.5, 4, 6.2 and 12.5 years. Children on PI based HAART regimens for at least 6 months.	To identify children on PI based HAART who presented with neurocognitive decline. Records reviewed and results of physical examinations, neuroimaging, blood tests, and neurocognitive tests reviewed. Tests: McCarthy Scales of Children's Abilities, WISC III, CPRS,	4 out of total of 107 experienced significant declines in neurocognitive scores <ol style="list-style-type: none"> 1. 12.5yo female (F). NFV, NVP, d4T. Decline reversed when d4T replaced with ZDV and ABC added. 2. 6yo male (M), Rit, d4T, DDI. Significant decline PIQ (by 16 points) and VIQ (by 22 points) at 18 months. 3. 2.5yo M, Rit, Didanosine (ddI) and ZDV. ZDV stopped due to bone marrow suppression. Global Neurocognitive Index (GCI) at 12 months was 24 points lower than baseline. 4. 4yo M, NFV, NVP, and d4T. GCI decreased by 17 points at 6 month follow up. Decline in expressive language observed. CNS examination revealed apraxia. CT 	Despite clinical and immune stability, some children do experience neurocognitive decline. Viral control not as effective in the CNS. May be due to poor penetrance of some ARV agents.

				revealed mild cortical atrophy.	
Gaughan DM <i>et al</i> 2004	Retrospective review (PACTG study)	1808 PHIV children < 15 years. Controls 1021 PHEU siblings.	To establish incidence of psychiatric hospitalisations in PHIV children. PACTG database explored to determine psychiatric hospitalisations between Sept 2000 and Dec 2002. Psychiatric hospitalisation and diagnoses, compared to hospitalisation rates in HIV - children	25 PHIV children hospitalised. Increased to 32 when age limit disregarded. Age at first admission 11 years. Significantly higher rates of psychiatric hospitalisations compared to population norms (6.17 cases per 1000). Majority depression, behavioural disorders, suicide attempts, or ideation. Disease status not associated with 1 st hospitalisation.	PHIV children are at increased risk of psychiatric hospitalisation and at high risk of depression and suicide.
Chiriboga C <i>et al</i> 2005	Prospective study	126 Mean age at baseline 23 months. 11 older than 3 years.	Determine impact of HAART on CNS status, rates of PHE and clinical outcomes. During 2000, neurological assessments performed, at baseline and 6 months. ADHD diagnosis made using DSM IV criteria. Tests: WISC III, BSID and Mc Carthy Scales of Infant Development	Rate of PHE 1.6% (n=2) in Cumulative prevalence arrested PHE 10% (n=13). 62% still had abnormal CNS assessments. 12 of 13 presented with developmental delay. 8 improved at follow up (after treatment). Significantly higher rates school placement in special education in children previously diagnosed with PHE. 28% diagnosed ADHD. ADHD diagnosis not significantly related to baseline VL, CD4, or CD8 percentages.	Marked decline incidence PHE demonstrated. May relapse if poor virological control, highest risk in arrested PHE. PHE diagnosis predicted by high viral load (VL). Despite improvements, high rates residual neurological, neurocognitive, scholastic problems in children with arrested PHE.

Jeremy R <i>et al</i> 2005	Prospective study (PACTG)	489 Age range 4 months – 17 years. Previously treated with ART but never with PIs	To assess impact of HAART on neuropsychological status and PHE and determine correlation with viral load. 7 different treatment combinations (6=PIs). Neurological examinations, CPRS, BSID 2 nd edition, WISC III, Stanford Binet. Tested at base line then per specified schedule over 48 weeks.	Baseline: neuropsychological scores significantly poorer compared to population norms. Mean neurocognitive and short term memory score 1 SD < norm. Mean IQ 83.5. 13% scores above mean of 100. 16% scores 2SDs below norm. CNS examination abnormal in 13%. Poorer neuropsychological performance associated with higher baseline VL. Neuropsychological performance not superior in those who achieved LDL. Post treatment with PI: No significant positive neuropsychological effect after 48 weeks of treatment.	Poorer neuropsychological functioning in PHIV children. Higher baseline VL predicts poorer cog functioning. Impact of PI therapy minimal, despite dramatic virological effect.
Shanbag M <i>et al</i> 2005	Retrospective cohort study	146 PHIV children born between 1990 and 2003	To assess long-term impact of ART on neurocognitive function and PHE. Data collected during two times: Pre and post HAART. Examined for Improvements in neurocognitive status.	Significant decline in diagnosis of PHE. Mean scores for all below norm of 100. Significant increase in neurocognitive scores between 2 times. All improved IQ scores of average 4.9 points. Higher caregiver child ratios and home environment associated with higher IQ. Lower VL and higher CD4 weakly associated with increase in IQ scores. No association CSF penetrating drugs and IQ scores.	Declines in prevalence of PHE and improvements in neurocognitive status since use HAART. Significant numbers still present with neurocognitive delays. May represent discordant patterns of viral resistance in plasma and CNS. CD4 and VL weakly predict future neurocognitive declines

Foster C <i>et al</i> 2006	Retrospective case note review	62 PHIV children, 2 categories according to disease severity. Mild disease (CDC category N, A or B) and severe (CDC category C)	Describe immunological, virological, neurocognitive outcomes of children younger than 3 years. Tests: Griffiths developmental test, BSID for infants, Mc Carthy Scales preschoolers.	50% severe disease (CDC category C). PHE in 22.5%. Significantly more CNS abnormality, lower CD4 count in CDC Category C. Similar VL responses. Infant assessment: Lower MDI and PDI scores compared to norms on Griffiths and BSID. Poorer expressive verbal scores. Group C scores lowest in all categories. Preschool assessment: Entire cohort lowers motor mean scores. Scores group C significantly lower than group A/B for perceptual- performance scores	Significant risk of neurological and developmental deficits in children presenting with severe disease at diagnosis. Trend is toward persistence despite immune reconstitution.
Martin P <i>et al</i> 2006	Cross sectional	41 Mean age 11.2 years.	Assess medical indices, neurocognitive function, and neuroimaging after 1 year on HAART. Neuroimaging done. WISC III administered.	Mean CD4 608,3. Mean CD4% 22. Mean VL 100 588. LVL in 17. Mean IQ and PSI (processing speed index) average range. However, most low average to borderline. Arithmetic scores significantly lower. Ventricular enlargement and subarachnoid dilatation commoner than white matter abnormalities and calcification.	CNS disease risk remains despite HAART. Those with brain scan abnormalities perform significantly more poorly. CD4 < 500, lower scores on processing speed. VL seems unrelated to neurocognitive scores.
Mellins C <i>et al</i> 2006	Cross sectional	47 32 on ART	Establish rate and type of DSM IV disorders Instruments: DISC IV, CBCL CDI. BDI and STAI to evaluate parents.	51% CD4 >500, 9% < 200. 55% psychiatric diagnosis of which 26% multiple diagnoses. Most common Anxiety, Disruptive Behaviour Disorders, Mood Disorders. Caregiver depression associated with CBCL problems. No association between CDI and caregiver mental health. Caregiver anxiety	High rates of psychiatric disorders, higher than population norms, comparable to high risk groups (ethnic minorities, chronically ill). Causes multifactorial

				significantly associated with CBCL problems.	
New MJ <i>et al</i> 2006	Cross sectional	57 PHIV children aged 6-12 years.	Prevalence of mental health problems (MHPs) and psychological adjustment in caregivers and children. Instruments: BSI (parents), (C-DISC 4, SCID, SSPQ, CBCL, WISC III).	Caregiver: 13 out of 57 had a psychiatric disorder. 37% HIV+. Child: 21% using psychotropic medication 14% previous or current Diagnosis of ADHD, 12% mood disorder, 5% both, 2% 'other' (anxiety, enuresis)	Despite reports of MHPs and psychotropic use, only small proportion met criteria for DSM IV diagnoses. May indicate resilience on the part of PHIV children or that caregiver information less reliable.
Nozyce M <i>et al</i> 2006	Cross sectional	298, mean age 7.2 yrs	Neurocognitive, behavioural and neuroimaging in clinically stable children on ART. Baseline CT/MRI. Test used WISC III	Mean FSIQ 86, significantly < population norms. 52% =behavioural problems. Neuroimaging: 7% basal ganglia or subcortical calcifications, 3% mild cortical atrophy, 1% white matter abnormalities, 1% focal mass lesion. No associated behaviour problems and CT/MRI findings	HIV+ children have a 4X increase rate of behavioural problems, lower neurocognitive scores than general pop. Higher rates behaviour problems than other chronically ill children. Lack of gender differences in ADHD symptoms may indicate HIV effect on brain. No link with illness severity. Aetiology likely multifactorial.
Wiener L <i>et al</i> 2006	Retrospective case note	64, mean age 15.3 years 94% on HAART	Document DSM IV diagnoses, psychotropic	45% prescribed medications: Anti -depressants 30%, stimulants 25%, atypicals 16%, and anxiolytics	Higher rates of psychotropic drug use than other chronic

	review		drug use. Establish link with medication use, loss of a parent	3%. Loss of biological parent associated with psychotropic med prescription. Psych diagnosis: 44% formal Diagnosis (90% on meds), Depression 10, ADHD 7, ADHD and depression 5, ADHD and mood 1, ADHD and psychosis 1, ADHD and Asperger's 1, psychosis 1, Anxiety 1, PD 1.	illness, similar to referred population. Depression important clinical issue in older children. May be related to high no stressors, genetic or immune status.
Menon A <i>et al</i> 2007	Cross sectional Zambia	127 11-15 years	Explore emotional and behavioural problems in Zambian adolescents, link with disclosure. Semi structured interviews. Instruments: SDQ, Parent and Youth Version.	58.3% not HIV aware, 73.2% on ART WHO staging: Stage 1(21%), 2 (39.4%), 3 (28.3%), 4 (5.5%). Compared with UK youth, Zambian youth (ZY) 2X likely to score outside normal range for total difficulties, 3X more likely to have extreme scores for emotional symptoms, 7X more likely abnormal scores for peer problems. Comparable rates of conduct disorder. Hyperactivity rates less than half in ZY .No relation WHO staging. No differences HIV aware, unaware.23/38 in favour of support group	High rates of emotional, peer group problems in HIV+ Zambian youth. Outcomes not related to health status or loss of a parent. Knowledge of HIV does not negatively impact on mental health. Disclosure may promote adherence and facilitate access to psychological support
Hazra R <i>et al</i> 2007	Prospective single arm study	12 Age range 7.2-18.5 years	Evaluate virological, immunological, and neuropsychological impact of 1 st HAART regimen, over 96 weeks. All received Stav, RTV, NVP Bloods at baseline and periodically. CT at	Median CD4 589, VL 3.9 log copies/ml. 2 had CNS disease at baseline. Median FSIQ 96.5 at baseline and remained same at 24, 48, 96 weeks. VIQ significantly lower than PIQ all times. 1had a decline in scores at 24 weeks (improved after ZDV added). 5 improvements to week 48.CNS disease in 3. All decrease in VL. 10 LDL by week 48. Maintained by 8 to week 96. Mean increase CD4 of	Most neurocognitively stable after initiation HAART, minimal CT brain abnormalities suggesting a neuroprotective effect of HAART.

			baseline, weeks 24, 48, and 96. Test: WISC III.	225 by week 48 and 307 week 96.	
Lindsey J <i>et al</i> 2007	Prospective study	1204 PHIV and PHEU children. 3 cohorts; 1 (born between 1992 and 1997, n 275). 2 (born after June 1997 n 929, 3 HIV+ children, n91 (1 or more BII assessment before started PI	Impacts of HIV on neurodevelopment before and after initiation of HAART containing PI. Method: BSID 1 st (BI) and second (BII) ed. Assessed at entry, 6 monthly till 2-3 years.	Cohort 1: Baseline (< 1 year): mean Mental (M) and Psychomotor (P) scores 105 and 107 in PHEU PHIV: mean M and P scores 85 and 77. More PHIV floor scores of <49. Higher P scores whose mothers initiated on ART during pregnancy. Significantly lower M and P scores at 6-24 mo in PHIV. Lower mean M and P scores if CD4 < 25%. Decline in M and P scores with increasing age, regardless of HIV status Cohort 2:PHEU: mean M and P 92 and 90.PHIV: 85 and 83.Scores for both significantly < norm. Higher % of floor scores in PHIV, no significant difference by maternal ART or drug use. No correlation CD4%, disease category, and M and P scores. Follow up 2 and 3 yrs: Trend for M and P scores to decline at greater rate in PHEU and for PHIV to improve relative to PHEU over time. Higher % PHIV with significant delays (<70), difference smaller over time. Greater % PHEU with significant delays with increasing age. Cohort 3: Significantly decreased rates of decline after started PI	HAART has a positive but limited impact on neurodevelopment. Children with more severe immune suppression are at greater risk of neuro-developmental deficits, which may predict survival. Initial difference in neurocognitive scores diminished with age, decline in scores in PHEU children highlights impact of other psychosocial factors, which negatively affect neuro-neurocognitive development.
Koekoek S <i>et al</i> 2008	Cross sectional	22, Median age 9.46 (6-17 years)	Prevalence of neurocognitive	Mean CD4=30 and LDL at 6 months of HAART. Mean IQ 95. Scores did not significantly deviate from	Gross neurocognitive deficits not evident in school age PHIV

			<p>impairments in school going children. Define risk and protective factors for neurocognitive functioning. Tests: R-SON, ANT Programme</p>	<p>norm. Five children scored 85 or lower, 9 between 85-100, 8 above 100. Neuropsychological tests: Significantly lower scores compared to norm in 4 out of 7 tests (verbal fluency, baseline speed, and pattern recognition, shift set. Poorer visuospatial tasks. Pursuit, tracking, tapping =norm). Mean reaction time associated with longer duration of treatment. Higher CD4 baseline associated with higher accuracy in pattern recognition.</p>	<p>children. Evidence of more subtle and specific executive functioning deficits. Specific neuropsychological tests are more sensitive than global measures PHIV children on HAART. Indices of processing speed particularly sensitive to detecting neurocognitive deficits.</p>
Smith L <i>et al</i> 2008	Prospective study South Africa	39 ambulant children, 14 of them. 6 yrs. and older Lam, Eva, Rit	<p>Impact of HAART on neurocognitive functioning, pre and post ART, over 6 months Assessed pre and 6mo post onset HAART. Tests: Griffiths, TROG, Ravens, DAP.</p>	<p>56% CDC category C. Significant improvement CD4, VL, and nutritional status after HAART onset. CNS examination abnormalities: 13 baselines, 11 follow up. Neurocognitive functioning: Most scores low average to borderline, No significant differences pre and post initiation of HAART. Language and visual perception deficits evident.</p>	<p>Highly prevalent CNS and neurocognitive deficits, remain static after 6 months on HAART. Language development greatest deficit, a predictor of long-term educational outcome. Recommend initiation of HAART in infancy, referral to early intervention programmes</p>
Brackis-Cott E <i>et al</i> 2009	Cross sectional	340 (206 HIV+) 9-16 yrs	<p>To describe school functioning, word recognition, and receptive language ability of older</p>	<p>PHIV children achieved significantly lower scores than PHEU children. 37% PHIV children attended special education vs. 28% PHEU. Mean CD4 602, VL 3150 copies/ml. HIV status significantly associated</p>	<p>Older HIV infected and affected children present with poor language skills. Educational intervention important, which</p>

			PHIV children compared to HIV – peers. Tests: PPVT III, WRAT-3.	with test scores.	if left unattended, will later on impact on health literacy.
Chernoff M <i>et al</i> 2009	Prospective study	575 (319 PHIV, 256 HNU controls)	Compare and describe behavioural interventions, psychotropic drug treatment patterns in PHIV and PHEU children. Instruments: CASI-4R, CI, and YSI.	Similar prevalence psychiatric symptom (61% each group one psychiatric condition). Degrees of impairment similar. More conduct problems in PHEU group. PHIV children more likely to have received interventions, psychotropic medication. Medications prescribed: Methylphenidate (n59), amphetamine salts (32), Atomoxetine (13), Risperidone (13), Sertraline (12), Fluoxetine (12), and Bupropion (6). Stimulants prescribed across all age groups, SSRIs mostly adolescence.	PHIV positive and negative youth present with similar symptomatology and impairment. However, more PHIV children receive interventions for emotional and behavioural problems, higher lifetime rates of psychotropic medication use. This may reflect better access to healthcare systems for PHIV youth.
Mellins CA <i>et al</i> 2009	Cross sectional	206 PHIV, 134 PHEU youth aged 9-16 years.	To examine prevalence, type of psychiatric and substance use disorders. Examine the association between HIV and mental health outcomes. Instrument: DISC-IV.	High rates of psychiatric disorder in both groups, but significantly higher rates in the PHIV group. Commonest diagnoses Anxiety disorders. ADHD more prevalent in PHIV group with 2x greater likelihood compared to PHEU youth. PHIV youth significantly more likely to have seen a therapist for emotional and behavioural difficulties.	This study demonstrates an association between perinatal HIV infection and youth psychiatric outcomes. High rates of psychiatric disorders are evident in PHIV and PHEU youth. HIV treatment programmes should include mental health interventions to

					prevent long-term negative outcomes.
Mellins CA <i>et al</i> 2009	Cross sectional	340 (206 PHIV, 134 PHEU adolescents, aged 9-16 years. Mean age 12.6 years.	To explore link between sexual and drug behaviour and youth mental health. Explore impact of caregiver mental health and family functioning on MHPs and risk behaviours. Instruments used: DISC- IV, CDI, STAI (child version), BDI and STAI, PCRI	Most prevalent substance was alcohol in both groups, followed by cannabis, and cigarettes. 3% diagnosis Substance Use Disorder (SUD). 58% not sexually active. Unprotected sex reported in 33% (40% PHIV and 26% PHEU youth). No direct association of caregiver mental health or family functioning with youth substance abuse. There was an indirect effect of caregiver psychiatric symptoms on youth substance use via youth mental health symptoms. No association between HIV status and psychiatric symptoms or risk behaviour.	PHIV and PHEU youth are engaging in sexual behaviours and substance use with high rates of unprotected sex reported. Caregiver and youth mental health may play critical roles in influencing risk behaviours. Highlights need for integrated mental health services, risk reduction strategies that could be incorporated into existing mental health programmes.
Puthanakit T <i>et al</i> 2009	Prospective study	122 children aged 6-12 years. PHIV (n 40), PHEU (n 40) and HNU (n 42)	To evaluate neurocognitive functioning in school children pre and post HAART initiation (6 months and 30 months). Test: WISC-III.	Mean FSIQ =79 PHIV vs. 88 PHEU vs. 96 HNU controls. Post treatment: PIQ remained same in all groups, VIQ significantly decreased in all 3 groups. 21% PHIV vs. 49% PHEU vs. 76% HNU controls had IQ scores in average range. More infected children scored in the neurocognitively handicapped range. HIV infection was significantly associated with poor neurocognitive performance. 20% of infected children were in lower than age appropriate grades.	Poorer neurocognitive functioning in PHIV children than age matched PHEU and HNU children. Long-term ART does not result in improvement in neurocognitive functioning despite virological control, immune reconstitution. Early neurodamage may be

					irreversible. Early initiation of ART should be a consideration to preserve neurocognitive functioning.
Van Loon SE <i>et al</i> 2009	Cross sectional	81 PHIV children aged 6-16 years. Mean age 9.8 years. 86 HIV- children (siblings or children from community).	To compare neurocognitive functioning of HIV+ and HIV- children. Examine effect of stage of disease, CD4%, medication, and child-to-adult ration on neurocognitive functioning. Test: RCM	PHIV children achieved lower mean scores on RCM than PHEU children even after controlling for differences in age. No significant correlation between neurocognitive functioning, stage of disease and CD% percentages. No association between neurocognitive functioning and specific ART regimens. No significant differences related to 'child- to- adult ratio'.	PHIV children perform more poorly in tests of neurocognitive functioning regardless of stage of disease, immune status, and type of medication or child to adult ratio.
Van Rie A <i>et al</i> 2009	Prospective DRC	158 (35 PHIV, 35 PHEU, 90 HNU controls). Age range 18-71 months. All HAART naïve and initiated on d4T, 3TC and NVP (children > 15kg) and AZT, Lam and NVP if < 15kg	Impact of HAART on neurocognitive functioning, pre, and post initiation of HAART. Tests used: BSID, SON, PDMS.	Mean scores lowest in PHIV (65.8), intermediate for PHEU (74.8) and highest for controls (84.6) at baseline. Improvement in scores in all 3 groups after 1 year, statistically significant for motor but not neurocognitive scores (84.3 vs. 87.6 vs. 96.5). Mean scores PHIV children similar to PHEU but lower than controls, after 1 year. Increases in neurocognitive scores higher among children presenting early (in disease process) for treatment. There was an age related acceleration of IQ scores, with accelerated neurocognitive and motor scores observed in younger children (aged < 29 months)	Neurocognitive and motor development of PHIV poorer than PHEU children and healthy controls prior to initiation of HAART. Improvements in neuro - development evident in PHIV children but only substantial in motor domains. Neurocognitive improvements remain restricted, as PHIV children do not achieve similar

					neurocognitive scores as controls, after 1 year of HAART. Greatest gains achieved in children who present for treatment early in the course of the disease process.
Wood S <i>et al</i> 2009	Retrospective cohort study	81 PHIV children, median age 15 years. Median age treatment initiation 3 years.	To examine relationship between severity of HIV disease, psychiatric and neuro- cognitive outcomes. 3 monthly follow ups, annual neuropsychiatric testing using WISC-IV, WASI. Psychiatric diagnoses via clinical assessments.	48% (n39) had psychiatric diagnosis, 18.5% (n15) had multiple comorbidities. Mood disorders most prevalent (30.8%), the ADHD (18%), psychotic disorder (8.6%), non-ADHD behavioural disorders (13.6%), eating disorders (2.5%). 16% ever hospitalised for psychiatric illness and 32% ever prescribed psychotropic medication. Mean FSIQ =87. Learning disability (LD) diagnosed in 42%. 35.8% received specialized learning support. Lifetime diagnosis PHE 17%. Significant association between lifetime history of psychiatric diagnosis and more severe disease (Class C diagnosis). Significant association between lower FSIQ, presence of a LD, specialized learning support and Class C diagnosis. No significant differences in FSIQ between patients initiated on HAART before or after AIDS diagnosis.	High rates of psychiatric illness, hospitalisation, and learning difficulties experienced by PHIV adolescents. There is an increased risk of psychiatric and neuro- cognitive impairment in perinatally infected adolescents with a distant history of an AIDS diagnosis. Results support early initiation of HAART during infancy or before AIDS diagnosis.
Thomaidis I <i>et al</i> 2010	Matched case control study	20 PHIV children. Age range 3-18 years. Mean	To assess impact of HAART on neurocognitive	75% (n 15) no neuroimaging abnormalities (NAs) (group 1), 5 NAs (group 2). Of those 3/5 had	Greater risk of neurocognitive impairment in children

		age 11.76 years.	functioning compared to normal controls. Establish association of social /emotional problems with neuroimaging abnormalities. SDQ, WISC III, and Griffiths. CT or MRI, neurological examinations.	abnormal neurological examinations. Age of initiation of HAART or duration of treatment did not differ between 2 groups. Higher neurocognitive scores in group 1 compared to controls: 40% average, 20% mild, 40% moderate vs. PHIV:0% average vs. 20% mild, 40% moderate, 40% severe. Majority normal SDQ scores in group 1, abnormal social, and hyperactivity scores. Peer relationship problems in group 2.	presenting with neuroimaging abnormalities. Patients without neuroimaging abnormalities are more likely to suffer maladjustment in emotional and activity spheres as opposed to those with neuroimaging abnormalities, who may present with compromised social skills.
Gadow K <i>et al</i> 2010	Cross sectional	323 PHIV, 259 HIV- controls (HNU living with HIV+ person or HNEU children). Age range 6-17 years old.	To compare rates of PHIV and HIV- peers. Instruments: CASI, ASI, YSI, SAFQ, subscales of the WISC IV (to test attention, processing speed, memory), parent questionnaire.	Higher rates of psychopathology in both groups compared to population norms. Most common in both groups was ADHD, similar rates in older group (11 HIV+, 12% controls) but higher rates in younger group (17.05 vs. 12.6%). Higher rates of somatisation in PHIV group and higher rates of aggressive and antisocial behaviour in control group. Lower rates mood disorders in HIV+ group. Higher rates of interventions for academic and psychiatric problems in PHIV group. Higher rates severe oppositional and defiant behaviour, separation anxiety, and negative life events reported in HIV aware group. PHIV group lower scores for processing speed.	Both PHIV and community based peers at high risk of psychopathology, with no differences in overall rates of psychiatric problems. HIV negative peers are at greater risk of disruptive behaviour disorders, which may reflect greater access to interventions by PHIV youth. Higher rates of psychiatric interventions are evident in the PHIV group, which may suggest that lifetime rates of psychiatric

					problems are higher than these results suggest.
Souza E <i>et al</i> 2010	Cross sectional Brazil	49 PHIV adolescents aged 10-19 years. Mean age 12.5 years. All onset HAART after AIDS diagnosis.	To examine long-term outcome of HIV illness, psychological and school function. Instruments: QOLA (5 domains of psychological, physical, social/school functioning, health perception, HIV symptoms).	89.8% attended school. HIV status disclosed to staff in only 38.6%. School failure and dropout reported in 51% and 28.6% respectively. 36.7% felt discriminated against because of HIV status. High score achieved in all 5 domains, highest for physical functioning and lowest for social/school functioning.	Disclosure rates are low despite reaching adolescence. School failure and dropout rates are high. Improvements in HIV disclosure and early detection of school problems need to be a focus at clinic visits, as part of long-term follow up.
Malee K <i>et al</i> 2011	Cross sectional	295 PHIV, 121 PHEU children. Age range 7-16 years.	To establish impact of HIV infection by comparing PHIV children and PHEU children. To identify risk factors associated with mental health problems (MHP's). Instruments used: BASC-2, BASC-2 Self-Report of Personality (SRP), BASC-2 PRS. Two rating indices, the BSI) and ESI. Caregiver functioning: CDQ, WASI, PCR.	Higher rates of MHPs in both groups compared to US population. Higher prevalence of MHPs among PHEU than PHIV children (38% vs. 25%). BSI scores in 'at risk' or clinically significant range for 29% PHEU and 19% PHIV youth. ESI scores in 'at risk' or clinically significant range in 17% PHEU vs. 12% PHIV group. Lower child IQ, younger age, caregiver psychiatric disorder, caregiver functional limitations, caregiver limit setting problems, associated with a higher odds ratio of MHPs. Stronger association between caregiver psychiatric status and youth MHPs for youth living with biological mothers.	HIV exposed children regardless of infection are at increased risk of MHPs. Environmental risk factors such as caregiver psychiatric disorder are particularly associated with child MHPs. Higher rates of MHPs in PHEU youth may reflect less access to comprehensive medical and psychological care, than PHIV youth.

Lee B <i>et al</i> 2011	Cross sectional Study. Thailand	54 PHIV youth, mean age 15 years and aware of HIV diagnosis, 165 age matched PHEU children	Compare risk of depression among PHIV adolescents and matched controls. CDI Children's depression Inventory (Thai version) administered to all participants.	39.3% of all participants had a positive CDI score (15 and more). Mean score significantly lower among PHIV youth (27.8%) compared to controls (43%). No significant difference between groups in terms of suicidal thoughts, plans or attempted suicide. Positive correlation between positive CDI scores, planned or attempted suicide and reports of sexual intercourse.	Significantly decreased rates of possible depression were found among PHIV youth compared to school-based age and gender matched controls.
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Abbreviations:

SDQ: Strengths and difficulties questionnaire, Griffiths: Griffiths Developmental Scales, TROG: Test of Reception and Grammar, Ravens: Ravens Progressive Coloured Matrices, DAP: Harris-Goodenough Draw a Person Test, SON: Revised Snijders Oomen Non- verbal intelligence Test, ANT Amsterdam neuropsychological Tasks Programme, PDMT: Peabody Developmental and Motor Test, CASI-4R): Child and Adolescent Symptom Inventory, CI: Child Inventory, YSI: Youth Self Report Inventory, PPVT III: Peabody picture Vocabulary Test , WRAT-3: Wide Range Achievement Test , PCRI: Parent Child relationship Inventory, WASI: Wechsler Abbreviated Scale of Intelligence, ASI: The Adolescent Symptom inventory, YSI :Youth (self report) Inventory, SAFQ: Social and Academic Functioning Questionnaire, CDI: Children's depression Inventory, QOLA: Quality of Life Assessment, BASC-2: The Behavior Assessment System for Children-2nd edition, BASC-2 SRP: BASC-2 Self-Report of Personality (SRP), BASC-2 PRS: BASC-2 Parent Rating Scale (PRS), BSI: Behavioural Symptoms Index, ESI: Emotional Symptoms Index (ESI).CDQ: Client Diagnostic Questionnaire, WASI: Wechsler Abbreviated Scale of Intelligence (WASI), PCR: The Parent-Child Relationship Inventory . Screen Patient Questionnaire (SSPQ)

The majority of study subjects were from ethnic minorities and of low socioeconomic status (SES). Most studies did not indicate whether study subjects were exposed to illicit drugs prenatally. Sample sizes ranged from 17 to 1204. The age range was between infancy (<1 year) to 19 years and there was an equal male female ratio. Comparison groups were perinatally HIV exposed but uninfected (PHEU) or HIV negative, HIV unexposed (HNU) children. Population norms or published statistics of clinical samples such as psychiatrically uninfected youth were compared to the study samples. Disease stages ranged from asymptomatic (CDC category N) to severely ill (CDC category C).

3.3.2 Measures

- 1) A number of studies undertook serial blood and CSF samples. CD4 levels were measured in order to evaluate the response to treatment. CSF and plasma viral loads were measured, both to assess treatment effects and to establish whether there was a differential impact of the medication on plasma levels compared to CSF levels of the virus. Genotype analysis of blood and CSF was conducted to measure the emergence of mutations associated with viral resistance to treatment.
- 2) Neurological examinations were conducted to establish the presence of neurological deficits, particularly progressive encephalopathy.
- 3) Neuroimaging tests such as CT and MRI brain scans were conducted and severity ratings ascribed and matched with medical variables and neurocognitive scores.
- 4) Neurocognitive tests were conducted. The following tests were commonly used:
 - a) The Wechsler Intelligence Scale for preschool and primary school children older than 6 years was used. The Wechsler Intelligence Scale for Children-Revised (WISC-R) or the 3rd edition (WISC III (Kaufman AS 1998)). Scores of the Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) were examined, as well as, the Processing Speed and the Freedom from Distractibility indexes.

- b) McCarthy Scales of Children's Abilities were administered (Bradley-Johnson S 2001).
 - c) The first and second edition of the Bayley Scale of Infant Development (BSID), were administered (Lee LLS et al 2005, Bradley-Johnson S 2001).
 - d) The Stanford Binet Intelligence Scale was used to test short term memory and vocabulary (Becker KA 2003).
 - e) Neuropsychological testing was conducted. The subtests of the WISC III were used to assess language, memory, attention, visuomotor and visual spatial processing, academic measures, and motor performance. Subtests used were Digit Span, Arithmetic, Digits Backward, Picture Completion, Picture Arrangement, Block Design, and Coding. Executive functions such as Sequencing and Planning, Attention to Detail, and Visual Spatial Organization were tested.
 - f) The Griffiths neurodevelopmental test for infants and preschoolers was used (Aylward GP 1997, Lee LLS 2005).
- 5) Psychiatric evaluations were conducted by using clinical interviews and well validated diagnostic scales. The following rating scales and checklists were commonly used to assess the children: The Child Behaviour Checklist (CBCL) (Achenbach TM *et al* 2000), the Childhood Depression Inventory (CDI) (Kovacs M 1982), the Diagnostic Interview Schedule for Children (DISC IV) (Schaffer D *et al* 2000), the State Trait Anxiety Scale (Marteau TM *et al* 1992). Parental psychopathology was assessed by means of The Beck Depression Inventory (BDI) (Beck AT *et al* 1961), State Trait Anxiety Inventory (STAI), the Screen Patient Questionnaire (SSPQ), and the Clinical Diagnostic Questionnaire (CDQ), which also assessed maternal Post Traumatic Stress Disorder (PTSD) and substance abuse (Blake DD *et al* 1995, Mellins CA *et al* 2002, New M *et al* 2006).

Table 7: A list of rating scales and checklists most commonly used.

Rating Scales	Description	Checklists	Description
Diagnostic Interview Schedule for Children (DISC IV)	Highly structured diagnostic instrument to detect common DSM IV diagnoses. Lay interviewers require training to administer.	Child Behaviour Checklist (CBCL), parent version.	113 item scale (completed by parents), which assesses behavioural and emotional functioning in children aged 4 to 18 years. Standardized scores obtained for internalizing and externalizing behaviour.
		Childhood Depression Inventory (CDI)	For children aged 7-19 years. Assesses for symptoms of depression.
		*Beck Depression Inventory (BDI)	21 items to assess depressive symptoms in adults.
		*State Trait Anxiety Inventory (STAI)	20 items to measure anxiety symptoms and how the client feels in general.
		*Clinical Diagnostic Questionnaire (CDQ)	A substance abuse and mental health screening instrument that can be administered by lay interviewers.

* Denotes scales used to assess caregivers.

3.3.3 Antiretroviral Treatment (ART) Regimens

Some studies detailed the drug regimens administered (which consisted of combinations of NRTI's, NNRTI's and PI's) but did not include the CNS penetration ratings. Prospective studies documented neurodevelopment pre and post HAART, from baseline to treatment periods ranging from 6 months to 3 years. Retrospective studies conducted chart reviews that documented changes in CNS and neurocognitive functioning during several years of HAART treatment.

3.4 KEY FINDINGS FROM THE LITERATURE REVIEW

3.4.1 Impact of HAART across the spectrum of HAND

Studies specifically exploring the impact of HAART on PHE all demonstrated dramatic declines in incidence, that PHE is a reversible complication of HIV, with high degrees of neurological improvement, after initiation of HAART (Sanchez-Ramon S et al 2003, Chiriboga CA et al 2005, Shanbag MC et al 2005. Initiating

ART before the onset of PHE is neuroprotective and appears to alter the natural history of neurological outcome, in the majority of cases (Toledo-Tamula MAT *et al* 2003, Sanchez Ramon S *et al* 2003, Hazra R *et al* 2007). However, there is a risk of relapse if viral control is lost. The highest risk of relapse is in the group of children with arrested encephalopathy. Improvements in children who were previously diagnosed with PHE are less impressive after ART. There are higher rates of residual neurocognitive, neurological and scholastic difficulties compared to those with no prior diagnosis of PHE (Chiriboga CA *et al* 2005). Neurocognitive testing indicates that scores generally improve (compared to neurocognitive performance of untreated children), with IQ scores clustering in the average range compared to low average to borderline range in untreated children (Martin SC *et al* 2006). However, scores remain lower than population norms, with a trend for scores to be poorer than Perinatally HIV Exposed Uninfected (PHEU) children and HIV negative children (HNU). In children with arrested PHE, IQ scores either remain static or do not increase significantly, remaining well below the standard mean of 100 (Chiriboga CA *et al* 2005). A few studies, however, indicate that despite virological stability, some children can experience significant declines in neurocognitive functioning that is not explained by environmental risk factors. This appears to reverse when HAART regimens are changed to CNS penetrating drugs (Toledo-Tamula MAT *et al* 2003, Shanbag MC *et al* 2005). Most studies demonstrated persistent and significant neuropsychological deficits, particularly in language, verbal fluency, working memory, attention deficits, processing speed, and visuospatial tasks.

3.4.2 Neurocognitive performance in older school going children and adolescents receiving HAART

Studies specifically exploring the neurocognitive and school functioning of older children and adolescents demonstrate that school aged HIV positive children have lower neurocognitive functioning than aged matched PHEU and HNU children (Puthanakit T *et al* 2010). However, compared to age matched ART unexposed children, IQ scores are higher, clustering within the normal range. Despite this improvement in overall neurocognitive functioning, this group still perform more poorly academically compared to HIV negative controls and PHUE children. Significant percentages of children continue to require specialized educational input or referral to special schools (Brackis-Cott E *et al* 2009, Souza E *et al* 2010). Neuropsychological testing reveals that executive functioning problems persist in

these children. This may explain their relatively poorer academic performance despite their composite IQ scores falling within the average range (Koekoek S *et al* 2008). The findings of a study by Brackis-Cott demonstrated that older HIV infected and affected children and adolescents present with poor language skills (poor verbal skills, limited vocabulary and basic reading skills). The findings highlight the importance of educational interventions to address this problem that, if not remediated, may affect the overall health literacy (and adherence) in infected youth as they age and assume greater treatment responsibility (Brackis-Cott E *et al* 2009).

3.4.3 Specific medical and CNS variables associated with global and/or specific neurocognitive functioning

Most studies demonstrated consistent increases in CD4 counts and significant decreases in viral loads after ART. However, studies exploring the neurocognitive impact of long-term ART do not demonstrate significant improvements in neurocognitive functioning, despite virological control and improvements in neuro-immune indices. The findings suggest that early neurotoxicity occurring during the first years of life may be irreversible and that early initiation of ART in infants and young children should be a consideration in order to preserve neurocognitive functioning (Puthanakit T *et al* 2010). Studies linking neurocognitive outcomes with immune indices and viral loads differed with regard to outcomes. A study by Lindsey demonstrated that more severe immune suppression was associated with a greater risk of problems in neurodevelopment. However, the study by van Loon demonstrated that HIV positive children show poorer neurocognitive performance than HIV negative children do, regardless of their stage of disease, immune status, or type of ART (Lindsey JC *et al* 2007, Van Loon S *et al* 2009). Similarly, some studies suggested poorer neurocognitive outcomes (development of PHE) in children with higher baseline viral loads (Chiriboga CA *et al* 2005, Jeremy RJ *et al* 2005) and others not (Martin SC *et al* 2006). There was, however, a significant relationship between Processing Speed and CD4 measures, in effect; children with CD4 counts of below 500 had significantly poorer processing speed than children with CD4 counts of above 500. Children with CD4 counts of above 500 performed significantly better on tests such as Digits Backwards, Coding, Symbol Search, and Picture Arrangement (Martin SC *et al* 2006).

However, other studies linking neurocognitive functioning with disease stage demonstrated that children presenting with severe disease at diagnosis were at

greater risk of neurocognitive and neurological deficits and that these deficits persisted despite initiation of HAART. This suggests that early initiation of HAART (before onset of neurocognitive deficits or during infancy) is necessary in order to preserve the developing CNS. Other studies also indicated that the greatest neurocognitive gains were achieved in younger children started on treatment early in the disease process and poorer gains in older children, again demonstrating irreversibility of early pervasive damage (Smith L *et al* 2010, Sanchez-Ramon S *et al* 2003).

3.4.4 Impact on Cerebrospinal Fluid (CSF) viral load

Shanbag *et al* demonstrated a significant decline in the prevalence of PHE and improvement in overall neurocognitive status in a sample of 146 perinatally infected children initiated on HAART. However, a significant number of children continued to present with neurocognitive delay, suggesting discordant patterns of viral resistance between plasma and CSF (Shanbag MC *et al* 2005). Similarly, a prospective study conducted by Mc Coig *et al* measured CSF viral loads in plasma and CSF, and revealed discordant patterns of viral evolution, with mutations emerging associated with resistance to certain ART regimens particularly 3TC (Mc Coig C *et al* 2002). Other studies demonstrated neurocognitive declines despite significant reduction in viral loads suggesting poor CSF penetrance of certain antiretroviral agents. This neurocognitive decline was reversed or arrested when patients were changed to CSF penetrating regimens (Toledo-Tamula MAT *et al* 2003, Shanbag MC *et al* 2005).

3.4.5 Neurological status

Those studies that included neurological examination and neuroimaging assessments consistently demonstrated that neurocognitive and neuropsychological performance of children with neurological deficits and brain scan abnormalities is significantly poorer than those without (Foster C *et al* 2006, Thomaidis L *et al* 2010). Some studies demonstrate that neuroimaging abnormalities persist after 6-12 months on HAART, with ventricular enlargement and subarachnoid dilatation commoner than white matter abnormalities and calcifications (Martin SC *et al* 2006, Smith L *et al* 2008, Thomaidis L *et al* 2010). Others report minimal CT brain abnormalities after 96 weeks of HAART, suggesting a neuroprotective effect of HAART (Hazra R *et al* 2007). The study by Martin *et al* demonstrated that while HIV

infected children on HAART were performing in the normal range for composite neurocognitive scores and specific indexes, subsets of children with neurological deficits performed more poorly on neuropsychological tests. This was particularly so on those testing working memory, logical sequencing and planning, visual spatial organization and attention to visual details (Martin SC *et al* 2006).

3.4.6 'Non HAART' variables

Higher caregiver-child ratios and positive home environments which included parental involvement and the provision of stimulation were associated with higher full scale IQ's, indicating the need to focus on early intervention in socio-economically deprived infected children (Shanbag MC *et al* 2005). The study by Lindsey *et al* demonstrated differences in neurocognitive scores between PHIV and PHUE children, with poorer functioning in the infected group. The differences between the two groups, however, diminished over time, suggesting that other (probably psychosocial) factors had affected neurocognitive functioning (Lindsey JC *et al* 2007).

3.4.7 Psychopathology

High rates of psychiatric disorders and psychiatric hospitalization were found in HIV infected children. Prevalence rates ranged between 25% and 52% in some studies. This rate exceeded population norms and rates in other chronically ill children, but was similar to that of clinical samples of psychiatrically referred youth (Gaughan DM *et al* 2004, Mellins CA *et al* 2006, Nozyce M *et al* 2006, Wood SM *et al* 2009). Later studies demonstrated equal rates of psychopathology in PHIV and PHEU older children and adolescents (Chernoff M *et al* 2009, Mellins CA *et al* 2009, Gadow K *et al* 2010, Mallee K *et al* 2011), indicating a risk of psychopathology regardless of infection in HIV exposed youth. This was thought to be due to the in utero exposure to HIV, similar psychosocial stressors. The authors suggest that the lack of differences in rates of psychopathology could be related to increased access to services by HIV positive youth, who may receive more comprehensive interventions for behavioural and emotional problems (than PHEU youth). Two studies reported low rates of depression and DSM IV disorders respectively (Lee B *et al* 2011, New MJ *et al* 2006), indicating possible resilience in HIV positive youth, but also underreporting on the part of caregivers. The study by New also reported high numbers of children in the intellectually disabled range, which in the opinion of the

authors impacted on the utility of the screening instrument used (C-DISC 4), a computerized scale (New MJ *et al* 2006).

The commonest psychiatric presentations were mood disorders, disruptive behaviour disorders (particularly ADHD), anxiety disorders, and substance use disorders (SUDs) (Misdrahi D *et al* 2004, Mellins CA, Elkington KS *et al* 2009, Mellins CA, Brackis-Cott *et al* 2009, Wiener L *et al* 2006). There was a lack of gender differences in samples presenting with ADHD, suggesting a direct impact of HIV on the brain (Nozyce M *et al* 2006). Later studies focused on psychopathology in adolescents and revealed high rates of depression, non-disclosure (of HIV status in school settings), school dropout, sexual risk behaviour, and SUDs (Mellins CA, Elkington KS *et al* 2009, Souza E *et al* 2010). A study by Wiener revealed high rates (45%) of psychotropic drug use compared to the normative population, but similar to psychiatric populations. The most prescribed medications were antidepressants (30%, Sertraline most commonly used), followed by stimulants (25%), then atypical antipsychotics (16%). Higher rates of psychotropic medication use was found in children who had lost a parent to HIV, suggesting that mourning may be complicated by factors such as secrecy, stigma, and previous losses. The study also demonstrated high rates of depression in the older sample of youth, which was particularly associated with parental loss but which may also have been related to other psychosocial stressors, genetic or immune factors (Wiener L *et al* 2006). Similarly, a study by Chernoff revealed high lifetime rates of psychotropic drug use in HIV positive youth, despite equal rates of symptomatology and impairment between HIV positive and HIV negative (HIV exposed) youth (Chernoff M *et al* 2009).

Studies which explored the aetiology and risk factors associated with psychopathology did not consistently reveal specific links with HIV, neuroimaging abnormalities, or other disease related factors, concluding that the aetiology was likely to be a multifactorial combination of biological and environmental factors. However, a study by Woods *et al* examined the relationship between severity of HIV disease and psychiatric and neurocognitive outcomes. Results demonstrated a significant association between lifetime history of psychiatric illness and severe HIV disease (category C diagnosis) (Woods SM *et al* 2009). Another study revealed that lower child IQ, younger age, caregiver psychiatric disorder, and limit setting problems from caregiver to child were associated with higher odds of presenting with mental health problems (Malee K *et al* 2011). A similar study by Mellins *et al*,

demonstrated an indirect effect of caregiver psychiatric symptoms on youth psychiatric symptoms and substance use (Mellins CA, Elkington KS *et al* 2009). Later studies revealed PHEU youth to be at equal or greater risk of psychopathology. This may be due to shared factors such as in utero exposure to HIV and shared genetic and environmental stressors (Chernoff M *et al* 2009, Mellins CA, Elkington KS *et al* 2009, Mellins CA, Brackis-Cott *et al* 2009). Equal or lower rates of psychopathology in HIV positive youth may also be due to greater access to comprehensive interventions for emotional and behavioural problems by HIV positive youth. Service related issues that were highlighted were those related to the link between caregiver mental health and youth outcomes, recommending integrated mental health services for caregivers and children, and greater access to services for HIV affected (uninfected) youth. Effective strategies for reducing HIV transmission and reducing risk behaviour would be to incorporate interventions into existing mental health programmes (Mellins CA, Elkington KS *et al* 2009).

3.5 STRENGTHS AND WEAKNESSES OF THE STUDIES REVIEWED

The studies generally were of a high quality but with relatively few prospective studies (9). Sample sizes varied widely, ranging from infancy through to adolescence. Comparison groups consisted of HIV exposed but uninfected children or HIV unexposed HIV negative children from similar ethnic and socio-economic backgrounds. This however may still lack generalizability as most studies were conducted in the developed world. Well validated neurocognitive tests, neuropsychological batteries, and instruments to test psychopathology were used. Later studies considered multiple variables that may impact on neurobehavioural presentations. However, the relatively small sample sizes in some studies could have influenced their statistical power to identify the specific biological and environmental factors that impact on the neurocognitive and mental health outcomes in PHIV children and adolescents. Few of the prospective studies particularly explored neurobehavioural functioning pre and post HAART. No studies explored the potential neurotoxic side effects associated with HAART. None of the studies explored the nature of the ADHD diagnosis in HIV positive children and how this may differ compared to HIV negative children in terms of diagnostic criteria, specific neuropsychological deficits, and the impact of treatment with stimulants.

This is of potential significance considering that early studies suggest that aetiologically, an ADHD diagnosis may indicate a direct effect of the virus (derived from the lack of the usual ADHD gender differences in HIV positive children). This, coupled with the high prevalence of neuropsychological deficits revealed on testing, may indicate that an ADHD diagnosis is associated with significant neuropsychological deficits, showing early HIV encephalopathy in otherwise asymptomatic PHIV children. The lack of prospective study design and the small number of studies exploring HAART impact, particularly adverse neurocognitive and behavioural effects of Efavirenz, represents a gap in the current literature, which should be further explored.

3.6 CONCLUSION

A review of the literature exploring the neurobehavioural profile of PHIV children in the post HAART era reveals that despite higher rates of survival and substantially lower rates of PHE, a small percentage may still present with neurocognitive decline and neurological impairments, particularly those with known CNS disease and more severe immunosuppression. However, most children on neuropsychological testing demonstrate improved composite IQ scores, but continue to present with milder neurocognitive deficits, particularly language and memory deficits, and problems with processing speed. Such deficits negatively impact on academic performance and may impact on health literacy (and adherence) as they assume increased responsibility for their treatment during adolescence and early adulthood. Furthermore, PHIV children continue to perform more poorly than PHEU and HNU children do, despite shared perinatal and psychosocial stressors in the PHEU group. This may indicate a possible viral aetiology for neurocognitive problems. Studies reveal that the greatest neurocognitive gains are achieved in younger children initiated on HAART early in the disease process, suggesting that slower gains in older children demonstrate irreversibility of pervasive early damage. Furthermore, greater neurocognitive improvements may be achieved in children on HAART regimens with high CNS penetration. Recommendations include serial neurocognitive (neuropsychological) testing and neuroimaging in children on HAART, early initiation of HAART ideally during infancy or early in the disease process, with antiretroviral medication that has high CNS penetration.

Studies that explored the nature and rates of psychopathology in PHIV youth, demonstrate high school dropout rates and non-disclosure of HIV status among PHIV adolescents. A number of studies demonstrated high rates of behavioural problems, psychiatric diagnoses, and risk taking behaviours in both PHIV and PHEU youth. Commonest psychiatric diagnoses are mood disorders (particularly during adolescence), ADHD (higher in PHIV youth) and anxiety disorders. Causes are likely multifactorial with no direct link with disease severity found. Caregiver mental health may influence youth risk behaviour highlighting the importance of interventions for caregivers and the need for integrated mental health services (for children and adults). Some studies identified PHEU youth as a high risk group, with higher rates of psychopathology, a reflection of increased access to more comprehensive services for PHIV youth. Recommendations include comprehensive and integrated mental health services at HIV clinics, for caregivers, PHIV, and PHEU youth. Early detection of academic problems should be a focus at such clinics. Incorporation of HIV prevention programmes and interventions to reduce risk behaviours may be an effective method of reducing HIV transmission by sexually active PHIV youth.

The following and final chapter consists of the discussion and concluding remarks. It will provide a brief summary and aetiological formulation of the clinical review of the patients evaluated at the neuropsychiatric clinic. This will be related and compared to the findings of the comprehensive literature review (chapter 3) in order to make clinical and educational recommendations as well as suggestions for future clinical research.

CHAPTER FOUR

This chapter, the discussion and concluding remarks, comprises an elaboration and aetiological formulation of the clinical case series with reference to the findings of the systematic literature review. Clinical, educational and research recommendations will be discussed.

4.1 DISCUSSION

The clinical cohort reviewed is a group of institutionalized South African PHIV children who were born prior to the national rollout and who were initiated on ART years after HIV diagnosis. Therefore, it could be anticipated that such a group was likely to present with HAND, despite immune reconstitution. In all of them, treatment was initiated relatively late and after the disease had progressed clinically. The nine children indeed presented with significant learning and behavioural problems necessitating transfer to special schools, as well as referrals for psychiatric evaluation. Explanations for the neurocognitive and psychiatric presentations are likely to be a combination of biological and psychosocial factors that may have impacted on these children.

Aetiological factors for the poor academic performance of the clinical cohort were biological factors such as pre- or perinatal insults to the brain, the direct CNS effect of HIV, neurological complications and the impact of co-morbid illnesses associated with HIV. Unfortunately, detailed histories of the pre and perinatal period were not available. However, one child was formally diagnosed with FAS and another presented with microcephaly and facial features of FAS, which is known to be associated with neurocognitive and behavioural deficits (Riley EP *et al* 2005). An additional two children may have been prenatally exposed to alcohol, as there were confirmed histories of longstanding alcohol abuse by the mothers. It was, however, not possible to identify a direct effect of HIV on the brain in the absence of a control group and in such a small sample. Furthermore, it was not possible to establish whether neurocognitive performance of this HIV infected group of children was poorer than an age matched group of HIV negative (PHEU or unexposed children) as suggested in the literature. However, test scores were similar to that reported in the literature, and clustered between borderline IQ and moderate intellectual

disability. A direct correlation between IQ scores and degree of immunocompromise was not established in the cohort, most likely due to the small sample size. It was, therefore, not possible to verify the findings of the literature review which suggest an association between poor neurocognitive performance, degree of immune compromise and higher baseline viral loads.

The literature review revealed that neurological impairments are associated with poorer neurocognitive outcomes and an overall poorer prognosis. In the case of the clinical cohort reviewed, most of the children did not present with significant HIV-related CNS deficits. The exceptions were EEG examinations, which were abnormal in two of the children, both of whom tested within the lowest IQ range for the group (composite IQ's less than 60). The abnormal EEG, therefore, may have been a sign of early encephalopathy in the absence of neurological impairment, as suggested in studies exploring the association between EEG, onset of encephalopathy and disease progression (Roy S *et al* 1992, Udgirkar VS *et al* 2003, Vigliano P *et al* 1997).

Environmental factors associated with a negative impact on the children's neurocognitive and academic performance may be those related to institutional care, multiple caregivers and poor quality of caregiver/child interaction. Greater levels of behaviour problems, growth, neurocognitive, and language development deficits have been demonstrated in institution reared children for more than fifty years (MacLean K *et al* 2003, Rutter M *et al* 2007). Studies that are more recent confirm serious impairments in social behaviour (Zeanah CH *et al* 2005) with disturbances in cortisol regulation, presumed to be due to high levels of stress (Carlson M *et al* 1997). A study by Smyke *et al* demonstrated that children were not equally affected by institutional care and that predictors of children's' development were related to length of institutional care, but mostly to the quality of caregiving (Smyke AT *et al* 2007). Dobrova Krol 2010 *et al* explored the effects of perinatal HIV infection and compared the stress regulation, neurocognitive, and physical growth of family reared and institution reared HIV positive children. They demonstrated that physical and neurocognitive development of family reared HIV positive children, even of a compromised quality, was more favourable than institution reared children, despite adequate provision of healthcare and nutrition. Elevated levels of diurnal cortisol in institutionalized children suggested that the

institutional environment might have been a source of daily intermittent stress (Dobrova-Krol NA *et al* 2010).

The clinical sample was resident at a children's home, which unfortunately experienced a high turnover of staff. Some of the children were also exposed to inconsistent parenting by multiple caregivers and 'fraught' caregiver-child relationships during their early years (later on the children were placed in cottages with two consistent carers), which may have contributed to a poorer quality of caregiving environment.

School related environmental factors that may have negatively affected the children's academic performance are those related to high rates of absenteeism (frequent hospitalizations and clinic visits) and placement at mainstream schools, where they coped poorly with the academic demands and pace of work. These schools were unlikely to have provided the specialized educational support that these children required. Large classes, in excess of thirty five children per grade, would also have reduced opportunities for regular 'one on one' contact with the class teacher. Those of the children who attended special schools did benefit from smaller classes, regular teacher contact, and a more appropriate curriculum suited to their intellectual ability.

Aetiological factors that contributed to the psychiatric presentations of the children assessed were biological factors such as genetic predispositions to mental illness, pre- or perinatal factors, HIV factors, possible adverse effects of ART, psychological and psychosocial factors. It was not possible to identify family histories of major mental illness as the information was not available in the case records and contact with family members was either absent or minimal. However, two of the mothers were known to abuse alcohol and experienced emotional difficulties. Prenatal exposure to alcohol was known in the case of two children, one of whom was formally diagnosed with FAS. This may have predisposed them to ADHD that is highly prevalent among children with FAS. No specific virally-related causes for the behavioural presentations of the clinical cohort could be established. It does however; provide detailed insights into the lived experiences of children living with HIV in South Africa and highlights the complex interwoven factors that have contributed to the clinical presentations. This clinical case series may therefore

provide an opportunity for hypothesis development, for future research studies with larger samples and comparison groups.

The comprehensive literature review similarly failed to definitively establish a HIV-related cause for psychiatric presentations and suggest that the aetiology of psychiatric presentations is a combination of biological and psychosocial factors. While it was not possible to identify a direct link between the psychiatric presentations and the antiretroviral medications prescribed, possible neurotoxic side effects were considered, as eight of the nine children were on a regime containing the NRTI AZT, which is associated with neuropsychiatric complications such as mania, depression, agitation, confusion and insomnia. One of the children presented with confusion, inattention, and perceptual disturbances. She was on a medication regime containing Efavirenz, which is associated with perceptual disturbances, agitation, confusion, stupor, amnesia, and impaired concentration. No studies, however, were identified in the literature review that specifically explored adverse behavioural and neurocognitive side effects of ART in children.

Psychological factors considered were attachment disturbances and the psychological impact of chronic illness: this group of children were mostly abandoned during infancy and placed in a children's home. They were, therefore, unlikely to have experienced secure attachments to a primary caregiver. This was demonstrated in the quality of attachment to the caregivers from the children's home, which was ambivalent and in most instances showed patterns of 'insecure' or 'disorganized' attachment. The attachment disturbances appeared to be pervasive and the source of the interpersonal difficulties between the children, their peers, and their caregivers at the children's home. The psychological impact of chronic illness was related to frequent episodes of illness, hospitalization and exposure to the death of their peers and fears of their own death, all of which was likely to be highly anxiety provoking and linked to their prior abandonment experiences.

Psychosocial factors that contributed to the psychiatric presentations of the children were those related to the school environment, institutionalization, and the impact of placement plans and reunification with family. This sample of institutionalized HIV positive children were largely shielded from the known psychosocial stressors experienced by HIV positive children living in the community, such as poverty,

parental illness, parental mental illness, substance abuse, and parental loss. However, a different set of factors impacted significantly on their psychological wellbeing, such as poor coping in mainstream schools and having to negotiate the transition to adolescence (with the added complication that they would be faced with leaving the children's home). A number of stressors appeared to be more specific and unique to this sample. These included being in institutionalized care, factors related to the particular children's home they were resident at, issues related to the socio-economic disparity between the children and their biological families, cultural, and language differences. The impact of the national 'roll out' could also be viewed as a stressor as the children's improved health led to an increased impetus to reunite the children with their families of origin, an experience which was not always experienced positively during the initial period of contact between the children and their families.

4.2 CLINICAL, EDUCATIONAL AND RESEARCH RECOMMENDATIONS.

By reviewing the findings of the case series and relating them to the systematic literature review, the following clinical educational and research recommendations are proposed.

4.2.1 Clinical recommendations

Baseline evaluation of the HIV positive child at diagnosis should ideally consist of medical, neurological, and developmental assessments, as well as a mental health screen. This type of comprehensive assessment is likely to be limited by service constraints in a resource-limited setting such as South Africa, where routine developmental and neurocognitive assessments would not be feasible for all HIV positive children. Scaled up delivery of ART to PHIV South African children has progressed significantly during the past few years and increasing numbers of studies have reported favourable outcomes (Bock P et al 2008, Eley BS *et al* 2011). Services, however, are not integrated, with limited interdisciplinary collaboration and liaison.

A realistic aim for a comprehensive assessment would be to adopt a biopsychosocial approach at primary level in order to address multiple risk factors for poor neurocognitive outcomes. Richter *et al* propose integrated and family based models of care whereby mothers and children are managed within the same setting, in order to strengthen 'Prevention of Mother-to-Child Transmission Therapy' (PMTCT), early diagnosis and ART initiation (Richter L *et al* 2009). Within this integrated system, one could then also implement psychosocial interventions such as parenting education and support, as well as early childhood intervention services. The creation of useful, but simple, screening instruments are essential. These could then be used by a clinician, in a primary care setting, as a valuable and cost effective method of early identification of problems. The aim of the initial screening would be to identify early neurological and neurocognitive deficits as well as behavioural problems, which form the clinical triad of PHE. Such brief screening instruments do not to my knowledge exist, but would take the form of brief 'checklists' screening for motor problems, neurocognitive, and behavioural changes.

The second 'tier' of assessment should be offered by multidisciplinary teams consisting of Paediatric Neurologists, Developmental Paediatricians, Child Psychiatrists, Clinical, or Neuropsychologists at secondary levels of care. The aim of the multidisciplinary assessments and follow-up would be to identify, monitor, and evaluate CNS symptoms, neurocognitive deficits, and psychiatric presentations, including ADHD. Multidisciplinary clinics would strengthen and promote integrated models of family based care, which ideally should provide medical and mental health services for caregivers as well as the children within the same clinic at all levels of HIV care. Children identified as 'at risk' of encephalopathy, or who present with psychopathology, may then be referred to specialist services at tertiary level.

Early initiation of HAART for mother and child is an important aspect of the management of the HIV positive child, in order to achieve favourable outcomes and to prevent and treat HAND. Recent studies demonstrate clear indirect benefits to the child when their parents are treated, such as decreases in diarrhoea, hospitalisations, and mortality, as well as improvements in school enrolment and nutritional status. These studies also show that family members significantly impact on adherence, mental health, and treatment outcomes of other family members (Mermin J *et al* 2008, Leeper SC *et al* 2010). These findings support models of

integrated care for the child in the context of the family, in order to achieve improved outcomes. Antiretroviral agents with known CNS penetration should be the treatment of choice in children presenting with neurocognitive deficits or neurological and psychiatric symptoms. Detection and monitoring of adverse CNS effects of ART should be undertaken by clinicians involved in the care of the child and reported to the infectious diseases clinician responsible for HIV treatment.

Early screening and intervention strategies should go hand in hand with services to enhance children's development and prevention of mental health problems. The former may be strengthened via state-supported preschool programmes, free education and health care, school feeding and removing barriers to ART. Prevention and intervention strategies for mental health problems in children and adolescents could be achieved via provision of strengthened child protection services, provision of social skills, HIV awareness, and sex education groups for HIV positive adolescents. Parenting interventions, psycho-education and mental health intervention for caregivers, home visits, and provision of increased numbers of mental health practitioners at all levels of care would add support.

4.2.2 Educational recommendations

Early detection and intervention of educational difficulties are often logistically problematic, as in many instances, educators and school psychologists are not aware of the child's HIV status. However, in cases where a child's status is known and consent by the caregiver granted, the creation of a database of children infected with HIV at various schools should be considered. This confidential record could be centralized and managed by school psychology services in the province. In that way, children's academic progress, school attendance, behavioural profiles and school transfers could be monitored on a regular basis. A coherent plan of intervention, referral, and liaison with healthcare providers may then be formulated. At school level, referral of a child identified as at 'risk' by the educator could feasibly be to the educational psychologist assigned to the school. This would be in order to evaluate and monitor academic progress and to refer to specialist medical services, should there be a suspicion of neurocognitive decline. The educational psychologist along with the teacher may then formulate a specific educational plan. They could implement educational support for the child, and refer for placement to an ELSN

school, if deemed necessary. While it is acknowledged that additional remedial support to address the educational needs of HIV infected children will be necessary if there is to be any hope of success, funding constraints would significantly impact on the Education Department's capacity to provide the additional human resources to intensify remediation or conduct regular routine psychometric testing of all HIV positive learners. For this reason, it is recommended that a task team be created in order to compile a framework within which submissions could be made to the national department to consider specialized funding streams for remedial interventions for children infected with HIV.

4.2.3 Research Recommendations

The literature review reveals a paucity of studies exploring the psychiatric sequelae of HIV in children. A number of remaining questions about the neurocognitive and psychiatric outcomes need to be answered. This could be done via further long-term prospective studies, which would be a useful way to track the long-term outcome of HIV positive children previously diagnosed with psychiatric disorders during childhood and followed up to adolescence and early adulthood. Studies exploring treatment effects (treatment response, drug interactions), including the psychiatric side effects of ART as well as the impact of long-term ART on the course and outcome of psychiatric presentations, should be further explored. A local study which would compare a group of psychiatrically referred HIV positive children, to a group of infected, psychiatrically asymptomatic children, will be useful to identify the unique risk factors for psychopathology in HIV positive children and adolescents in South Africa. Another local study examining school attendance, placement at special schools and the presence of academic problems in a sample of PHIV children, will be extremely useful in clarifying the educational needs of infected children in the South African context.

4.3 CONCLUSIONS

HIV in the HAART era continues to impact significantly on children's long-term survival, neurodevelopment, and mental health. Despite the longstanding record of proven efficacy of ART, access to HIV care in middle and low income countries

remains unacceptably low for HIV infected children compared to adults (Leeper SC *et al* 2010). This is of particular concern in Sub Saharan Africa, where substantial numbers of children remain at risk of being infected with HIV, as average 'Prevention of Mother to Child Transmission Therapy' (PMTCT) coverage remains only 58% (Richter LM *et al* 2009). Studies conducted in South Africa are few and correspond with the literature, confirming poorer neurocognitive performance in PHIV compared to PHEU and HNU children. High rates of neurocognitive deficits, particularly language deficits are evident, despite having been initiated on HAART. The authors suggest that this finding may be a reflection of the relatively late initiation of ART in South African children and recommend early HAART, during infancy, before the onset of neurocognitive deficits (Smith L *et al* 2008).

My impression (based on years of assessing children referred for psychiatric evaluation) is that significant numbers of South African children continue to present late at diagnosis and as a result, they are late for treatment initiation and therefore remain at risk of the irreversible neurocognitive and CNS sequelae of HIV. Adverse social circumstances are in many instances a barrier to care and delay ART initiation, as reliable adults need to be identified and counselled to assume responsibility for follow up visits and administration of medication at home. Other difficulties are that among some children living at home, adherence and clinic visits are erratic. Mothers themselves experience poor physical and mental health, and some abuse substances, all of which negatively impact on the care of the child. Children then have to rely on multiple surrogate caregivers (often grandmothers) within extended families to monitor treatment. The unfortunate consequence is that some of them develop treatment failure due to viral resistance. Significant numbers of such children merit referral to social services for investigation and monitoring of their home circumstances, but my impression is that referrals are either relatively few or that those referred experience limited services or intervention by statutory agencies. The majority of such children remain enrolled at school but present with significant learning problems when presenting for psychiatric evaluation. Many of them are not receiving specific remedial interventions.

Holistic interventions which aim at early initiation of ART, prevention, detection of and early intervention of neuropsychiatric problems will improve long-term outcomes of HIV infected children as they survive into adulthood. Comprehensive and integrated services with a focus on the family can be implemented in the developed

and developing world settings and produces good outcomes in terms of adherence and retention, service uptake and clinical prognoses (Leeper SC *et al* 2010). These need to be taken into consideration by those involved with healthcare policy and planning so that infrastructural capacity and healthcare personnel may be strengthened (Callaghan M *et al* 2010, Chopra M *et al* 2009, Lund C *et al* 2009).

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REFERENCES

- Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review* 2000;21(8):265-271.
- Achmat Z, Simcock J. Combining prevention, treatment and care: lessons from South Africa. *AIDS* 2007;21:S11.
- Aylward EH, Butz AM, Hutton N, Joyner ML, Vogelhut JW. Neurocognitive and motor development in infants at risk for human immunodeficiency virus. *Archives of Pediatrics and Adolescent Medicine* 1992;146(2):218.
- Aylward GP. Infant and early childhood neuropsychology. Roberts MC and La Greca AM (EDS.) Book 1997 Plenum Press New York.
- Bagenda D, Nassali A, Kalyesubula I, Sherman B, Drotar D, Boivin MJ, Olness, K. Health, neurologic, and neurocognitive status of HIV-infected, long-surviving, and antiretroviral-naïve Ugandan children. *Pediatrics* 2006;117(3):729.
- Bartlett J, Ferrando S. Identification and management of neurologic and psychiatric side effects associated with HIV and HAART. *Medscape* Retrieved April 2004;25:2007.
- Beard BJ. Orphan care in Malawi: Current practices. *J of Community Health Nursing* 2005;22(2):105
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4(6):561.
- Becker KA. History of the Stanford–Binet Intelligence Scales. Content and psychometrics (Stanford-Binet Intelligence scales, Fifth edition Assessment Service Bulletin no 1) Itasca IL: Riverside publishing 2003

- Belman AL, Diamond G, Dickson D, Horoupian D, Llana J, Lantos G, Rubenstein, A. Pediatric acquired immunodeficiency syndrome: neurologic syndromes. *Archives of Pediatrics and Adolescent Medicine* 1988;142(1):29-34.
- Belman A, Taylor F, Nachman S, Milazzo M. HIV-1-associated CNS disease syndromes in infants and children. *Neurology* 1994;44:168-169.
- Bhana N, Ormrod D, Perry CM, Figgitt DP. Zidovudine: a review of its use in the management of vertically-acquired pediatric HIV infection. *Pediatric Drugs* 2002;4(8):515-553.
- Bisiacchi PS, Suppiej A, Laverda A. Neuropsychological evaluation of neurologically asymptomatic HIV-infected children. *Brain Cogn* 2000;43(1-3):49-52.
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. *J Trauma Stress* 1995;8(1):75-90.
- Blanchette N, Fernandes-Penney A, King S, Read S. Neurocognitive and motor development in children with vertically transmitted HIV infection. *Brain Cogn* 2001;46(1-2):50-53.
- Blanchette N, Smith ML, King S, Fernandes-Penney A, Read S. Neurocognitive development in school-age children with vertically transmitted HIV infection. *Dev Neuropsychol* 2002;21(3):223-241.
- Bock P, Boule A, White C, Osler M, Eley B. Provision of antiretroviral therapy to children within the public sector of South Africa. *Trans R Soc Trop Med Hyg* 2008;102(9):905-911.
- Boivin MJ, Green SDR, Davies AG, Giordani B, Mokili JKL, Cutting WAM. A preliminary evaluation of the neurocognitive and motor effects on pediatric HIV infection in Zairian children. *Health Psychology* 1995;14(1):13.

- Bose S, Moss HA, Brouwers P, Pizzo P. Psychological adjustment of human immunodeficiency virus-infected school-age children. *Journal of Developmental and Behavioral Pediatrics* 1994;15(3) s26 .
- Brackis-Cott E, Kang E, Dolezal C, Abrams EJ, Mellins CA. The impact of perinatal HIV infection on older school-aged children's and adolescents' receptive language and word recognition skills. *AIDS Patient Care STDS* 2009;23(6):415-421.
- Bradley-Johnson S. Neurocognitive assessment for the youngest children: A critical review of tests. *Journal of Psychoeducational Assessment* 2001;19(1):19-44.
- Brouwers P, Moss H, Wolters P, Eddy J, Balis F, Poplack DG, Pizzo P. Effect of continuous-infusion zidovudine therapy on neuropsychologic functioning in children with symptomatic human immunodeficiency virus infection. *J Pediatr* 1990;117(6):980-985.
- Brouwers P, Tudor-Williams G, DeCarli C, Moss HA. Relation between stage of disease and neurobehavioral measures in children with symptomatic HIV disease. *AIDS* 1995;9(7):713-720
- Brown LK, Lourie KJ. Children and adolescents living with HIV and AIDS: a review. *Journal of Child Psychology and Psychiatry* 2000;41(1):81-96.
- Callaghan M, Ford N, Schneider H. Review A systematic review of task-shifting for HIV treatment and care in Africa.. *Human Resources for Health* 2010; 8(8) 2-9.
- Carlson M, Earls F. Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. *Ann N Y Acad Sci* 1997;807(1):419-428.
- Chase C, Vibbert M, Pelton SI, Coulter DL, Cabral H. Early neurodevelopmental growth in children with vertically transmitted human immunodeficiency virus infection. *Archives of Pediatrics and Adolescent Medicine* 1995;149(8):850.

- Chase C, Ware J, Hittelman J, Blasini I, Smith M, Llorente A, Anisfeld E, Diaz C, Fowler MG, Move J. Early neurocognitive and motor development among infants born to women infected with human immunodeficiency virus. *Pediatrics* 2000;106(2):e25.
- Chen LF, Hoy J, Lewin SR. Ten years of highly active antiretroviral therapy for HIV infection. *Med J Aust* 2007;186(3):146.
- Chernoff M, Nachman S, Williams P, Brouwers P, Heston J, Hodge J, Di Poalo V, Devogoo NS, Gadow KD. Mental health treatment patterns in perinatally HIV-infected youth and controls. *Pediatrics* 2009;124(2):627.
- Chiriboga CA, Fleishman S, Champion S, Gaye-Robinson L, Abrams EJ. Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active anti-retroviral therapy (HAART). *J Pediatr* 2005;146(3):402-407.
- Chopra M, Daviaud E, Pattinson R, Fonn S, Lawn JE. Saving the lives of South Africa's mothers, babies, and children: can the health system deliver? *The Lancet* 2009;374(9692):835-846.
- Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, Tamburrini E, Cauda R, De Luca A, Silveri MC. Efavirenz associated with neurocognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011;76(16):1403-1409.
- Coscia JM, Christensen BK, Henry RR, Wallston K, Radcliffe J, Rutstein R. Effects of home environment, socioeconomic status, and health status on neurocognitive functioning in children with HIV-1 infection. *J Pediatr Psychol* 2001;26(6):321.
- Crawford JR. Advances in Pediatric Neurovirology. *Current Neurology and Neuroscience Reports* 2010;10(2):147-154.
- Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. *Neuropsychol Rev* 2009;19(2):169-185.

Dahl V, Josefsson L, Palmer S. HIV reservoirs, latency, and reactivation: prospects for eradication. *Antiviral Res* 2010;85(1):286-294.

Davies MA, Keiser O, Technau K, Eley B, Rabie H, van Cutsem G, Giddy J, Wood R, Boulle A, Egger M, Moultrie H. Outcomes of the South African National Antiretroviral Treatment Programme for children: the IeDEA Southern Africa collaboration. *S Afr Med J* 2009 Oct;99(10):730-737.

de Martino M, Tovo PA, Balducci M, Galli L, Gabiano C, Rezza G, Pezzotti P. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. *JAMA: The Journal of the American Medical Association* 2000;284(2):190-197.

Department of Health. Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa. Pretoria: Department of Health, 2003 www.info.gov.za/otherdocs/2003/aidsplan.pdf. accessed 3/12/2011

Diamond GW. Developmental problems in children with HIV infection. *Ment Retard* 1989;27(4):213-217.

Diamond GW, Kaufman J, Belman AL, Cohen L, Cohen HJ, Rubinstein A. Characterization of neurocognitive functioning in a subgroup of children with congenital HIV infection. *Archives of Clinical Neuropsychology* 1987;2(3):245-256.

Diaz C, Hanson C, Cooper ER, Read JS, Watson J, Mendez HA, Pitt J, Rich K, Smerglio V, Lew JF. Disease progression in a cohort of infants with vertically acquired HIV infection observed from birth: the Women and Infants Transmission Study (WITS). *JAIDS J Acquired Immune Defic Syndromes* 1998;18(3):221.

Dobrova-Krol NA, Van IJzendoorn MH, Bakermans-Kranenburg MJ, Juffer F. Effects of perinatal HIV infection and early institutional rearing on physical and neurocognitive development of children in Ukraine. *Child Dev* 2010;81(1):237-251.

- Donenberg GR. Youths and HIV/AIDS: Psychiatry's role in a changing epidemic. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005;44(8):728-747.
- Drotar D, Olness K, Wiznitzer M, Guay L, Marum L, Svilar G, Horn D, Fagan JF, Ndugwa C, Kiziri-Mayengo R. Neurodevelopmental outcomes of Ugandan infants with human immunodeficiency virus type 1 infection. *Pediatrics* 1997;100(1):e5.
- Dubé B, Benton T, Cruess DG, Evans DL. Neuropsychiatric manifestations of HIV infection and AIDS. *Journal of Psychiatry and Neuroscience* 2005;30(4):237.
- Eley B, Davies MA, Apolles P, Cowburn C, Buys H, Zampoli M, Finlayson H, King S, Nuttal J. Antiretroviral treatment for children. *South African Medical Journal* 2006;96(9):988-993.
- Eley BS, Meyers T. Antiretroviral therapy for children in resource-limited settings: current regimens and the role of newer agents. *Paediatr Drugs* 2011 Oct 1;13(5):303-316.
- Faye A, Le Chenadec J, Dollfus C, Thuret I, Douard D, Firtion G, Lachassinne E, Levine M, Nicolas J, Monpoux F. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1. *Clinical Infectious Diseases* 2004;39(11):1692-1698.
- Feingold AR, Rutstein RM, Meislich D, Brown T, Rudy BJ. Protease inhibitor therapy in HIV-infected children. *AIDS Patient Care STDS* 2000;14(11):589-593.
- Ferrand R, Corbett E, Wood R, Hargrove J et al AIDS among older children and adolescents in Southern Africa: projecting the time course and magnitude of the epidemic. *AIDS* 2009;23(15): 2039-2046
- Fishkin PE, Armstrong FD, Routh DK, Harris L, Thompson W, Miloslavich K, Lew JD, Johnston A, Morrow C, Branstra ES. Brief report: relationship between HIV infection and WPPSI-R performance in preschool-age children. *J Pediatr Psychol* 2000;25(5):347-351.

- Foster C, Biggs R, Melvin D, Walters M, Tudor-Williams G, Lyall E. Neurodevelopmental outcomes in children with HIV infection under 3 years of age. *Developmental Medicine & Child Neurology* 2006;48(8):677-682.
- Fundaro C, Miccinesi N, Baldieri NF, Genovese O, Rendeli C, Segni G. Neurocognitive impairment in school-age children with asymptomatic HIV infection. *AIDS Patient Care STDS* 1998;12(2):135-140.
- Gadow KD, Chernoff M, Williams PL, Brouwers P, Morse E, Heston J, Hodge J, Di Poala V, Devgoo NS, Nachman S. Co-occurring psychiatric symptoms in children perinatally infected with HIV and peer comparison sample. *Journal of Developmental and Behavioral Pediatrics* 2010;31(2):116-118.
- Garvey L, Winston A, Walsh J, Post F, Porter K, Gazzard B, Fisher M, Leen C, Pillay D, Hill T. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. *Neurology* 2011;76(8):693-700.
- Gaughan DM, Hughes MD, Oleske JM, Malee K, Gore CA, Nachman S. Psychiatric hospitalizations among children and youths with human immunodeficiency virus infection. *Pediatrics* 2004;113(6):e544.
- Gavin P, Yogev R. Central nervous system abnormalities in pediatric human immunodeficiency virus infection. *Pediatr Neurosurg* 1999;31(3):115.
- Gay CL, Armstrong FD, Cohen D, Lai S, Hardy MD, Swales TP, Morrow CJ, Scott GB. The effects of HIV on neurocognitive and motor development in children born to HIV-seropositive women with no reported drug use: birth to 24 months. *Pediatrics* 1995;96(6):1078.
- Geddes R, Giddy J, Butler LM, Van Wyk E, Crankshaw T, Esterhuizen TM, Knight S. Dual and triple therapy to prevent mother-to-child transmission of HIV in a resource-limited setting—lessons from a South African programme. *South African Medical Journal* 2011;101(9):651-654.

- Gonzalez A, Everall IP. Lest we forget: neuropsychiatry and the new generation anti-HIV drugs. *AIDS* 1998;12(18):2365.
- Gortmaker SL, Hughes M, Cervia J, Brady M, Johnson GM, Seage III GR, Song LY, Danker WM, Oleske JM. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med* 2001;345(21):1522-1528.
- Habibi P, Strobel S, Smith I, Hyland K, Howells D, Holzel H, Brett, EM, Wilson J, Morgan G, Levinsky RJ. Neurodevelopmental delay and focal seizures as presenting symptoms of human immunodeficiency virus I infection. *Eur J Pediatr* 1989;148(4):315-317.
- Havens JF, Whitaker AH, Feldman JF, Ehrhardt AA. Psychiatric morbidity in school-age children with congenital human immunodeficiency virus infection: A pilot study. *Journal of Developmental and Behavioral Pediatrics* 1994;15(3, suppl) s18-s25.
- Hazra R, Jankelevich S, Mackall CL, Avila NA, Wolters P, Civitello L, Christensen B, Jacobsen F, Steinberg SM, Yarchoan R. Immunologic, virologic, and neuropsychologic responses in human immunodeficiency virus-infected children receiving their first highly active antiretroviral therapy regimen. *Viral Immunol* 2007;20(1):131-141.
- Hazra R, Siberry GK, Mofenson LM. Growing Up with HIV: Children, adolescents, and young adults with perinatally acquired HIV infection*. *Annu Rev Med* 2010;61:169-185.
- Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, Corkan SH, Duarte NA, Clifford DB, Woods SP. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011;17:3-16
- Henry RR, Christensen BK, Coscia JM, Cohen F, Moore E. Relationship between neurocognitive and immune functioning in children born to HIV-1 seropositive women. *Dev Neuropsychol* 1996;12(3):283-298.

- Horwood C, Vermaak K, Rollins N, Haskins L, Nkosi P, Qazi S. Paediatric HIV management at primary care level: an evaluation of the integrated management of childhood illness (IMCI) guidelines for HIV. *BMC Pediatrics* 2009;9(1):59.
- Ijumba P, Poole C, Georgeiii G, Grayiv A. Access to antiretroviral therapy. Published by the Health Systems Trust 2004:319.
- Jaspan H, Myer L, Madhi S, Violari A, Gibb D, Stevens W, Dobbles E, Cotton M. Utility of clinical parameters to identify HIV infection in infants below ten weeks of age in South Africa: a prospective cohort study. *BMC Pediatrics* 2011;11(1):104.
- Jeremy RJ, Kim S, Nozyce M, Nachman S, McIntosh K, Pelton SI, Yogev R, Wiznia A, Johnson GM Krogstad P. Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV-infected children. *Pediatrics* 2005;115(2):380.
- Joska JA, Gouse H, Paul RH, Stein DJ, Flisher AJ. Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. *J Neurovirol* 2010;16(2):101-114.
- Kapetanovic S, Leister E, Nichols S, Miller T, Tassiopoulos K, Hazra R, Gelbard HA, Brouwers P, Malle KM, Kammerer B. Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth. *AIDS* 2010;24(10):1481.
- Katz DG, Dutcher GA, Toigo TA, Bates R, Temple F, Cadden CG. The AIDS Clinical Trials Information Service (ACTIS): a decade of providing clinical trials information. *Public Health Rep* 2002;117(2):123.
- Kaufman AS, Kaufman NL, Dougherty EH, Tuttle KSC. Kaufman WISC-III Integrated interpretative system (K-WIIS). *J of Psychoeducational Assessment* 1998;16:365-384.

- Kieck J, Andronikou S. Usefulness of neuro-imaging for the diagnosis of HIV encephalopathy in children: clinical images: SAMJ forum. 2004;94(8):628-630
- Kimani C, Cheboswony M, Kodero H, Misigo B. The self-concept and academic performance of institutionalized and non-institutionalized HIV/AIDS orphaned children in Kisumu municipality. Education Research and Review 2009;4(3):106-110.
- King E, De Silva M, Stein A, Patel V. Interventions for improving the psychosocial well-being of children affected by HIV and AIDS. Cochrane Database Syst Rev 2009;2.
- King JR, Acosta EP, Chadwick E, Yogev R, Crain M, Pass R, Kimberline DW, Sturdevant MS, Aldrovandi GM. Evaluation of multiple drug therapy in human immunodeficiency virus-infected pediatric patients. Pediatr Infect Dis J 2003;22(3):239.
- King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. Clin Pharmacokinet 2002;41(14):1115-1133.
- Knorth E, Harder A, zandberg T, Kendrick A. Undre one roof: A review and selective meta-analysis on the outcomes of residential child and youth care. Children and Youth Services Review 2008;30:123-140
- Koekkoek S, de Sonnevill LMJ, Wolfs TFW, Licht R, Geelen SPM. Neurocognitive function profile in HIV-infected school-age children. European Journal of Paediatric Neurology 2008;12(4):290-297.
- Kovacs M. The Children's Depression Inventory: A self-rating depression scale for school-aged youngsters. Unpublished manuscript, University of Pittsburgh 1982.
- Kullgren KA, Morris MK, Bachanas PJ, Jones JS. Prediction of neurocognitive, adaptive, and behavioral functioning in preschool and school-age children with HIV. Children's Health Care 2004;33(4):241-256.

- Langford TD, Letendre SL, Marcotte TD, Ellis RJ, McCutchan JA, Grant I, Mallory ME, Hansen LA, Archibald S, Jernigan T. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. *AIDS* 2002;16(7):1019.
- Laughton B, Grove D, Kidd M, Springer P, Dobbels E, van Rensburg AJ, Violari A, Babiker AG, Madhi SA, Jean-Phillippw P. Early antiretroviral therapy is associated with improved neurodevelopmental outcome in HIV infected infants: evidence from the CHER (Children with HIV Early Antiretroviral Therapy) trial. Abstract MOPEB080 2009.
- Lee B, Chhabra M, Oberdorfer P. Depression among Vertically HIV-Infected Adolescents in Northern Thailand. *Journal of the International Association of Physicians in AIDS Care (JIAPAC)* 2011;10(2):89.
- Lee LLS, Harris SR. Psychometric properties and standardization samples of four screening tests for infants and young children: a review. *Pediatric Physical Therapy* 2005;17(2):140.
- Leeper SC, Montague BT, Friedman JF, Flanigan TP. Lessons learned from family-centred models of treatment for children living with HIV: current approaches and future directions. *Journal of the International AIDS Society* 2010;13(Suppl 2):S3.
- Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Morgello S. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol* 2008;65(1):65.
- Levenson Jr RL, Ann Mellins C, Zawadzki R, Kairam R, Stein Z. Neurocognitive assessment of human immunodeficiency virus-exposed children. *Archives of Pediatrics and Adolescent Medicine* 1992;146(12):1479.
- Lindsey JC, Malee KM, Brouwers P, Hughes MD. Neurodevelopmental functioning in HIV-infected infants and young Children before and after the introduction of

protease inhibitor–based highly active antiretroviral therapy. *Pediatrics* 2007;119(3):e681.

Lowenhaupt EA, Matson K, Qureishi B, Saitoh A, Pugatch D. Psychosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. *Clinical Infectious Diseases* 2007;45(10):e128.

Lund C, Boyce G, Flisher AJ, Kafaar Z, Dawes A. Scaling up child and adolescent mental health services in South Africa: human resource requirements and costs. *Journal of Child Psychology and Psychiatry* 2009;50(9):1121-1130.

Lwin R, Melvin D. Annotation: Paediatric HIV infection. *Journal of Child Psychology and Psychiatry* 2001;42(4):427-438.

Lyon M, D'Angelo LJ, Schuman WB, Tipnis T, Mrazek DA. Psychiatric diagnoses in adolescents seropositive for the human immunodeficiency virus. *Archives of Pediatrics and Adolescent Medicine* 2000;154(3):240.

Maclean K. The impact of institutionalization on child development. *Dev Psychopathol* 2003;15(04):853-884.

Madvahan S. Fosterage patterns in the age of AIDS: continuity and change. *Social Science and Medicine* 2004;58:1443-1454.

Malee K, Williams PL, Montepiedra G, Nichols S, Sirois PA, Storm D, Farley J, Kammerer B. The role of neurocognitive functioning in medication adherence of children and adolescents with HIV infection. *J Pediatr Psychol* 2009;34(2):164.

Malee KM, Tassiopoulos K, Huo Y, Siberry G, Williams PL, Hazra R, Smith RA, Allison SM, Garvie PA, Kammerer B. Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure. *AIDS Care* 2011; 1-12, iFirst.

- Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). *British Journal of Clinical Psychology* 1992;31(3):301-306.
- Martin SC, Wolters PL, Toledo-Tamula MA, Zeichner SL, Hazra R, Civitello L. Neurocognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antiretroviral therapy (HAART). *Dev Neuropsychol* 2006;30(2):633-657.
- McCoig C, Castrejón MM, Castaño E, de Suman O, Báez C, Redondo W, McClernon D, Danehower S, Lanier ER, Richardson C. Effect of combination antiretroviral therapy on cerebrospinal fluid HIV RNA, HIV resistance, and clinical manifestations of encephalopathy. *J Pediatr* 2002;141(1):36-44.
- McGrath N, Fawzi WW, Bellinger D, Robins J, Msamanga GI, Manji K, Tronick E. The timing of mother-to-child transmission of human immunodeficiency virus infection and the neurodevelopment of children in Tanzania. *Pediatr Infect Dis J* 2006;25(1):47.
- McKinney Jr RE, Cunningham CK. Newer treatments for HIV in children. *Curr Opin Pediatr* 2004;16(1):76.
- Mekmullica J, Brouwers P, Charurat M, Paul M, Shearer W, Mendez H, Diaz C, Read JS, Mondal P, Smith R. Early immunological predictors of neurodevelopmental outcomes in HIV-infected children. *Clinical Infectious Diseases* 2009;48(3):338.
- Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. Psychiatric disorders in youth with perinatally acquired human immunodeficiency virus infection. *Pediatr Infect Dis J* 2006;25(5):432.
- Mellins CA, Brackis-Cott E, Leu CS, Elkington KS, Dolezal C, Wiznia A, McKay M, Bamji M, Abrams EJ. Rates and types of psychiatric disorders in perinatally human immunodeficiency virus-infected youth and seroreverters. *Journal of Child Psychology and Psychiatry* 2009;50(9):1131-1138.

- Mellins CA, Ehrhardt AA. Families affected by pediatric acquired immunodeficiency syndrome: sources of stress and coping. *Journal of Developmental and Behavioral Pediatrics* 1994;15(3 Suppl) 554-560. Mellins CA, Levenson RL, Zawadzki R, Kairam R, Wetson M. Effects of pediatric HIV infection and prenatal drug exposure on mental and psychomotor development. *J Pediatr Psychol* 1994;19(5):617
- Mellins CA, Elkington KS, Bauermeister JA, Brackis-Cott E, Dolezal C, McKay M, Wiznia A, Bamji M, Abrams EJ. Sexual and drug use behavior in perinatally HIV-infected youth: mental health and family influences. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(8):810-819.
- Mellins CA, Havens J, McCaskill E, Leu C, Brudney K, Chesney M. Mental health, substance use and disclosure are significantly associated with the medical treatment adherence of HIV-infected mothers. *Psychol , Health Med* 2002;7(4):451-460.
- Mellins CA, Smith R, O'Driscoll P, Magder LS, Brouwers P, Chase C, Blasini I, Hittleman J, Llorente A, Matzen E. High rates of behavioral problems in perinatally HIV-infected children are not linked to HIV disease. *Pediatrics* 2003;111(2):384.
- Menon A, Glazebrook C, Campaign N, Ngoma M. Mental health and disclosure of HIV status in Zambian adolescents with HIV infection: Implications for peer-support programs. *JAIDS J Acquired Immune Defic Syndromes* 2007;46(3):349.
- Mermin J, Were W, Ekwaru JP, Moore D, Downing R, Behumbiize P, Lule JR, Coutinho A, Tappero J, Bunnell R. Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study. *The Lancet* 2008;371(9614):752-759.
- Meyers T, Moultrie H, Naidoo K, Cotton M, Eley B, Sherman G. Challenges to pediatric HIV care and treatment in South Africa. *J Infect Dis* 2007;196(Supplement 3):S474.

- Misdrahi D, Vila G, Funk-Brentano I, Tardieu M, Blanche S, Mouren-Simeoni M. DSM-IV mental disorders and neurological complications in children and adolescents with human immunodeficiency virus type 1 infection (HIV-1). *European Psychiatry* 2004;19(3):182-184.
- Mitchell CD. HIV-1 encephalopathy among perinatally infected children: Neuropathogenesis and response to highly active antiretroviral therapy. *Ment Retard Dev Disabil Res Rev* 2006;12(3):216-222.
- Mitchell W. Neurological and developmental effects of HIV and AIDS in children and adolescents. *Ment Retard Dev Disabil Res Rev* 2001;7(3):211-216.
- Moss H, Bose S, Wolters P, Brouwers P. A preliminary study of factors associated with psychological adjustment and disease course in school-age children infected with the human immunodeficiency virus. *Journal of Developmental and Behavioral Pediatrics* 1998;19(1):18-25.
- Msellati P, Lepage P, Hitimana DG, Van Goethem C, Van de Perre P, Dabis F. Neurodevelopmental testing of children born to human immunodeficiency virus type 1 seropositive and seronegative mothers: a prospective cohort study in Kigali, Rwanda. *Pediatrics* 1993;92(6):843-848.
- Nath A, Geiger J. Neurobiological aspects of human immunodeficiency virus infection: neurotoxic mechanisms. *Prog Neurobiol* 1998;54(1):19-33.
- New MJ, Lee SS, Elliott BM. Psychological adjustment in children and families living with HIV. *J Pediatr Psychol* 2006;32(2):123.
- Nozyce M, Hittelman J, Muenz L, Durako S, Fischer M, Willoughby A. Effect of perinatally acquired human immunodeficiency virus infection on neurodevelopment in children during the first two years of life. *Pediatrics* 1994;94(6 Pt 1):883. Upgeu

- Nozyce ML, Lee SS, Wiznia A, Nachman S, Mofenson LM, Smith ME, Yogey R, McIntosh K, Stanley K, Pelton S, . A behavioral and neurocognitive profile of clinically stable HIV-infected children. *Pediatrics* 2006;117(3):763.
- Ojikutu B, Jack C, Ramjee G. Provision of antiretroviral therapy in South Africa: unique challenges and remaining obstacles. *J Infect Dis* 2007;196(Supplement 3):S523.
- Ojukwu IC, Epstein LG. Neurologic manifestations of infection with HIV. *Pediatr Infect Dis J* 1998;17(4):343.
- Pao M, Lyon M, D'Angelo L, Schuman W, Tipnis T, Mrazek D. Psychiatric diagnoses in adolescents seropositive for human immunodeficiency virus. *Archives of Pediatric and Adolescent Medicine* 2000;154 (5), 240-244.
- Patel K, Ming X, Williams PL, Robertson KR, Oleske JM, Seage III GR. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. *AIDS* 2009;23(14):1893.
- Pearson DA, McGrath NM, Nozyce M, Nichols SL, Raskino C, Brouwers P, Lifschitz MC, Baker CJ, Englund JA. Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning. *Pediatrics* 2000;106(6):e76-e76.
- Penazzato M, Donà D, Wool PS, Rampon O, Giaquinto C. Update on antiretroviral therapy in paediatrics. *Antiviral Res* 2010;85(1):266-275.
- Peterson NJ, Drotar D, Olness K, Guay L, Kiziri-Mayengo R. The relationship of maternal and child HIV infection to security of attachment among Ugandan infants. *Child Psychiatry & Human Development* 2001;32(1):3-17.
- Pizzo PA, Eddy J, Falloon J, Balis FM, Murphy RF, Moss H, Wolters P, Brouwers P, Jarosinki P, Rubin M. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med* 1988;319(14):889-896.

- Pliszka S, AACAP Working Group. Practice parameter for the assessment and treatment of children and adolescents with Attention Deficit Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;46(7):894
- Pollack H, Kuchuk A, Cowan L, Hacimamutoglu S, Glasberg H, David R, Krasinski K, Borkowsky W, Oberfield S. Neurodevelopment, growth, and viral load in HIV-infected infants. *Brain Behav Immun* 1996;10(3):298-312.
- Prado J, Prendergast A, Thobakgale C, Molina C . Replicative capacity of Human Immunodeficiency Virus Type 1 transmitted from mother to child is associated with pediatric disease progression rate. *J of Virology* 2010;84(1):492-502
- Purchase SE, Van der Linden DJ, McKerrow NH. Feasibility and Effectiveness of Early Initiation of Combination Antiretroviral Therapy in HIV-infected Infants in a Government Clinic of Kwazulu-Natal, South Africa. *J Trop Pediatr* 2011.
- Puthanakit T, Aurpibul L, Louthrenoo O, Tapanya P, Nadsasarn R, Insee-Ard S, Sirisanthana V. Poor neurocognitive functioning of school-aged children in Thailand with perinatally acquired HIV infection taking antiretroviral therapy. *AIDS Patient Care STDS* 2010;24(3):141-146.
- Rao D, Sagar R, Kabra S, Lodha R. Psychiatric morbidity in HIV-infected children. *AIDS Care* 2007;19(6):828-833.
- Raskino C, Pearson DA, Baker CJ, Lifschitz MH, O'Donnell K, Mintz M, Nozyce, Brouwers P, McKinney RE, Jimenez E . Neurologic, neurocognitive, and brain growth outcomes in human immunodeficiency virus-infected children receiving different nucleoside antiretroviral regimens. *Pediatrics* 1999;104(3):e32-e32.
- Richter L. The impact of HIV/AIDS on the development of children. [www.issafrica.org/pubs/monographs/no_109/Chapter 2.2004](http://www.issafrica.org/pubs/monographs/no_109/Chapter_2.2004)

- Richter LM, Sherr L, Adato M, Belsey M, Chandan U, Desmond C, Drimie S, Haour-Knipe M, Hosegood V, Kimou J. Strengthening families to support children affected by HIV and AIDS. *AIDS Care* 2009;21(S1):3-12.
- Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. *Exp Biol Med* 2005;230(6):357-365.
- Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS* 2007;21(14):1915.
- Robinson MJ, Qaqish RB. Practical psychopharmacology in HIV-1 and acquired immunodeficiency syndrome. *Psychiatr Clin North Am* 2002;25(1):149.
- Roy P, Rutter M, Pickles A: Institutional care: associations between over activity and lack of selectivity in social relationships. *Journal of child psychology and Psychiatry* 2004; 45(4): 866-873
- Roy S, Geoffroy G, Lapointe N, Michaud J. Neurological findings in HIV-infected children: a review of 49 cases. *The Canadian Journal of Neurological Sciences* 1992;19(4):453.
- Rutstein RM, Feingold A, Meislich D, Word B, Rudy B. Protease inhibitor therapy in children with perinatally acquired HIV infection. *AIDS* 1997;11(12):107.
- Rutter M. Children in substitute care: Some conceptual considerations and research implications. *Children and Youth services review* Sept-Oct 2000;22(9/10):685
- Rutter M, Beckett C, Castle J, Colvert E, Kreppner J, Mehta M, Stevens S, Sonuga-Barke E. Effects of profound early institutional deprivation: An overview of findings from a UK longitudinal study of Romanian adoptees. *European Journal of Developmental Psychology* 2007;4(3):332-350.
- Sánchez-Ramón S, Resino S, Bellón Cano JM, Ramos JT, Gurbindo D, Muñoz-Fernández A. Neuroprotective effects of early antiretrovirals in vertical HIV infection. *Pediatr Neurol* 2003;29(3):218-221.

- Sharko AM. DSM psychiatric disorders in the context of pediatric HIV/AIDS. *AIDS Care* 2006;18(5):441-445.
- Schwartz L, Major EO. Neural progenitors and HIV-1-associated central nervous system disease in adults and children. *Current HIV research* 2006;4(3):319-327.
- Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clinical Infectious Diseases* 2003;37(8):1112.
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(1):28-38.
- Shanbhag MC, Rutstein RM, Zaoutis T, Zhao H, Chao D, Radcliffe J. Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy. *Archives of Pediatrics and Adolescent Medicine* 2005;159(7):651.
- Smith K, Kuhn L, Coovadia A, Meyers T, Hu CC, Reitz C, Barry G, Strehlau R, Sherman G, Abrams EJ. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS* 2009;23(9):1097.
- Smith L, Adnams C, Eley B. Neurological and neurocognitive function of HIV-infected children commenced on antiretroviral therapy. *South African Journal of Child Health* 2010;2(3).
- Smith R, Malee K, Charurat M, Magder L, Mellins C, Macmillan C, Hittleman J, Laskey T, Llorente A. Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment. *Pediatr Infect Dis J* 2000;19(9):862.

- Smith R, Malee K, Leighty R, Brouwers P, Mellins C, Hittelman J, Chase C, Blasini I. Effects of perinatal HIV infection and associated risk factors on neurocognitive development among young children. *Pediatrics* 2006;117(3):851.
- Smyke AT, Dumitrescu A, Zeanah CH. Disturbances of attachment in young children: The continuum of caretaking casualty. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002; 41:972-982
- Smyke AT, Koga SF, Johnson DE, Fox NA, Marshall PJ, Nelson CA, Zeanah CH. The caregiving context in institution-reared and family-reared infants and toddlers in Romania. *Journal of Child Psychology and Psychiatry* 2007;48(2):210-218.
- Souza E, Santos N, Valentini S, Silva G, Falbo A. Long-term follow-up outcomes of perinatally HIV-infected adolescents: Infection control but school failure. *J Trop Pediatr* 2010;56(6):421.
- Tlali T. Intelligence Testing. *Psychology an Introduction*. Chapter 15, pg 197. Book chapter . Ed Swartz L, de la Rey C, Duncan N. Oxford University Press. 2004
- Taussig H, Clyman R, Landsverk J. Children who return home from foster care: a 6-year prospective study of behavioural health outcomes in adolescence. *Pediatrics* 2001;108(1):1-7
- Toledo-Tamula MAT, Wolters PL, Walsek C, Zeichner S, Civitello L. Neurocognitive decline with immunologic and virologic stability in four children with human immunodeficiency virus disease. *Pediatrics* 2003;112(3):679.
- Tardieu M. HIV-1-related central nervous system diseases. *Curr Opin Neurol* 1999;12(4):377.
- Tardieu M, Janabi N. HIV-1 and the Developing Human Nervous System: In vivo and in vitro Aspects. *Dev Neurosci* 1994;16(3-4):137-144.

- Tardieu M, Le Chenadec J, Persoz A, Meyer L, Blanche S, Mayaux MJ. HIV-1-related encephalopathy in infants compared with children and adults. *Neurology* 2000;54(5):1089-1095.
- Tardieu M, Mayaux MJ, Seibel N, Funck-Brentano I, Straub E, Teglas JP, Blanche S. Neurocognitive assessment of school-age children infected with maternally transmitted human immunodeficiency virus type 1. *J Pediatr* 1995;126(3):375-379.
- Thobakgale C, Prendergrast A, Crawford H, Mkhwanazi N. Impact of HLA in mother and child on disease progression of pediatric Human Immunodeficiency Virus Type 1 infection. *J of Virology* 2009;83(19):10234-10244.
- Thomaidis L, Bertou G, Critselis E, Spoulou V, Kafetzis D, Theodoridou M. Neurocognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study. *BMC Pediatrics* 2010;10(1):99.
- Thompson A, Silverman B, Dzung L, Treisman G. Psychotropic medications and HIV. *Clinical Infectious Diseases* 2006;42(9):1305.
- Thorne C, Newell ML, Botet FA, Bohlin AB, Ferrazin A, Giaquinto C, deJosé Gomez I, Mok JYQ, Mur A, Peltier A. Older children and adolescents surviving with vertically acquired HIV infection. *JAIDS J Acquired Immune Defic Syndromes* 2002;29(4):396.
- Treisman GJ, Angelino AF, Hutton HE. Psychiatric issues in the management of patients with HIV infection. *JAMA: The Journal of the American Medical Association* 2001;286(22):2857.
- Udgirkar VS, Tullu MS, Bavdekar SB, Shaharao VB, Kamat JR, Hira PR. Neurological manifestations of HIV infection. *Indian Pediatr* 2003;40(3):230-234.

- Utlmann M, Diamond G, Ruff H, Belman A, Novick B, Rubinstein A, Cohen HJ. Developmental abnormalities in children with acquired immunodeficiency syndrome (AIDS): a follow-up study. *Int J Neurosci* 1987;32(3-4):661-667.
- Validity SI. The structured clinical interview for DSM-IV axis I disorders (SCID-I) and the structured clinical interview for DSM-IV axis II disorders (SCID-II). *Comprehensive Handbook of Psychological Assessment: Personality assessment* 2004;2:134.
- Van Dyk R, Rich k, DiMauro S, Geffner M, Gravel J, lipschitz S, Mellins CA, Malee K, Miller T, Moscicki A, Rice M, Smith R. Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP) Protocol PH 200. 2008. <https://phacs.nichclinicalstudies.org/publicDocs/AMP-Final-Version-1.0-11>.
- Van IJzendoorn M, Lujik M, Juffer F. IQ of children growing up in children's homes. A meta-analysis on IQ delays in orphanages. *Merrill Palmer Quarterly* 2008;54(3)341-366
- Van Loon S. The Neurocognitive Functioning of Children Infected with HIV/AIDS on Antiretroviral Treatment Compared to a Control Group in South Africa. Master thesis, Department of Developmental Psychology, Utrecht University.2009
- Van Rie A, Dow A, Mupuala A, Stewart P. Neurodevelopmental trajectory of HIV-infected children accessing care in Kinshasa, Democratic Republic of Congo. *J Acquir Immune Defic Syndr* 2009;52(5):636.
- Van Rie A, Harrington PR, Dow A, Robertson K. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. *European Journal of Paediatric Neurology* 2007;11(1):1-9.
- Vigliano P, Rigardetto R, Capizzi G, Arfelli P, Barbicinti I, Boffi P, Bonassi E, Cavallo P, Crosa P, Gandione M. EEG diagnostic and predictive value on HIV infection in childhood*. *Neurophysiologie Clinique/Clinical Neurophysiology* 1994;24(5):367-379.

- Vigliano P, Russo R, Arfelli P, Boffi P, Bonassi E, Gandione M, Rainn E, Tovo PA, Taglianti Mv, Rigardetto R. Diagnostic value of multimodal evoked potentials in HIV-1 infected children. *Clinical Neurophysiology* 1997;27(4):283-292.
- Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean-Phillippe P, McIntyre JA. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008;359(21):2233-2244.
- Wachsler-Felder JL, Golden CJ. Neuropsychological consequences of HIV in children:: A review of current literature. *Clin Psychol Rev* 2002;22(3):441-462.
- Wachtel RC, Tepper VJ, Houck D, McGrath CJ, Thompson C. Neurodevelopment in pediatric HIV infection. *Clin Pediatr* 1994;33(7):416.
- Whetten K, Osterman j, Whetten R, pence B, O'Donnell K, Messer L, Thielman N. A comparison of the wellbeing of orphans and abandoned children ages 6-12 in institutional and community-based care settings in 5 less wealthy nations. *Plos One* www.plosone.org Dec 2006;4(12) e8169
- Wiener L, Battles H, Ryder C, Pao M. Psychotropic medication use in human immunodeficiency virus-infected youth receiving treatment at a single institution. *Journal of Child & Adolescent Psychopharmacology* 2006;16(6):747-753.
- Williams PL, Leister E, Chernoff M, Nachman S, Morse E, Di Poalo V, Gadow KD. Substance use and its association with psychiatric symptoms in perinatally HIV-infected and HIV-affected adolescents. *AIDS and Behavior* 2010:1-11.
- Wilmshurst JM, Burgess J, Hartley P, Eley B. Specific neurologic complications of human immunodeficiency virus type 1 (HIV-1) infection in children. *J Child Neurol* 2006;21(9):788.
- Wood SM, Shah SS, Steenhoff AP, Rutstein RM. The impact of AIDS diagnoses on long-term neurocognitive and psychiatric outcomes of surviving adolescents with perinatally acquired HIV. *AIDS* 2009;23(14):1859.

Zeanah CH, Smyke AT, Koga SF, Carlson E. Attachment in institutionalized and non-institutionalized Romanian children. *Child Development* 2005;76(5):1015-10

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