Cognitive and Motor Development in Children with Vertically Transmitted HIV Infection

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Acknowledgements

There are a number of people I need to thank for their time and effort in helping me prepare my thesis. I thank the Ontario HIV Treatment Network and the Institute of Medical Science for providing the funding for my research. Most importantly, I am grateful to the children and their families who provided me with the opportunity to do what I have done. They have taught me a lot about courage and strength and I am a better person for having worked with them. I need to thank Dr. Read and Dr. Smith for their guidance and support and for allowing me the freedom to be creative and for reeling me in when I was going astray. Thank you both for giving me a second chance and providing me with a great opportunity. A special thanks to Alda Fernandes-Penney for helping me learn about testing and helping me get the job done. Also, thank you to Cheryl Arneson, Debra Louch, Robin Slater-Goldie, Dale DeMatteo, Carol Harrison, Jerry Brunner and Susan King who have all at one time or another helped me by providing sound advice and frank answers to my questions. As a group, the HIV/AIDS Team at HSC has shown me what dedication, hard work and love can mean to a program, children and their families. By showing me a great example of a health care team everyone in their own way has helped me decide to continue to pursue my goals and stick to my convictions. Finally, to my Mum, Dad, Mike, Drew, Phil and Karen thank you for not allowing me to give up on my dreams. I love you for it.

Toronto
June 14, 2000

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List of Abbreviations

AIDS – Acquired Immunodeficiency Syndrome

AZT – Azidothymidine; zidovudine

BSID I or II – Bayley Scales of Infant Development, 1st or 2nd Edition

CT – Computed tomography

DNA – Deoxyribonucleic Acid

EOWVT – Expressive One Word Vocabulary Test

ESL – English as a Second Language

HAART – Highly active antiretroviral therapy

HIV – Human Immunodeficiency Virus

HSC – The Hospital for Sick Children, Toronto, Ontario, Canada

FSIQ – Full Scale Intelligence Quotient

MDI – Mental Development Index

PDI – Psychomotor Developmental Index

PIQ – Performance Intelligence Quotient

PPVT-R or III – Peabody Picture Vocabulary Test – Revised or 3rd Edition

RNA – Ribonucleic Acid

VIQ – Verbal Intelligence Quotient

WISC-III or R – Wechsler Intelligence Scale for Children – III or Revised

WPPSI-R – Wechsler Preschool and Primary Scales of Intelligence – Revised

WRAT-R or III - Wide Range Achievement Test, Revised or 3rd Edition

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Cognitive and Motor Development in Children with Vertically Transmitted HIV Infection

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Abstract

We examined a broad range of neuropsychological functioning in three distinct cohorts of infants, preschool, and school-age children with vertically transmitted HIV infection. Our results are the first to assess development in a group of Canadian children with vertically transmitted HIV infection. Children were administered a battery of age-appropriate developmental or neuropsychological tests assessing, where possible, intelligence, receptive language, expressive language, visual and verbal memory, visual-motor speed and coordination, fine motor skill, and academic achievement. At the time of assessment, the children were on different antiretroviral therapies consistent with clinical practice at the time of testing. Results revealed that infants with HIV-infection are significantly delayed in mental, motor and adaptive functioning. The preschool cohort showed results that indicated that mean overall IQ for the group was reflective of average performance. A relative weakness was documented on a measure of receptive vocabulary. School-age children with vertically transmitted HIV infection showed many areas of cognitive function within the normal range. However, subtle motor impairments were documented and our results are the first report of fine motor and motor strength deficits in school-age children with HIV. The results should not be used to generalize a developmental trajectory for children with vertically transmitted HIV infection because the three studies are cross-sectional in design.

Epidemiology and Transmission

Acquired immunodeficiency syndrome (AIDS), which is caused by the human immunodeficiency virus (HIV), has become pandemic. In Canada, the epidemic is changing from one that initially appeared to affect gay men and people who received blood or blood products. It is now known that the infection occurs among all individuals and populations, with an increasing incidence among women and secondarily their newborns. Nationally, over the past decade the number of infants born to HIV-infected mothers has increased steadily (Health Canada, 1999). Despite the many medical and scientific advances that have occurred in HIV/AIDS research over the past two decades, HIV infection has become a major source of morbidity and mortality in infants, children and adults.

In Canada, as of December 31, 1999, a total of 45,534 individuals with positive HIV tests and 16,913 AIDS cases had been reported to the Laboratory Centre for Disease Control at Health Canada. Between 1989 and 1998, a total of 765 children were reported born to HIV-infected mothers. Of those, 232 have been confirmed HIV positive (vertical transmission) and an additional 61 have indeterminate status and are being monitored. In all provinces in Canada, HIV testing during pregnancy remains the choice of the individual woman. Consequently, not all of the pregnant women with HIV will be identified, and therefore the number reported by Health Canada does not capture the actual number of infants that are born to HIV-infected mothers or the number with vertically transmitted HIV infection. Although pediatric AIDS cases represent only 1.5-

2% of the total number of reported AIDS cases in the country, the number of children born to HIV-infected mothers is expected to rise (Health Canada, 2000).

The majority of infants and children who acquire the infection do so from a mother who is infected with the HIV virus. In Canada, up to December 31, 1998, 196 pediatric AIDS cases (children 0-14 years) were reported, and 153 (78%) were attributed to vertical transmission. As the prevalence of HIV is increasing among women of child-bearing age so is the number of children born with vertically transmitted HIV infection in both urban and rural communities. In Ontario, between 1984 and 1989, there were 34 HIV-infected infants born to HIV-positive mothers; during the period of 1990 to January 1997, the number of reported cases was 59. Overall, during the entire period, just over 58% of the mothers reported their risk factor for HIV as being from an endemic country, where heterosexual transmission of HIV is the most likely mode of transmission (Health Canada, 1999). The remainder of cases of vertical transmission can be associated with intravenous drug abuse by either the mother or her sexual partner, transfusion of blood or blood products to the mother, or unprotected sex with a non-intravenous-drug- abusing male (hemophiliac, bisexual) or immigration from an endemic country. Because the Canadian blood supply has been screened for HIV antibodies since the spring of 1985, transfusion as a method of HIV infection in children has been virtually eliminated.

HIV can be transmitted from a mother to her child via three routes: in utero, by transplacental passage; during the birth process through exposure to maternal blood or other body fluids; or through breastfeeding. All infants born to mothers infected with HIV have passively acquired maternal antibodies to the HIV infection; however, the mother to child transmission rate varies in different regions of the world. In Europe and

the United States, the rate ranges from 13-25%, whereas in developing nations it has been estimated to range from 25-35% (Giaquinto et al., 1998). It is now known that advanced maternal disease during or soon after pregnancy and general immunological deterioration associated with high concentrations of HIV ribonucleic acid (i.e., viral load) in the plasma and low CD4 counts have been correlated with increased rates of transmission (Mofensen, 1997).

A number of therapeutic interventions have been proposed to decrease the rate of mother to child transmission during pregnancy and labour. The results of the AIDS Clinical Trials Group's (ACTG) 076 trial of zidovudine (AZT) given to mothers during pregnancy, during delivery and to the newborn for 6 weeks, showed that transmission could be reduced by as much as two-thirds (Connor et al., 1994). Further, to prevent postpartum transmission, mothers are encouraged not to breast feed, when nutritional alternatives are available for feeding infants.

Natural History and Clinical Course

The clinical course of HIV-infection is variable in children who have vertically acquired HIV and those who acquired the infection as a result of exposure to contaminated blood or blood products. The interval between infection and the onset of symptoms has been shown to vary widely in therapy-naïve children. On average the latency period tends to be longer in children who have acquired the infection through transfusion and it tends to be longer in adults than it does in children (Rogers et al, 1987). In addition, several studies on survival of children with vertically acquired HIV-infection indicate a bimodal distribution in which the disease follows one of two patterns of progression (Blanche et al.,1990; Scott et al., 1989).

These reports have shown that mortality is highest (25-30 %) within the first two years of life. Further, death in the first years of life is strongly associated with opportunistic infections, such as pneumocystis pneumonia, severe encephalopathy and recurrent bacterial infections. In another subgroup, disease progression is slow without high rates of opportunistic infection and encephalopathy early in life. Both studies reported a survival rate at 5 years of around 65%. Other factors that have been shown to influence survival in pediatric cases are: low birth weight, growth failure, hepatitis, fever, diarrhea, anemia, and severe immunosuppression (Galli et al., 1995; Italian Register for HIV Infection in Children, 1994; Tovo et al., 1992). The mitigating factors that determine whether a child will experience rapid versus slow disease progression are not well understood. However, potential mediators have been suggested and include: timing of infection, host immune response, genetic factors, different strains of the virus and effects of antiretroviral therapy (Galli et al., 1995; Italian Register for HIV Infection in Children, 1994).

Virology

HIV is a ribonucleic acid (RNA) virus belonging to the lentivirus family of retroviruses (Connor & Ho, 1994). It is referred to as a retrovirus because of the way it copies its genetic code. In contrast with other RNA viruses, HIV replicates by reverse transcribing its RNA code into the DNA. Retroviruses are capable of producing profound immune system suppression and cancers. In people living with HIV, the virus causes immunosuppression by dysregulating and/or destroying the T-cell lymphocytes, increasing the risk of occurrence of opportunistic diseases (e.g. Pneumocystis carinii, lymphomas).

Medical Management

The management of pediatric HIV infection requires an interdisciplinary approach to be effective. Services should include medical care, psychosocial management, social services, educational planning, speech-language therapy, nutritional counseling, advocacy and service coordination.

Antiretroviral therapy is a critical component of the care of HIV-infected children and adults. In children, antiretroviral therapy can extend their lives, delay or prevent the onset of AIDS and improve several manifestations of HIV disease. There are several broad categories of antiretroviral agents. The two primary targets for action are the reverse transcriptase (RT). an enzyme unique to retroviruses, which copies the viral RNA template into a DNA molecule and the HIV-specific protease that is responsible for the posttranscriptional processing of viral proteins. Nucleoside analogues and non-nucleoside reverse transcriptase inhibitors act through disrupting RT function. As is evident in the name, the protease inhibitors block the posttranscriptional packaging of HIV proteins resulting in defective viral particles.

Combination antiretroviral therapy has been shown to be more effective than monotherapy and thus has been adopted as the therapeutic approach. There are disadvantages to this approach and they include cost, drug-drug interactions and more complex patterns of toxicity (McKinney, 1997). Also, complex drug regimens can decrease adherence and compliance amongst the patients. Despite these disadvantages, two approaches have been taken to the design of combination regimens. The first approach is to target multiple sites in the viral life cycle (such as RT and protease). Both

approaches appear to work, although which is the better has yet to be determined (McKinney, 1997). The other approach is to combine a number of drugs that act at the same biological site (the RT or protease). The rationale is that the conformational changes in the RT that produce resistance to one drug might make the virus more susceptible to the action of one of the other drugs.

Persistent low levels of HIV RNA in plasma are correlated with an improved outcome (Mellors et al., 1996). With the use of combination therapies it is possible in many cases to reduce the number of HIV RNA copies in plasma to undetectable levels. However, for several sites of virus replication in the body it remains unclear how effective combination therapy is at suppressing viral replication. One of these areas, sometimes referred to as a sanctuary for the virus, is the central nervous system (CNS) (Enting et al., 1998). Currently, knowledge on CNS entry of antiretroviral drugs in animals and humans is limited. Drug entry to the CNS is hindered by the blood-brain barrier, which acts to protect the brain from transient changes in blood composition. CNS entry probably occurs purely by diffusion because to date no antiretroviral drug transporters have been identified (Enting et al., 1998).

Another important component of treatment has been the use of prophylactic antibiotics (e.g. trimethoprim-sulfamethoxazole (TMP-SMX); pentamidine aerosols) to protect against the life-threatening pneumonia caused by the organism *Pneumocystis carinii*. Other prophylactic regimens are used to protect against other potentially threatening infections such as Mycobacterium avium-intracellulare (MAI) complex and certain fungal infections. Finally, a national multicenter study has confirmed the benefits and effectiveness of using infusions of intravenous immunoglobulins (IVIG) to support

the immune system. This treatment has been shown to reduce the incidence of fever, sepsis and hospitalizations. This effect was primarily seen in children who were not receiving TMP/SMX prophylaxis against PCP. Unfortunately, overall survival did not improve when using IVIG (National Institute of Child Health and Human Development, Intravenous Immunoglobulin Study Group, 1991).

Cognitive Development in Children with Vertically Transmitted HIV Infection

In categorizing the manifestation of HIV infection in children it is important to describe the extent and severity of central nervous system (CNS) involvement. The predominant cause of developmental delay or developmental regression in children seems to be the direct involvement of HIV in the CNS (Wolters et al, 1995), resulting in HIV-related encephalopathy.

Encephalopathy in HIV-infected children has been classified into two types: progressive and static (Belman, 1993). Progressive encephalopathy is further divided into a subacute progressive course and a plateau course. The subacute course is characterized by the loss of previously attained developmental milestones and by severe deficits in cognitive, motor, social-emotional, linguistic and adaptive functioning (Belman et al, 1988). Some children with subacute progressive encephalopathy may also display behaviours typically associated with autism, such as flat affect, staring, loss of speech and lack of social interest in others (Belman, 1993). In general, cognitive and social functioning are globally and severely impaired.

The plateau progressive encephalopathy subtype has a less severe course. Children do not exhibit the same pervasive deficits as are observed in the subacute course. Further, children usually do not lose previously acquired developmental

milestones (Belman, 1993). However, these children fail to make new developmental gains over time. Typically, what is observed is a pattern whereby the children attain lower standard scores on repeated developmental testing consistent with the failure to make new gains without actual loss of ability.

Children with static (or non-progressive) encephalopathy continue to make developmental gains but at a slower than expected rate (Belman, 1993). The initial level of functioning could vary from the average range to borderline/deficient; however, there is no progressive decline or cessation in development (Belman, 1993). The reasons for the observed differences in developmental functioning and encephalopathic course are still unknown. Several risk factors have been hypothesized to influence the process, such as in utero exposure to drugs, prematurity, nutritional status, perinatal complications and other medical conditions (Belman, 1993).

Children infected with HIV but not diagnosed with encephalopathy are frequently described as having selective neuropsychological impairments. This group of children is extremely heterogeneous with respect to cognitive and social functioning. Measures of their cognitive development often fall within the normal range globally, but, they display deficits in specific areas of neuropsychological functioning. For example, selective impairments have been noted in expressive language, attention, perceptual-motor abilities, and motor function (Wolters et al., 1995).

HIV and the developing nervous system

The manifestation of HIV-related CNS disease in pediatric populations is changing over time and variability is observed in different populations of children with the infection. In vertically acquired HIV infection, an infant may develop a chronic

infection that will, in some cases, result in a severe infantile disease with major neurological complications. However, this severe neurological involvement occurs in a low percentage of infants and around 60%-70% of HIV-infected children will be alive and pursuing a normal school curriculum at 10 years of age (Blanche et al., 1990; Tardieu et al., 1995).

It is well known that HIV can infect cells and replicate within the brain. HIV probably enters the central nervous system very quickly after infection and infects different cells within the brain. The most frequently infected cells within the CNS are macrophages. There are different categories of macrophages within the brain and the most frequent, present in high numbers in the white matter and basal ganglia, are resting resident microglial cells (Tardieu, 1998). Another set of macrophages, the perivascular microglia, are located in the area around brain vessels. Macrophages, resident microglia and their derivatives are the only cells that have consistently been shown to harbor HIV in the CNS (Belman, 1993). Unfortunately, the actual pathogenic mechanisms of HIV on the CNS are not well understood. It is thought that 20-30 % of vertical transmission cases are a result of infection in utero with the majority occurring around the time of birth (Giaquinto, 1998). This early penetration of the CNS means that the final stages of development both in utero and during the first few years of life could be disrupted by the chronic viral infection depending on the timing HIV transmission. However, the presence of infected cells is not enough to predict disease reliably. A mechanism of amplification and activation probably must exist after infection to induce CNS damage and neurological symptoms (Tardieu, 1998).

Most probably, neurons and oligodendrocytes are not infected by HIV yet symptoms of the disease result from neuronal death and white matter lesions. The way in which HIV induces neuronal death is probably an indirect and multifactorial process. A number of different mechanisms have been proposed. Neuronal death can result from the toxic effects of different soluble products secreted in excess by activated brain macrophages and astrocytes. The most likely candidates are free radicals and it has been demonstrated that human astrocytes can secrete $NO^{\cdot}$ and microglia $O_2^{\cdot}$ which can combine to form the neurotoxic peroxynitrate (Janabi, Chabrier, & Tardieu, 1996). The high levels of tumor necrosis factor secretion by activated glial cells could also be responsible for the white matter lesions observed in patients with HIV-infection. Further, it has been suggested that neuronal death could result from the binding of HIV to the neuronal membrane. Lannuzel et al. (1997) reported that, *in vitro*, the virus could induce neuronal apoptosis and activation of intracellular proteins responsible for signal transduction. In the animal literature, proton magnetic resonance spectroscopy revealed significantly increased glutamate levels in the brains of feline immunodeficiency virus infected cats (Power et al., 1997). Thus, Power et al. (1995) concluded that glutamate-mediated neurotoxicity is a major mechanism in the neuropathogenesis of retrolentiviral infections.

Neuroimaging has been used as a tool to understand CNS disease in children with HIV infection. Previous research has shown that HIV-infection in children is associated with the presence of computed tomography (CT) scan abnormalities. The most common of these are basal ganglia calcifications, white matter low attentuation, atrophy and ventricular enlargement (Brouwers, et al., 1995; DeCarli, et al., 1993; King, et al., 1997).

Calcification of the basal ganglia is considered a classic abnormality associated with HIV-infection in children (Belman, et al., 1986; DeCarli, et al., 1993). Previous research has shown that in general, CT scan abnormalities appear to correlate more closely with cognitive function in younger children with vertically acquired HIV infection than in older children with transfusion associated HIV disease (Brouwers et al., 1995). Although it has been suggested that brain calcifications appear to be restricted to children who acquire HIV through vertical transmission (DeCarli et al., 1993; Brouwers et al., 1995), King and colleagues (1997) reported basal ganglia calcifications in children infected through transfusion of blood or blood products. These children were probably infected in infancy, suggesting that basal ganglia calcifications are associated with infection early in life. Furthermore, the presence of intracerebral calcifications, independent of the degree of brain atrophy, was associated with significantly greater delays in neurocognitive development (Brouwers et al., 1995).

Family and Community Issues

Illness, particularly chronic, long-term or terminal illness, has a profound effect on families. While some of the aspects of other chronic childhood diseases can be applied to the study of pediatric HIV disease, it is widely recognized that HIV is a unique disease among chronic and disabling diseases.

With the largest proportion of children with HIV infection being infected through vertical transmission, a diagnosis of HIV or AIDS in a child often leads to the identification of HIV infection in the mother or vice versa. Thus, at least two individuals within these families are infected resulting in a multigenerational impact. Within Ontario, 58% of infected mothers report their risk factor for acquiring HIV as being from

an endemic country, where heterosexual transmission of HIV is the most likely mode of transmission. Previous Canadian research on children born to HIV-positive mothers has presented that 67% women reported that they became infected with HIV through heterosexual contact (Salter-Goldie et al., 1997). Thus, diagnosis leads to the realization that several or all members of a family may be infected. In the case of vertically transmitted HIV infection, all biological mothers will be HIV-positive and previous research has reported infection rates of 63% in fathers who participated in the study (Salter-Goldie et al., 1997). The implication is that the children's mothers and fathers may become ill and die themselves during the course of their children's lives. For vertically transmitted HIV infection, maternal guilt must be incorporated, thus adding a characteristic that has been previously identified in parents transmitting a deleterious gene or chromosomal abnormality to their children (Cohen, 1994).

Children with vertically transmitted HIV infection are typically found in three types of family units (Sherwen & Boland, 1994). Biological families are those in which at least one biological parent, the mother, is HIV infected. Extended or "kinship care" families include family or friends who have had a previous relationship with the child or the child's parents regardless of whether a blood tie exists. Usually, in these extended families, the caregiver is a grandparent. Finally, foster families involve the placement of children in the care of certified foster parents, who have not been previously involved in the child's life through any connection with the family. The nature of the family structure has been shown to affect the psychosocial development of children in different ways (Sherwen & Boland, 1994).

Unfortunately, some caregivers of children with HIV infection must also deal with the terminal illness, death, ostracism and stigmatization that still is associated with the infection. Further, ethnocultural issues arise because in most cultures HIV/AIDS raises difficult, often taboo, issues. Different cultures give different value to the issues of illness and death and factors that may lead to exposure to HIV such as drug use and unprotected and risky sexual behaviours (Cohen, 1994). Also, for people living in rural communities, information and education in the community about HIV/AIDS may be limited, thereby increasing the stress associated with diagnosis. In a small town, families often express worry over discrimination and loss of privacy and confidentiality when accessing services in a community "where everyone knows each other" (National Working Group on Comprehensive Care for Persons with HIV Disease, 1995).

Limitations and Methodologic Barriers to Research on Pediatric HIV Disease

Although psychological research is vital to establishing appropriate care delivery and improving quality of life for children living with HIV disease, there are formidable barriers to its conduct. As is outlined previously, HIV disease is unique and research is affected by the nature of the disease process, treatment protocols, and the nature of the population of children affected with HIV/AIDS. Some of the issues and variables affecting research include the following.

Wide Variation in Age at Diagnosis. Children are newly diagnosed at different points in their development. Combined with the migration of people into and out of a hospital's referral area, the child's developmental level becomes a factor that needs to be considered. While this factor is not unique to pediatric HIV, the small numbers of HIV infected children currently identified within Canada, presents a formidable barrier to

HIV-related research. Controlling for age at diagnosis will limit the number of available study participants. For this reason, many investigators have conducted research including both children with vertical and transfusion acquired HIV infection. This combination of different etiologies represents another potential confound, because the neurological and developmental manifestations may vary between the two routes of infection.

Length of Survival. Although many infected children are surviving for longer periods, children will die at various times after infection occurs, with a significant number dying within the first few years after infection. Similarly, biological parents and other family members may die during a defined study period.

Variation of Caregivers and Home Environments. As stated previously, children are found in homes with biological parent(s), with extended family members and with foster families. Furthermore, during the course of study, a child's caregiver and home environment may change, if for example their parent dies. The nature of the home environment may affect outcome measures on psychological testing.

Multiple Medical and Drug Treatment Protocols. Medical treatments for HIV are changing over time with advances in antiretroviral therapy. Psychosocial functioning may be directly influenced by the success of medical treatment. Furthermore, with other diseases the investigators may have the ability to exclude children receiving an experimental protocol or drug, whereas in HIV, those children usually are included with the other children to obtain an adequate sample. Children with HIV receive numerous drugs in various combinations that are unique to the individual case. Therefore, controlling for drug effects is difficult if not impossible.

Connection with Drug Culture. With vertical transmission, a frequently cited risk factor for HIV infection is substance abuse by the mother and/or her partner. If the biological mother was a drug user during pregnancy, the effects of perinatal exposure to drugs and the effects of HIV infection on the child are not easily differentiated. Use of drugs by the mother and/or partner may also affect the home environment for the child and family.

Poverty. Children and families living with HIV/AIDS often live in poverty. It is very difficult to assess the independent effects of HIV disease on a child who is also exposed to other risk factors associated with poverty. Some of these factors include: poor nutrition, inadequate medical and health care, crime, violence, poor education, unemployment, and poor housing. Many outcome measures will be profoundly affected by living in poverty.

Cultural and Ethnic Background. Often, children and families with HIV are from minority cultural and ethnic backgrounds. Some of the families will have had negative experiences with health care professionals and distrust the intentions of researchers. Furthermore, participating in research studies, especially ones that do not directly benefit them or their children, has little importance to some families. Families with HIV are often involved in multiple, often uncoordinated, systems of care that results in a chaotic schedule with a significant amount of time spent in hospitals and research may be viewed as an unnecessary burden.

Rationale and benefit of the present study

To our knowledge, the studies presented in this thesis will be the first to provide a description of cognitive and motor development in a group of Canadian children with

vertically transmitted HIV/AIDS. Further, being aware of the difficult methodologic barriers facing HIV researchers we have attempted to describe and match on risk factors other than HIV in our study and control groups. The present studies will document the development of infants, preschoolers and school-age children followed at the Hospital for Sick Children in Toronto, a large tertiary-care university-based hospital that follows over 90% of the children in its referral area.

The inclusion of CT results is important to our study. Previous research on CT brain scan abnormalities and neuropsychological functioning has been conducted on samples of children of different ages who acquired HIV both vertically and through exposure to contaminated blood or blood products without controlling for risk factors other than HIV. In our study, all the children have vertically transmitted HIV infection and most have CT results. Children who are followed for a period of one year or longer have a CT head scan done with follow up scans offered annually.

The research will be reported in three separate chapters. The chapters will report our findings on the infants, preschoolers and school age children respectively. We decided to separate the children according to age because it follows what had been reported in the literature previously. Further, the developmental issues and milestones reached will vary according to age. The majority of the neuropsychological test battery is also age-specific and is not appropriate for all children. It has also been consistently reported that younger children are more adversely affected by HIV infection, especially children who present with AIDS at a younger age (Belman et al., 1988). That younger children are more adversely affected is probably because this group of younger children includes those presenting with early AIDS, whereas, in the older groups, these children

would have died, at least prior to highly active antiretroviral therapies (HAART). Therefore, it is expected that we would observe differences in the level of cognitive and motor function between infants, preschoolers and school-age children. It is expected that the infant cohort results will reflect global delays in cognitive function whereas the preschoolers and school-age children will be affected by selective neuropsychological impairments. Following the presentation of the results a general discussion will be presented to draw overall conclusions and trends within the results. Also, the discussion will focus on the direction future research should take within Canada to further document the cognitive and motor development of Canadian children living with vertically transmitted HIV/AIDS.

Cognitive and Motor Development in Children with Vertically Transmitted HIV Infection: Birth to 36 Months

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Introduction

Although the association between human immunodeficiency virus (HIV) infection and neurodevelopmental delay has been documented in young children. research has failed to control for risk factors other than HIV that may affect development (Chase et al., 1995; Nozyce et al., 1994). Our study includes children who reflect the overall population of infants, born to HIV-positive mothers, who are followed at the Comprehensive Care HIV/AIDS Program at the Hospital for Sick Children in Toronto. We report on both a group of children with HIV and a control group of children exposed to but uninfected with the virus.

In children with vertically transmitted HIV, infection occurs while the CNS is still immature. It is estimated that in non-breastfeeding populations approximately 70-80% of infection is acquired around the time of birth whereas the remaining children are infected during intrauterine life (Giaquinto et al., 1998). HIV appears to invade the central nervous system early in infection, particularly among infants and children. Developmental delays attributable to the encephalopathic process are commonly observed in infants with HIV with varying patterns of encephalopathy noted (Aylward et al., 1992; Belman et al., 1988; Chase et al, 1995). Children with HIV-related encephalopathy usually exhibit global deficits in cognitive, language, motor and social skills, although there may be variability within some affected functions.

Infants are at particular risk for neurodevelopmental manifestations associated with their HIV infection. Studies have consistently reported delays in cognitive and motor development as measured by the Bayley Scales of Infant Development (Bayley, 1969; 1994). However, different patterns of neurodevelopment have been reported. For example, the age of onset of developmental delays range from as early as three months (Gay et al., 1995) to as late as 24 months (Chase et al., 1996). In some instances, both cognitive and motor development are impaired, and in other cases, one specific impairment in cognition or motor function may be observed in the presence of preserved functioning in the other (Belman. 1993).

Numerous studies have reported on neuropsychological evaluation done on children in a hospital setting, however, little research has investigated the relationship of HIV on children's everyday adaptive functioning in the home environment (Wolters et al., 1994). Evaluating the ability of children with HIV infection to perform various age-appropriate daily activities at home and in the community will provide an indicator of the impact of the infection on quality of life for both patients and their families. Therefore, independent observations of behaviour by parents can provide an additional assessment of developmental function in infants with HIV infection in their home environment.

Early studies have shown that neurological complications are common in children with HIV (Belman et al., 1988). Neurological studies have identified a variety of central nervous system abnormalities associated with HIV-infection. They include cortical atrophy, calcification of the basal ganglia and frontal white matter, ventricular enlargement and white matter low attenuation (DeCarli, et al., 1993; King, et al., 1997). The most important finding from a developmental perspective is that of myelinopathy.

During infancy the brain is still undergoing a period of rapid myelination. Infancy is also a time in which children attain a number of significant motor, cognitive and behavioural milestones. Any disruption in this process can be expected to produce developmental delays that may become more significant over time.

In summary, previous research has consistently reported deficits in both cognitive and motor function in infants with vertically transmitted HIV infection. However, many studies have been limited by potential confounds. The purpose of this study was to compare mental and motor functioning in a sample of infected and uninfected children (aged 6-37 months) born to HIV-infected mothers. The present study has managed to control for the confounding effects of substance exposure, English as a Second Language (ESL) and rate of maternal separation by using a control group of children who were not infected with HIV but who were born to HIV positive mothers. Another goal of the study is to examine computerized tomography (CT) scan data exclusively on children with vertically transmitted HIV infection in an attempt to observe whether the structural brain changes observed in these children with HIV-infection are associated with functional deficits.

Methods

Participants

All of the participants were followed through a tertiary-care university-based pediatric HIV/AIDS Comprehensive Care Program at the Hospital for Sick Children (HSC) in Toronto. This study was approved by the Research Ethics Board at HSC and

informed consent was obtained from parents. Fifty children born to HIV-infected mothers were included. Of these, 25 children had documented HIV infection and 25 tested negative for the HIV antibody by 15-18 months of age. All children in the infected group met one of the following criteria: positive cell HIV culture or HIV-DNA polymerase chain reaction assay after the neonatal period and/or positive HIV enzyme-linked immunosorbent assay (ELISA) and Western blot beyond 18 months of age. Since the beginning of the HIV/AIDS Program in October 1988, patients have been followed prospectively by two pediatric consultants. All patients followed for more than 1 year had a cranial CT scan, with follow-up CT scans offered annually. All patients are offered psychological evaluation. Existing data were collected for all infants who had undergone developmental testing, in the first 37 months of life, as part of their routine clinic follow-up from 1989 through 1999. Some children were assessed on more than one occasion; for these cases, the data analyses were conducted on the most recent assessment for each child. Exclusion criteria included children with known pre-existing non-HIV-related conditions such as Down's syndrome, congenital multiple handicaps, severe prematurity, significant perinatal trauma associated with developmental delays and severe intraventricular hemorrhage. **Table 1** contains descriptive data for the sample. Age was compared using a independent t-test, all the 2 x 2 tables using a Fischer's exact test and all the rest using a chi-squre.

All of the children, except for two, were on antiretroviral therapy at the time of assessment. Three children were taking a combination of drugs including two reverse transcriptase inhibitors and one protease inhibitor. Eighteen children were receiving a combination of drugs that included only nucleoside analogues. The average number of

drugs that the children were taking at the time of assessment was 2 (range 0-3). Seventeen children were receiving regular monthly infusions of intravenous gamma globulin and 14 children were on PCP prophylaxis.

According to the 1994 revised CDC Classification, children were classified into one of three immunologic categories that were established to categorize children by the severity of immunosuppression attributable to HIV infection (CDC, 1994). Eight children showed no evidence of suppression. 8 showed evidence of moderate suppression and 9 had evidence of severe suppression.

Table 1. Description of Sample by HIV Status.

	Infected (N = 25)	**Uninfected (N =25)**	**P-value**
Age ± SD (months)	24.7 ± 9.3	18.5 ± 8.2	0.016
Range	7 – 37	6 – 32	
Gender			
Males	12	17	
Females	13	8	0.126
Race			
Black	12	8	
White	6	14	
Other	7	3	0.061
Mothers Intravenous Drug Use	1	7	
Unknown	4	6	0.032
English as a Second Language	10	4	0.057
Any foster or kinship care	2	7	0.069

Procedure

This retrospective study was conducted to assess potential differences in motor and mental performance in a sample of children with vertically acquired HIV infection and children exposed to but not infected with HIV. Children were scheduled for assessment to monitor neurodevelopmental growth or neurodevelopmental decline. The Bayley Scales of Infant Development, BSID, (Bayley, 1969; 1994) and Vineland Adaptive Behavior Scales (Sparrow, et al., 1984) were administered according to standard testing procedures. Thirty-two children were administered the BSID and 18 children were given the BSID-II. Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores were recorded at each assessment. The Vineland Adaptive Behavior Scales, a semi-structured interview administered to the child's parent or primary caretaker, was used to assess adaptive functioning in the children. The parent answered questions about specific behaviours their child exhibited at the time. The Vineland Scales measure four domains and 10 subdomains of behaviour in children:

1.) Communication: receptive and expressive language.

2.) Daily Living: personal, domestic and community living skills

3.) Socialization: interpersonal, play/leisure and coping abilities

4.) Motor skills: fine and gross motor abilities

Domain standard scores from the Vineland Scales were used in the analyses.

To ensure comparability of data across children, individual MDI and PDI scores on the BSID-I were converted to BSID-II scores according to criteria described in the BSID-II Manual (Bayley, 1994). The manual contains a table that presents ranges of

expected BSID-II MDI and PDI scores for selected BSID scores. The ranges of expected BSID-II scores are relatively narrow near the middle of the index score distribution (e.g. 100) and wider at the upper and lower score levels. For each child who received the BSID, the index score was converted by taking the midpoint of the corresponding range of expected BSID-II MDI and PDU scores. It should be noted that there is a substantial amount of overlap in the content of the two BSID scales and the observed differences can be accounted for by theoretical and psychometric rationales.

Individual MDI and PDI scores were recorded at each assessment beginning in the first six months of life. As the lowest developmental index included in the normative tables of the BSID-II is 50, developmental index scores below 50 were recorded as 49. The degree of neurodevelopmental disability was classified according to Interpretive Guidelines of the BSID (1994); scores > 85: normal, scores of 70 – 84: mildly delayed, and scores < 69; significantly delayed.

The examiners were not uniformly blind to the child's HIV status because the assessments took place as part of the routine follow-up by the HIV/AIDS Programme. However, prior to the use of PCR, which started in1993, HIV status was indeterminate in these children before 15-18 months of age, providing a form of natural blinding to the examiner during this time.

Since the two groups differed in age, analysis of covariance was used to test for significant differences between the two groups. Independent t-tests were used to test for significant differences between children with and without evidence of CT scan abnormalities.

Results

Table 2 shows the number of children in each group classified according to their level of neurodevelopmental disability.

Using a model that corrected for age and English as a second language, HIV-infected infants obtained significantly lower scores than the uninfected infants on the Mental scale of the Bayley, $F(2,48)=11.45$, $p< 0.001$. On the Psychomotor scale of the Bayley, the HIV-infected infants also obtained significantly lower standard scores than the uninfected infants, $F(2,44)=14.31$, $p<0.001$.

Table 2. Neurodevelopmental disability by HIV status

	Infected		Uninfected	
	MDI[1] (N = 25)	PDI[2] (N = 23)	MDI (N = 25)	PDI (N = 22)
Mean (SD)	71.4 (21.4)	61.9 (15.4)	92.3 (18.9)	90.9 (24.7)
95% Confidence Interval	62.4 – 80.4	55.3 – 68.6	84.5 – 99.9	80.1 – 98.1
Level of Functioning				
Within normal limits	7	3	16	15
Mildly delayed	7	5	7	4
Significantly delayed	11	15	2	3

1.) MDI – Mental Scale
2.) PDI – Psychomotor Scale

Of the 25 children with HIV infection, CT scan data were available for 19 children. **Table 3** shows the number of children with normal and abnormal CT scan results classified by their level of functioning on the Bayley Scales of Infant Development. Of the 9 children with abnormal scans, brain atrophy was observed in 4

children, evidence of calcification in 7, ventricular enlargement in 4, and white matter low attenuation in 2. It should be noted that each scan could contain evidence of more than one specific abnormality.

The difference between MDI scores for children with and without evidence of brain abnormality was not significant, $t_{16} = -1.68$, $p = 0.12$. However, children with evidence of CT abnormalities performed significantly worse on the PDI than did children with normal CT results, $t_{15} = -3.07$, $p = 0.008$.

Table 4 shows the mean Domain Scores from the Vineland Adaptive Behavior Scales for the HIV-positive and HIV-negative infants. On all of the Domains of the Vineland Adaptive Behavior Scales, the HIV-infected infants obtained significantly lower standard scores than the uninfected infants.

Table 3. Neurodevelopmental functioning on the BSID by CT status in infants with HIV infection

	CT Abnormal		CT Normal	
	MDI (N = 9)	PDI (N = 8)	MDI (N = 10)	PDI (N = 9)
Mean (SD)	66.9 (23.0)	58.0 (15.5)	85.2 (23.4)	78.1 (14.5)
95 % Confidence Interval	50.0 – 86.1	50.0 – 71.0	68.5 – 101.9	66.9 – 89.3
Level of Disability				
Within normal limits	1	0	4	3
Mildly delayed	3	2	4	3
Significantly delayed	5	6	2	3

Table 4. Vineland Adaptive Behavior Scale Domain Scores by HIV status

	Infected (n =20) Mean ± SD (95% C. I.)	**Uninfected (n=20)** Mean ± SD (95% C.I.)	**F**	**P**
Domain				
Communication	85.4 ± 19.6 (76-95)	96.5 ± 16.2 (87-104)	10.9	<0.001
Daily Living	82.0 ± 19.3 (73-91)	96.2 ± 15.4 (89-103)	27.8	<0.001
Socialization	86.6 ± 20.1 (77-96)	98.7 ± 12.9 (93-105)	17.5	<0.001
Motor	76.5 ± 21.1 (67-86)	97.7 ± 9.6 (93-102)	11.5	<0.001

Table 5 shows the mean Domain Scores from the Vineland Adaptive Behavior Scales for children with normal and abnormal CT scan results. CT abnormalities were associated with lower scores in all domains of adaptive behaviour, although the differences were significant only for the motor area.

Table 5. Vineland Adaptive Behavior Scale Domain Scores by CT status in infants with HIV infection

	Abnormal CT (N = 7)	Normal CT (N = 8)		
	Mean (SD)	Mean (SD)	t	p
Domain				
Communication	75.0 (17.0)	93.6 (21.3)	-1.85	0.09
Daily Living	69.6 (17.5)	87.1 (14.8)	-2.10	0.06
Socialization	76.0 (21.4)	94.3 (18.6)	-1.77	0.10
Motor	63.4 (21.5)	86.4 (19.7)	-2.16	0.05

Pearson correlation coefficients indicated that that a lower absolute CD4 count was associated with poorer performance of MDI, PDI and all four domains of the Vineland Adaptive Behaviour Scales (in all cases $p < 0.05$).

Discussion

On measures of mental, motor and adaptive functioning, the children who were born to HIV-positive mothers but were not infected with the virus had mean scores that were considered indicative of normal performance. However, the children with HIV had mean scores that indicated a possible mild delay in performance on the MDI and significantly delayed performance on the PDI and measures of adaptive function. Further, among the children with HIV, those with observable CT brain abnormalities had mean scores that were indicative of significantly delayed performance on both scales of the Bayley whereas children without abnormalities had mean scores that indicate only mild delays. On measures of adaptive function, children with observable CT brain scan abnormalities showed a trend toward worse performance when compared with children with normal scans. A number of the children displayed evidence of basal ganglia calcifications, making our results consistent with previous findings that the presence of intracerebral calcifications are associated with greater delays in neurocognitive development (Brouwers et al., 1995).

Previous research on the neurodevelopment of HIV-infected children has been confounded by failing to control for risk factors other than HIV that may affect development, especially prenatal substance exposure (Chase, et al, 1995; Nozyce, at al., 1995). Some of the studies have included a drug-exposed control group; however, the inclusion of a drug-exposed comparison group does not effectively allow for the independent identification of the effects of HIV compared to those of substance abuse.

Early studies focused on clinically symptomatic children at different ages, infected by various routes of transmission. This study only included children who acquired HIV through vertical transmission with the vast majority being born to mothers who did not abuse substances during pregnancy. Our results indicate that children infected with HIV experience significant delays in mental and motor development when compared to a group of uninfected children. This delay is reflective of the fact that children with HIV are delayed in reaching developmental milestones. Further, such impairments are likely to become more severe as the children are expected to make more complex and integrative milestones.

The Adaptive Behaviour Domain Scores that were obtained form the Vineland Adaptive Behaviour Scales indicate that children with HIV infection are performing below average with respect to adaptive behaviour. Their scores were significantly different from children who were exposed to but not infected with the virus. This result is consistent with previous findings that suggest that all areas of adaptive functioning may be compromised in children with HIV-infection (Minden et al., 1992; Wolters et al., 1994). The Wolters et al. study compared adaptive behaviour before and after the start of zidovudine therapy in a group of children with both transfusion and vertically acquired HIV infection. After 6 months of AZT therapy, all behavioural domains, except for motor skills, showed significant overall improvement. On an individual basis, 48% (12 of 25) of the children exhibited clinically significant improvement, defined as improvement of 6 points or more, in their adaptive behaviour composite score after six months of AZT therapy. Despite the fact that the majority of children in the present study were on antiretroviral therapy, they remained delayed with respect to their adaptive

behaviour skills. These impairments may be secondary to the cognitive and motor delays that these children experience, indicating the impact of such deficits on skills required in everyday living.

We have included CT results in an attempt to correlate structural brain abnormalities with neuropsychological function in this cohort of children. Previous research on CT brain scan abnormalities and neuropsychological functioning has been conducted on mixed groups comprising children of different ages who acquired HIV both vertically and through exposure to contaminated blood or blood products without controlling for risk factors other than HIV. Previous research has shown that the presence and degree of CT brain scan abnormalities correlate strongly with cognitive dysfunction in children with vertically acquired HIV infection (Brouwers et al., 1995; King et al., 1997). In the present study, nine of the nineteen patients (47%) who had CT data available had some form of brain abnormalities. Further, the infected children who presented with brain abnormalities performed worse than infected children without observable brain abnormalities on measures of cognitive and motor development, although only the later reached statistical significance. Of the nine children with observable CT abnormalities, seven had recorded calcifications of the basal ganglia. These results are consistent with the Brouwers et al. (1995) finding that the presence of intracerebral calcifications was associated with significantly greater delays in neurocognitive development. Further, the presence of basal ganglia calcifications may be an indication that these children were infected in utero rather than during the intrapartum period (Brouwers, et al., 1995; DeCarli, et al., 1993). The exact cause of the observed CT brain abnormalities cannot be determined in this type of study. However, it seems

reasonable, based on the literature on HIV and the central nervous system, to assume that HIV infection plays a significant role, although other confounding factors, such as maternal drug abuse and coinfections during pregnancy could also influence such abnormalities (Chasnoff et al., 1998; Koren et al., 1998).

The differences in mental, motor, and behavioural development between the infected and uninfected infants and the CT brain abnormalities reported in this study developed over the first 3 years of life. Since neural development is not complete at two years of age, further developmental delays can be expected over time. In particular, myelination of the frontal and parietal regions continues throughout childhood. These regions are involved in such higher cortical functions as language, sequencing and the integration of multiple stimuli. Therefore, disruption of this process early in childhood can predictably lead to specific delays in these areas later in life. Further, it has become apparent that subcortical structures, traditionally associated with the regulation of motor control, are involved in higher-level cognitive processes (Aram & Eisele, 1992; Eisele & Aram, 1995). It has been shown that early lesions of subcortical nuclei have persistent cognitive effects, and may result in less plasticity than cortical lesions (Aram & Eisele, 1992). The range of developmental deficits associated with subcortical damage is not yet well defined, but language deficits have been reported (Aram, Rose, Rekate & Whitaker, 1983; Belman, 1992). Since many of the more advanced developmental skills do not develop until after 2 years of age, if these children survive, delays may be expected in areas such as visual-motor processing, verbal memory, processing speed and sequential processing.

While we were aware of the methodological barriers and issues associated with HIV research we still included a small group of children who were born to mothers who abused substances during pregnancy and came from families where English was the second language. Maternal substance use was an issue in our control group, with 7 of 25 children being exposed to drugs *in utero*. However, the control group still did better with respect to their neuropsychological development than did the children with HIV. With respect to ESL, for children less than two years of age the BSID does not include a large verbal component; it is more of a problem solving and visual-spatial task that requires the child to copy visual examples provided by the examiner. After the age of 2, labeling tasks are included, however, the children were encouraged to respond in their native language and the parent or guardian translated their response. Further, both ESL and maternal drug use were controlled for in an analysis of covariance, but neither proved to be having a significant effect on the variance and were excluded from the analysis.

Future studies should focus on longitudinal follow-up of infants infected with HIV in an effort to describe further developmental delays and to document the relationship between early brain pathology in childhood and later developmental and learning disabilities. Previous studies have documented that there is a good correlation between neuropsychological assessment and neuroimaging (Brouwers, et al., 1995; King et al., 1997). The use of neuropsychology complements the use of neuroimaging in HIV-related research through identifying the functional deficits associated with brain insult. It should be noted that while the monitoring of CT results is important, CT results are not a prognostic marker that can be used as an indicator of the onset of developmental abnormalities. As is seen in our results, the presence of CT scan abnormalities was

associated with developmental impairment, however, there were children who had CT scan abnormalities and were performing well with respect to their neurocognitive development. Lastly, there is a need for ongoing research into neuropsychological functioning in children with HIV infection because with advances in therapy and medical management the level of viral suppression achieved has improved. With much of the existing literature being conducted before the introduction of highly active antiretroviral therapy regimens, the need to study children on such therapies exists and should not be ignored.

Early Cognitive Development in Preschool Children with Vertically Transmitted HIV-Infection

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Introduction

Currently, few studies on HIV infection have focused on children of preschool age, which we define here as being between the ages of 3 and 6 years. There is a significant literature that focuses on infants (birth to 3 years) with HIV infection and recently there has been an interest on investigating the outcome in school-age children living with HIV infection. However, preschool children present an important study group because their nervous systems are still not fully mature and therefore they are vulnerable to the effects of HIV infection. The study of children between 3 and 6 years of age may provide some interesting insights into how the disease affects young children. Previous research on the natural history of pediatric HIV has shown that mortality is highest within the first two years of life. Children with HIV who survive beyond the few of years of life usually exhibit a slower progression of infection and better clinical course than children with an early rapid disease progression. Thus, preschool age children may present a first glance at the effects of HIV on neurocognitive development in a group of children with slower disease progression.

Our study is cross-sectional in nature and presents results on a group of preschool children followed by the Comprehensive HIV/AIDS Program at the Hospital for Sick Children in Toronto. Some of the children whose infants assessments were used in our study on the effects of HIV on children between birth and 36 months of age (see previous chapter) also had assessments as preschoolers and their results are used in the present analysis. Not all of the children previously reported in the infant study are included here

because they either died before 3 years of age, were lost to follow-up at the clinic or had not yet reached preschool age. It is expected that as a group, preschool children will perform better than the infant cohort did on developmental testing. Fewer delays in overall general cognitive function are expected because it is anticipated that the children who experienced the most severe developmental delays as infants will have died before reaching three years of age. However, we forecast the presence of more subtle and selective neuropsychological impairments experienced in specific domains of developmental function.

Previous research by Englund and colleagues (1996) reported results on a large cohort of HIV-infected children. Their results represent the largest intensive study in ethnically diverse, therapy-naïve symptomatic HIV-infected children conducted. Their objective was to provide clinical and laboratory characteristics and determine age-related distinctions for their cohort. They divided the children into four age categories with one consisting of children between the ages of 30 months and six years. This group consisted of 190 children with perinatally acquired HIV-infection. In this group, cognitive function was assessed using the General Cognitive Index of the McCarthy Scales of Children's abilities. Results indicated that 21% of children who spoke English as their primary language and 44% of children who did not speak English as their first language scored below 70 on this measure (population mean standard score = 100). Further, they reported that 14% of children had abnormal behaviour and 11% had abnormal motor function. Their results also indicated that younger children, specifically children less than thirty-months of age, had significantly higher rates of growth, cognitive and developmental abnormalities before antiretroviral therapy than did older children.

Specific impairments in both expressive and receptive language function have been noted in HIV-infected children (Coplan et al., 1998; Wolters et al., 1995; Wolters et al., 1997). In 1995, Wolters and colleagues indicated that expressive language was affected more than receptive language in children with symptomatic disease. Consistent with the Wolters et al. (1995) result, in a longitudinal 24-month follow-up study of a cohort including both vertically and transfusion infected children, expressive language was consistently more impaired than receptive language (Wolters et al., 1997). Both receptive and expressive language declined significantly over the follow-up period despite antiretroviral therapy, although cognitive functioning remained stable. The presence of a specific expressive language deficit suggested that some domains of development may be more vulnerable to the effects of HIV and that global measures of cognitive function may mask deficits in a specific area of neuropsychological functioning.

The purpose of this present study was to further the results from previous research conducted with mixed cohorts by investigating a group consisting of only children with vertically acquired HIV infection. Further, it will be the first to assess the development of a group of Canadian preschool children with vertically acquired HIV infection. The inclusion of CT results is an important part of this study. This study will be unique in that it will report on an extensive battery of tests that assess a broad range of neuropsychological function as well as reporting CT data on the majority of the children studied. For this group of children no control group was available. The children in the control group in study 1 had been discharged from the clinic prior to 3 years of age and were not followed-up. At the time the study was conducted there were not enough siblings of children with HIV, between the ages of 3 and 6, to form a control group.

However, the lack of a control group was compensated for by comparing our results with the published norms of the psychological measures that were administered to the children. The norms of the psychological measures provided us a basis for comparing cognitive function of the HIV-infected children with a group of their same-aged peers in the general population.

Methods

Participants

Seventeen HIV-infected children, all of whom had been born to HIV-positive mothers, were included in the study were recruited through the Comprehensive Care HIV/AIDS Program at the Hospital for Sick Children. This study was approved by the Research Ethics Board at HSC. Informed consent was obtained from the parents. The children ranged in age from 3.3 to 6.0 years of age. All children had documented HIV-infection by positive plasma or cell culture or polymerase chain reaction assay (after the neonatal period) or positive HIV enzyme-linked immunosorbent assay (ELISA) and Western blot beyond 18 months of age. All participants were followed at the HIV/AIDS Comprehensive Care Program at the Hospital for Sick Children in Toronto. Existing data were collected for all children between the ages of 3 and 6 years of age who had undergone developmental testing as part of their routine follow-up from 1989 through 1999. Exclusion criteria included children with known pre-existing non-HIV-related conditions such as Down syndrome, congenital multiple handicaps, severe prematurity,

significant perinatal trauma associated with developmental delays and severe intraventricular hemorrhage. **Table 1** contains descriptive data for the sample.

Since the beginning of the HIV/AIDS Program in October 1988, patients have been followed prospectively by two pediatric consultants. All patients followed for more than 1 year had a cranial CT scan, with follow-up CT scans offered annually. All patients are offered psychological evaluation.

Table 1. Description of the sample of 17 HIV-positive preschool age children

Age (years)	4.8 ± 0.9
Gender	
Males	7
Females	10
Race	
Black	8
White	6
Other	3
Socioeconomic Status	
$40,000 +	4
$30-39,000	2
$20-29,000	3
$15-19,000	6
less than $15,000	1
Unknown	1
Mother's Intravenous Drug Use	2
English as a Second Language	2
Any foster or kinship care	5

Fifteen of the 17 children were on antiretroviral therapy at the time of assessment. At the time of testing 3 children were taking a combination of drugs including two

reverse transcriptase inhibitors and one protease inhibitor. Ten children were receiving a combination of drugs that included only nucleoside analogues. Two children were only receiving AZT at the time of assessment. The average number of drugs that the children were taking at the time of assessment was 2 (range 0-4). Seven children were receiving regular infusions of intravenous gamma globulin and 8 children were on PCP prophylaxis.

Table 2 contains a number of medical variables which were recorded as an indicator of disease status. Viral load was not available for the majority of children at the time of testing.

Table 2. Medical variables for 17 preschool age children with vertically-acquired HIV-infection.

Variable	Mean ± SD	Reference	N
Height (%ile)	30.9 ± 24.1	50	13
Weight (%ile)	41.9 ± 30.3	50	13
WBC (10^9/L)	6.3 ± 1.9	5.0-12.0	17
Hgb (g/L)	111.9 ± 11.3	110-140	17
MCH (pg)	28.9 ± 5.5	24-31	17
Plt (10^9/L)	280.5 ± 89.8	150-400	17
Lymphocytes (10^9/L)	2.7 ± 1.1	2.0-8.0	17
Polymorphs (10^9/L)	2.8 ± 1.5	1.5-8.5	17
CD4 (λL)	781.4 ± 542.6	500-1000	17
CD8 (λL)	1014.0 ± 469.9	500-1000	17

Five children had total CD4 counts below 500 at the time of assessment. According to the 1994 CDC Classification, the children were classified into three immunologic categories established to categorize children by the severity of immunosuppresion attributable to HIV infection (CDC, 1994). Based on this system, six

children showed no evidence of suppression, six showed evidence of moderate suppression and 5 showed evidence of severe suppression.

Table 3 classifies the children into immunologic and clinical categories according to the CDC 1994 guidelines. Of the seventeen children, one was clinically asymptomatic at the time of assessment. Twelve children had experienced only non-AIDS defining illnesses and 5 children had experienced both a non-AIDS and an AIDS defining illness. The types of medical conditions found in this sample were similar to those described in the literature for children with HIV infection. The most frequent medical problems were as follows: recurrent upper respiratory infections (50%), persistent generalized lymphadenopathy (36%), candidiasis, recurrent oropharyngeal (29%) and lymphoid interstitial pneumonia (36%).

Table 3. Classification of children into immunologic categories according to CDC (1994) guidelines

	Number of Signs/Symptoms		
	None	Mild/Moderate	Severe
Immunologic Categories			
No Evidence of Suppression (CD4 ≥ 1000)	1	5	0
Evidence of Moderate Suppression (CD4 500 – 999)	1	3	2
Evidence of Severe Suppression (CD4 ≤ 500)	0	2	3

Psychological Evaluation

Seven children underwent more than one neuropsychological assessment between the ages of 3 to 6 years. Data were obtained from the assessments that provided the longest outcome measure. Test administration required 4-6 hours to complete. In the majority of cases the assessments were completed in two testing sessions conducted in 1 day with a break for lunch between testing sessions. Participants were offered short breaks during the sessions to control for fatigue. Some of the children did not complete all the tests due to fatigue and time constraints, leading to a slight variation in sample size across analyses. The neuropsychological evaluation included the following tests grouped together according to functional area:

General Intelligence measures: Intelligence measures were obtained using the Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R), (Wechsler, 1974). Full Scale, Verbal Scale and Performance Scale IQ scores were determined.

Language: WPPSI-R Vocabulary, Comprehension and Similarities subtests; Peabody Picture Vocabulary Test (PPVT-R & PPVT-III) (Dunn & Dunn, 1981); Expressive One Word Vocabulary Test (EOWVT), (Gardner, 1990).

Memory: WPPSI-R Sentences and Information subtests; Bead Memory

Visual-Spatial Processing and Reasoning: WPPSI-R Picture Completion, Block Design, Picture Completion and Object Assembly subtests.

Visual-Motor Speed and Coordination: WPPSI-R Animal Pegs and Geometric Design subtests and the Developmental Test of Visual-Motor Integration (Beery, 1989)

Adaptive Behaviour: Vineland Adaptive Behavior Scales (Sparrow, 1984)

The level of functioning on the IQ scales was classified according to the following criteria (Wechsler, 1974). The child was determined to be functioning at a superior level

if the score was 125 or above; high average between 116-124; within normal limits if the score was 90-115; low-average between 80 and 89; borderline between 70-79; and deficient at 69 and below. On all other tests participants who showed results that deviated from published normal values by approximately 1 standard deviation or more in either direction were considered above average (+1 SD) or below average (-1 SD) with respect to their level of functioning.

CT Scan Evaluation

Staff neuroradiologists, who were not blinded to the clinical status of the patients, rated the computed tomography (CT) scans for presence and degree of ventricular size, presence of basal ganglia and other calcifications, white matter attenuation and cerebral atrophy. All CT scans were performed on GE 9800 and GE Advantage CT scanners. All patients had unenhanced scans. In addition, enhanced scans were performed if the neuroradiologist considered that the unenhanced scan showed lesions for which enhancement might provide further information.

Clinical Management

The clinical management of the patients was provided by two pediatric consultants, and the use of antiretroviral therapy was consistent with the recommendations of the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, the National Pediatric and Family HIV Resource Center (1993). The patients whose results were used in this study received various

antiretroviral drugs and drug combinations consistent with clinical practice at the time of testing.

Data Analysis

Given the sample size and the number of tasks, steps were taken in order to reduce the likelihood of committing a Type I error. In order to reduce the number of analyses conducted when comparing the children with evidence of brain abnormalities on CT scan to those without, composite variables were created (perceptual organization, verbal, language, attention, visual spatial, memory, motor). Each composite score was comprised of the group of measures that would fall into that specific area of psychological function, as described above in the section on psychological evaluation. *Z*-scores were calculated for each variable using the data for all participants as a whole. For each participant, the mean of the z-scores for each group of tasks was taken as the composite score. Preliminary group comparisons were conducted on the composite scores using independent t-tests, with a plan to undertake individual test comparisons only if the composite scores indicated group differences.

Results

Table 4 shows the mean test scores on all the tests. The majority of the cognitive scores fell within the Average range. The only exception was from the measure of receptive vocabulary, on which the mean score was in the low average range. Adaptive behaviour skills were within the borderline to low average range. The mean scores for

the 17 children with HIV were compared with the general population mean standard scores on the psychological measures by using one-sample t-tests.

For this group of children, the mean FSIQ was within the Average range and there was little difference between the mean VIQ and PIQ, both of which fell within the Average range. One child has an FSIQ indicative of high average intelligence, ten of the children had a FSIQ in the Average range, two in the low average range, two were in the borderline range and two children were in the deficient range.

The scores on the following tasks differed from the mean normative values: the Similarities (t_{16}=-2.18, p = 0.05) and Geometric Design subtasks (t_{16}=-2.15, p = 0.05) of the WPPSI-R; the PPVT (t_{12}=-3.60, p = 0.004); and all four domains of the Vineland Adaptive Behavior Scale; Communication (t_{12}=-2.99, p = 0.01), Daily Living (t_{12}=-4.14, p = 0.001), Socialization (t_{12}=-3.64, p = 0.003), and Motor (t_{12}=-3.14, p = 0.01).

Language measures revealed a contrast between receptive and expressive vocabulary. Although the group mean score for expressive vocabulary was in the average range, receptive vocabulary fell more than one full standard deviation below the mean. Forty-six percent (46%) of children showed borderline or deficient results on the Peabody Picture Vocabulary Test, a measure of receptive vocabulary. The mean score for the general population on each of these tests is 100 (SD = 15). Mean standard scores for receptive language were significantly lower than expected based on mean Full Scale IQ scores in these children. There was a specific weakness noted in receptive language, as the difference between FSIQ and PPVT standard scores was significant (F = 4.80; p = 0.049). However, the children's scores on the EOWVT language measure fell within a range that was consistent with their FSIQ (F = 0.631; p = 0.44).

Table 4. Mean Scores (± SD) for Areas of Neuropsychological Functioning by Preschool Age Children with Vertically Transmitted HIV Infection

	N	Mean (SD)	p-value	95 % C.I.
General Intelligence				
[1]Full Scale IQ	17	93.6 (16.4)	0.13	85.2 - 102.1
[1]Verbal IQ	17	92.0 (16.9)	0.08	83.1 - 101.1
[1]Performance IQ	17	97.1 (18.1)	0.53	87.5 - 106.8
Language				
[2]Vocabulary[a]	17	9.5 (3.2)	0.51	7.8 - 11.1
[2]Comprehension[a]	17	8.9 (3.3)	0.18	7.2 – 10.6
[2]Similarities[a]	17	8.4 (3.1)	0.05*	6.7 – 9.9
[1]PPVT	13	81.9 (18.1)	0.004*	71.0 – 92.9
[1]EOWVT	15	96.3 (17.9)	0.43	86.3 – 106.2
Memory				
[3]Bead Memory	10	45.2 (8.5)	0.11	39.2 – 51.3
[2]Information[a]	17	8.6 (3.1)	0.09	7.1 – 10.2
[2]Sentences[a]	16	8.2 (3.3)	0.01*	6.8 – 9.6
Visual Spatial Processing and Reasoning				
[2]Block Design[a]	17	9.7 (3.2)	0.71	8.1 – 11.3
[2]Object Assembly[a]	17	10.4 (2.9)	0.62	8.9 – 11.9
[2]Picture Completion[a]	17	11.4 (3.6)	0.15	9.5 – 13.2
Visual-Motor Speed and Coordination				
[2]Animal Pegs[a]	16	10.0 (2.5)	0.92	8.8 – 11.4
[2]Geometric Design[a]	17	8.4 (3.2)	0.05*	6.7 – 9.9
[1]VMI	13	97.7 (11.8)	0.51	90.6 – 104.9
Adaptive Behaviour				
[1]Communication[b]	13	89.8 (12.3)	0.01*	82.4 – 97.3
[1]Daily Living[b]	13	76.5 (23.2)	0.001*	74.7 – 92.2
[1]Socialization[b]	13	83.5 (14.4)	0.003*	62.5 – 90.6
[1]Motor[b]	10	81.0 (19.1)	0.01*	67.3 – 94.7

[1]General population mean standard score is 100 ± 15
[2]General population mean standard score is 10 ± 3
[3]General population mean standard score is 50 ± 8.
[a] Sub-tests of the WISC-III or R.
[b] Domain scores from the Vineland Adaptive Behavior Scales.
* significant difference at the p = 0.05 level.

CT scans were available for 14 of the 17 children with HIV. **Table 5** shows the number of children with normal and abnormal CT scan results classified by their level of neurodevelopmental disability. For the children with CT scans, 42 percent (6) had abnormal scans: brain atrophy was observed in no children, calcification in 3, ventricular enlargement in 1 and white matter abnormalities in 3. It should be noted that each scan could contain evidence of more than one specific abnormality.

On the general intelligence measures, children with evidence of CT abnormalities showed similar scores on the Verbal IQ and Performance IQ scales as did children with normal CT scans ($t_{12} = 0.35$; $p=0.74$ and $t_{12} = -0.33$; $p=0.75$). A comparison of the composite scores by domain for children with visible CT scan abnormalities and children with normal scans revealed no significant differences in any area of cognitive function. All of the composite comparisons in this thesis are reported in Appendix # 1.

Table 5. Level of intelligence by CT status

	CT Abnormal (n = 6)		CT Normal (n = 8)	
	VIQ	PIQ	VIQ	PIQ
Mean ± SD	91.8 ± 18.9	98.0 ± 17.9	88.9 ± 13.9	101.6 ± 22.3
95% Confidence Interval	72.0 – 111.7	79.2 – 116.8	77.9 – 99.9	83.0 – 120.3
Classification				
High Average	0	1	0	2
Average Range	4	4	4	4
Low Average	1	0	3	1
Deficient	1	1	1	1

Pearson correlation coefficients showed that no association existed between lower absolute CD4 counts and poorer performance in any area of neuropsychological function.

Discussion

Our results indicate that preschool-age children with vertically transmitted HIV infection show many areas of cognitive development within the normal range. A relative weakness was documented on a measure of receptive vocabulary. This finding is consistent with reports that children with HIV show language impairments. Longitudinal follow-up of these children will determine whether these results represent delays in the acquisition of language or long-term deficits in language function. Measures of adaptive behaviour were also in the low average and borderline ranges and were significantly lower than the general population mean standard scores. However, among the children with HIV, those with observable CT brain abnormalities had mean scores that were similar to those children with normal brain scans. No significant differences were noted in any area of cognitive function between children with observable CT scan abnormalities and those with normal scans.

Our results support previous reports of language impairments in children with HIV infection (Belman et al, 1988; Condini et al, 1991; Coplan et al, 1998; Wolters et al., 1995; Wolters et al, 1997). Early reports were based primarily on general observations of behaviour, tests of cognitive development or tests that assessed limited language skills. Many of the studies had small numbers, were composed of children with both vertical and transfusion acquired HIV infection, and rarely controlled for various medical and environmental factors that may affect the cognitive development of children and confound the effects of HIV infection on language functioning. This study only included

children who acquired HIV through vertical transmission with the vast majority being born to mothers who did not abuse substances during pregnancy. Our results indicate that children infected with HIV from birth experience significant delays in receptive language development when compared with overall general cognitive function. Analyses indicated that HIV infection was not associated with overall global developmental delays early in childhood.

The results of this study contrast with previously reported results that expressive language function is differentially affected in pediatric HIV infection and that expressive language is more impaired than receptive language function (Moss et al, 1996; Wolters et al, 1995; Wolters et al; 1997). In both of the Wolters' studies (1995, 1997) the sample consisted of children with vertically and transfusion acquired HIV infection. Their results indicated that pediatric HIV disease is associated with differential receptive and expressive language functioning in which expressive language is significantly more impaired than receptive language. They compared the results in the infected group to a group of uninfected siblings and concluded that the observed language impairments are associated with the direct effects of HIV-related central nervous system disease. The language assessment included the Reynell Developmental Language Scales, which evaluates receptive and expressive language in children aged from 1 to 7 years. Further, they used Clinical Evaluation of Language Fundamentals Revised, a measure that evaluates language disorders in children aged 5-16 years by assessing content (semantics), form (syntax and morphology), and memory through a comprehensive battery composed of 11 subtests. In our present study, we used the Peabody Picture Vocabulary Test and the Expressive One Word Vocabulary Test to assess receptive and expressive language

respectively. The differences between our findings and those previously observed may result from the testing materials used. The PPVT is a receptive vocabulary test whereas the Reynell Developmental Language Scale is more of a receptive language or communication task. In addition, the norms for the respective tests were established at different times using different populations.

Further, while the previous studies had established exclusion criteria, patients who were exposed to drugs *in utero* were not excluded and the rate of maternal drug use during pregnancy was high in some cases. These previous researchers also did not indicate any information about patient demographics such as English as a second language or family income.

Probably the largest difference between our study population and those studied by Wolters et al. is the number of children displaying evidence of HIV-related encephalopathy (>50% of their sample). Using the classification of encephalopathy used by Wolters and colleagues (1997), only 2 of the seventeen children who participated in our study would have been classified as having HIV-related encephalopathy (12%). This is much lower than the rate reported in both of the studies published by the Wolters group. Finally, our study lacked a control group and it is possible that if these children were compared with siblings or some other appropriate comparison group, different conclusions might be drawn about the effect of HIV on receptive and expressive language.

The study by Coplan et al (1998) was a prospective evaluation of language development in infected and in exposed but uninfected infants and young children. Nine children were infected with HIV and 69 were exposed to but uninfected by the virus.

Using the Early Language Milestone Scale, 2nd edition, which assesses auditory expressive, auditory receptive, visual, and global language ability in children from birth to 36 months of age, these investigators found that children with HIV-infection had mean global language scores that were lower than for uninfected participants. They noted that a high percentage of the HIV-positive children experienced some form of language deterioration. However, their results are limited by a small sample size, lack of data on maternal drug use and the number of children in foster or kinship care. They did not report on separate indices of receptive and expressive language, making it difficult to compare their results with our findings.

Our results indicate that only two children (12%) had scores on general intelligence measures that were consistent with a classification within the deficient range of functioning. This percentage is lower than that provided by Englund and coworkers (1996). One clear difference between the two studies is the use of antiretroviral therapy. The results reported by Englund and colleagues reflect performance in a group of antiretroviral therapy-naïve patients. In our study, the vast majority of children were taking a combination of antiretroviral drugs at the time of assessment. Previous research has shown that the start of antiretroviral therapy is associated with significant improvement in cognitive and adaptive behaviour. Wolters and colleagues (1994) reported that all behavioural domains, except for motor skills, as assessed by the Vineland Adaptive Behavior Scales, showed overall significant improvement following 6 months of zidovudine (AZT) therapy. Further, the same group of investigators reported significant improvement in neurodevelopmental and cognitive function of HIV-infected children after the start of AZT therapy (1990). A significant overall increase of 15.5 (SD

= 3.3) IQ points from baseline was observed with mean scores improving from 78.2 to 93.7 on the Wechsler Intelligence Scale for Children-Revised. Analysis indicated that significant gains were made in both VIQ and PIQ. These results would support the explanation that the differences observed between the Englund (1996) study and our present report may be a result of differences relating to antiretroviral therapy.

The Adaptive Behavior Domain Scores that were obtained from the Vineland Adaptive Behavior Scales indicate that children with HIV infection are performing below average with respect to adaptive behaviour. The inclusion of adaptive behaviour in the test battery is important because it provides an indication of how the children are interacting within their home and community. Our result showing delays in behavioural functioning is consistent with previous findings that suggest that all areas of adaptive functioning may be compromised in children with HIV-infection (Wolters et al, 1994). Their study compared adaptive behaviour before and after the start of AZT therapy in a group of children with both transfusion and vertically acquired HIV infection.

These results suggest that adaptive behaviour may be compromised in children with HIV infection. Indeed, some of the direct effects of HIV infection may play a role in the poor performance. For example, some children with HIV will experience recurrent diarrhea and therefore the child may not be toilet trained until later in life. Further, in children, growth delays are common and may also influence some age-appropriate behaviours. However, adaptive behaviour is influenced by many factors, and thus it is possible that some of the indirect effects of HIV are influencing the children's behaviour. For instance, the poor performance may reflect the parent(s) not allowing the child to engage in a wide variety of activities due to overprotectiveness, or because of the

parent(s)' own medical condition prevents opportunities for training their children in age-appropriate activities. In 1997, a Canadian study including many families from Toronto reported that 59% felt that HIV had not dramatically changed how they parented although they described their parenting as more "focussed" (Salter-Goldie, et al., 1997). Further studies are needed to explore the complex relationship between the direct and indirect effects of HIV infection on behaviour.

The finding that both the Similarities and Geometric design subtasks of the WPPSI-R were significantly different from the mean normative values needs to be interpreted with caution. In both cases the mean group score of the HIV-positive children is still within the normal range. Further, if any significant impairment were present it could be expected that other tasks that tapped the same skills and were included in the individual composite scores would also show differences. Within the visual-motor speed and coordination composite, the geometric design task of the WPPSI-R was the only significant difference. The Similarities task of the WPPSI-R was included in the language composite and the only other significant difference was observed in the receptive language measure.

From our patient population, six children who had psychological assessments as infants also had psychological assessment as preschoolers. The second chapter in this thesis reported results on 25 infants with vertically transmitted HIV infection. Of those 25, 10 have died as a result of AIDS related complications, 9 did not or have not yet had preschool evaluations and 6 had preschool evaluations. As infants, the children who have had an assessment between the ages of 3-5 years, were achieving significantly higher scores on the Mental and Psychomotor Performance Scales of the BSID than did children

who did not have assessments between the age of 3-5 years. The six children who had assessments as preschoolers had mean scores as infants of 89.8 (SD = 20.1) on the MDI and 82.3 (SD = 9.1) on the PDI. The seventeen preschoolers who did not have assessments after infancy had mean scores of 69.6 (SD = 23.2) on the MDI and 60.2 (SD = 15.1) on the PDI. Further, the children who had assessments as preschoolers had better scores on all domains of the Vineland Adaptive Behavior Scales as infants compared with the infants who did not have assessments as preschoolers. While the results did not indicate that the differences achieved statistical significance the results definitely reflect an important clinical difference.

These differences between the children who had serial assessments as preschoolers and those who did not support previous results published by Englund et al (1996). They reported that young children, between birth and 30 months of age, had significantly higher rates of cognitive abnormalities than did older children. More precisely, their results indicates that children between birth and 30 months had higher rates of abnormal motor function and a greater percentage attained scores reflective of deficient global cognitive function than did children above 30 months of age. Our results confirm what has been previously described in the literature related to the natural history and clinical course of pediatric HIV infection. Furthermore, our results show that the difference in function across the age groups also applies when children receive drug therapies. Children who survive to the age of 3 years have an improved prognosis and the majority of these children experience a slow disease progression with fewer neurological and cognitive impairments being observed than would be experienced by a younger cohort of children (Blanche et al,1990; Scott et al, 1989).

One of the interesting parts of our study is the inclusion of CT scan data. In our sample of children, 14 of 17 had available data at the time of assessment. Six of the children had observable abnormalities recorded by a neuroradiologist. However, no significant differences in functioning were observed between children who had abnormal CT scans and those who did not. The fact that no significant differences in performance were observed may be a result of a number of distinct factors. Firstly, the results may reflect early brain plasticity in children with CT scan abnormalities. Secondly, the measures we used may not have detected a difference that would have been observed if a different battery were used. Finally, because these children are young they may indeed grow into more noticeable deficits later in life. Since many complex developmental milestones, such as reading and writing, are achieved after the ages of 3 to 6 years the absence of impairment early does not preclude the development of impairment later during the school-age years. The present results contrast with those reported in our infant cohort from the same hospital in which children with observable CT scan abnormalities performed significantly worse on both cognitive and motor function than did children with normal scans (see previous chapter). The discrepancy between the infant and preschool cohorts may be accounted for by the selection bias of children who survived to preschool age and more children in the preschool cohort were receiving combination antiretroviral therapy.

This study has some limitations that need to be considered when interpreting our findings. One such limitation is the lack of a comparison group. At the time of data collection, there were not enough uninfected siblings between the ages of 3 and 6 to form a comparison group. Sibling controls are the best comparison group that can be recruited

because siblings will share some of the unique environmental and familial factors that are associated with HIV infection. Another limitation is the small sample size. It is clear that the standard deviations and confidence intervals are large, thus the results must be interpreted with caution. The cohort in this study is smaller than the previous chapter reported in this thesis because children in the infant cohort died, were lost to follow-up or had not reached preschool age yet. Finally, the children had assessments at different points in time and were exposed to different drug therapies in accordance with their medical needs and standards of clinical practice at the time of assessment.

In summary, the results indicate that preschool children with vertically transmitted HIV infection show many areas of cognitive development in the normal range. Thirteen of the 17 children had mean FSIQ's that were reflective of average performance. A relative weakness was documented on a measure of receptive vocabulary. This finding is consistent with reports that children show language impairment. Longitudinal follow-up of these children will determine whether the results represent delays in the acquisition of language or long-term deficits in language function. Future studies should focus on following this cohort prospectively over time. Prospective longitudinal follow-up of these children will provide an indication of whether the children are continuing to perform well with respect to their neuropsychological functioning or if they are experiencing greater deficits as they grow older. Finally, follow-up of the children receiving combination drug therapies will provide an indication of the benefits and limitations of highly active antiretroviral therapy on neuropsychological functioning in children.

Cognitive Development in School-Age Children with Vertically Transmitted HIV Infection

Introduction

In the past five years, there has been a growing interest in investigating the long-term effects of HIV infection on school children. School-age children represent an important group because, with improvements in antiretroviral therapy, children are living longer and healthier lives. It has been reported that 65% of vertically infected children are alive and well at 5 years of age (Scott et al., 1989; Blanche et al., 1990). Also, studies have shown that significantly more children under 3 years of age show evidence of central nervous system (CNS) disease as compared to children over the age of 6 years (Blanche et al., 1990; Englund et al., 1996; Tardieu et al., 1995). Our study is cross-sectional in design and presents results on a group of school-age children followed by the Comprehensive HIV/AIDS Program at the Hospital for Sick Children in Toronto. Some of the children who had assessments used in our study of the effects of HIV on preschool children (see previous chapter), also had assessments as school-age children which are used in this analysis. Not all of the children previously reported in the preschool study are included here because they were either lost to follow-up at the clinic, had not yet reached school-age or have not yet had a school-age evaluation. It is expected that as a group these children will perform generally well with respect to their cognitive development. As was seen in the preschool children, we will expect to observe selective neuropsychological impairments in these children. Further, the school-age children may have deficits that are have developed with the attainment of more complex developmental milestones.

Prior to 1985, a significant number of children were infected through exposure to blood products received before donor-screening became widely available. Individuals with hemophilia were at increased risk because they received pooled blood products (Levine, 1985). A number of studies have reported results on neuropsychological functioning in school-age children with hemophilia who are also infected with the HIV virus. The studies have shown no significant differences in neuropsychological functioning between children with hemophilia and HIV when compared with a control group of children with only hemophilia (Loveland et al., 1994; Sirois et al., 1998; Smith et al., 1997; Whitt et al., 1993). However, children infected with HIV at a younger age experienced more difficulty on verbal and perceptual tasks than children infected later in life (Sirois & Hill, 1993). However, in this specific study, the sample size was small, which limits the ability to generalize their findings.

The results of a longitudinal study conducted with premature children infected through neonatal blood transfusion also reports the effects of early HIV infection on neuropsychological functioning. Cohen et al. (1991) compared such children, varying in age from 3 to 9 years, to a non-infected group with similar birth histories who had also received blood transfusions. Their results showed slight but statistically significant differences between the groups on measures of motor speed, visual scanning, cognitive flexibility, reading and arithmetic. Further, the differences seemed to be accentuated over time. It should be noted that children born prematurely are at risk for developing cognitive deficits (Janowsky & Nass, 1987) and it is possible that this risk interacts with the mechanisms of HIV on the central nervous system to produce more significant impairments than would be observed in children born full-term.

In 1995, Tardieu et al. reported on a group of 33 school-age children with vertically transmitted HIV infection. Of the 33 patients, 24 had neuropsychological, language and psychoaffective evaluations. Their results indicated that 67% of the children followed had normal academic abilities and most scored within normal limits on tests that evaluated general intelligence, language and motor function. Specific cognitive impairments were observed in individual children. Fifty-four percent of the patients had abnormal results on visual-spatial and time orientation tasks. A trend toward poorer academic achievement and poorer results on visual-spatial or temporal orientation tests was seen in children with lower percentages of circulating CD4 lymphocytes. When compared to the national average, the participants had more frequent difficulties or failed at school (33%) more often than would be expected.

A study published in 1998 by Frank, Foley, and Kuchuk, presented results on a group of 27 HIV-positive school-aged students who had been infected with the virus through vertical, transfusion and sexual transmission. All the children were on antiretroviral therapy at the time of assessment. Results indicated that as a group, Performance and Full Scale IQs, as assessed by the Wecshler Intelligence Scale for Children-Revised (WISC-R), were within the normal range and Verbal IQ was in the low average range. It was also noted that children with vertically acquired HIV-infection had significantly higher Full Scale IQs than did children infected by either blood transfusion or sexual abuse. This result is surprising because all 19 mothers who transmitted the disease to their children at birth were using drugs at the time. Previous research has shown an association between developmental delay in childhood and maternal use of

alcohol, cocaine or heroin during pregnancy (Singer et al., 1993; Wheeler, 1993). Further, all 19 children were in foster homes at the time of the study.

The results reported by Tardieu et al. (1995) and Frank et al. (1998) contrasted with an earlier study that documented higher levels of neurodevelopmental delay among school children with vertically transmitted HIV disease (Papola et al., 1994). In a sample of 90 school-age children with presumed perinatally acquired HIV infection, it was shown that 56% of all children were functioning at a borderline or lower range of intelligence. Furthermore, over half of the children (63%) were referred for placement in special education. These results need to be interpreted with caution because this study and other research (Frank et al., 1998) has failed to control for risk factors other than HIV that may affect development.

Previous research has documented specific areas of neuropsychological functioning that may be differentially affected by pediatric HIV disease. As reviewed in the previous chapter on preschoolers, Wolters et al. (1997) examined language functioning of children (mean age 8.5 years) with symptomatic HIV. The group consisted of both children with vertically transmitted and transfusion-acquired HIV (11 and 6 children respectively). Their results indicated that expressive language was consistently more impaired than receptive language over 24 months. Moreover, while general cognitive function remained stable both receptive and expressive language declined significantly over 24 months despite the use of antiretroviral therapy. Thus, the authors concluded that some domains of neuropsychological functioning may be more vulnerable to the effects of pediatric HIV infection and that these domains might be masked by global measures of cognitive function.

Since neuropsychology identifies the functional consequences of CNS abnormalities it is important to understand the brain insults associated with pediatric HIV infection. A variety of CNS abnormalities have been associated with HIV-infection including: cortical atrophy, calcification of the basal ganglia and frontal white matter, ventricular enlargement and white matter low attenuation (Brouwers et al., 1995; DeCarli et al., 1993; King et al., 1997). The most important finding from a development perspective is that of myelinopathy. During infancy the brain is still undergoing a period of rapid myelination, which coincides with the attainment of significant motor, cognitive and behavioural milestones. Any disruption in this process can be expected to produce developmental delays that may become more significant over time. However, in children who have experienced a slow disease progression, as have school-age children with HIV infection, disruptions may be more subtle, allowing children to attain normal age-appropriate developmental milestones. Subsequently, older children living with vertically acquired HIV infection can be expected to perform within the average range in some areas of neuropsychological funtion with subtle individual deficiencies noted.

In summary, since not much comprehensive research has been conducted on neuropsychology in school-age children with vertically transmitted HIV, we chose to measure a broad range of cognitive skills with a comprehensive battery of tests selected for their utility with school-age children. Previous research on school-aged children with hemophilia and HIV infection has consistently shown no evidence of neurodevelopmental disability. However, the previous research on children with vertically transmitted HIV infection has reported contradictory findings. One European study (Tardieu et al., 1995) reported that 67% of their sample showed normal academic abilities, whereas one large

American study (Papola et al., 1994) reported that 67% of children were referred for placement in special education classes. The purpose of this present study was to compare cognitive, language and motor functioning in a sample of children and adolescents with vertically transmitted HIV infection with a control group of school-age siblings who are not infected with the virus. This study is unique in that it will document a description of cognitive and motor development in a group of Canadian school children with vertically transmitted HIV/AIDS. Further, the inclusion of a control group is an important strength of our study and has not been included in the previous literature. Another difference between our cohort and previous research is our group has lower rates of maternal substance exposure, English as a second language (ESL) and rate of maternal separation than has been reported previously in studies on school-age children with HIV infection. This study also examines CT brain scans to determine whether the structural brain changes observed in school age children with HIV-infection are associated with functional deficits.

Methods

Participants

The participants for this study were 14 children with vertically transmitted HIV infection ranging in age from 6.3 to 14.2 years and 11 control participants (4 siblings of children with vertically transmitted HIV, 7 siblings of a children with transfusion-acquired HIV) who ranged in age from 6.9 to 14.9 years. All participants were recruited through the Comprehensive HIV/AIDS Program at the Hospital for Sick Children. This

study was approved by the Research Ethics Board at HSC. Informed consent was obtained, with participants aged 16 years and older providing their own consent. All of the HIV-positive children had documented HIV-infection by positive plasma or cell culture or polymerase chain reaction assay (after the neonatal period) or positive HIV enzyme-linked immunosorbent assay (ELISA) and Western blot beyond 18 months of age. All of the children with HIV were followed at the HIV/AIDS Comprehensive Care Program at the Hospital for Sick Children in Toronto. Existing data were collected for all school-aged patients who had undergone developmental testing as part of their routine follow-up from 1989 through 1999. Since the beginning of the Comprehensive Care HIV/AIDS Program in October 1988, all patients followed for more than 1 year had a cranial CT scan, with follow-up CT scans offered annually. All patients are offered neuropsychological evaluation. Children were considered school age if they were over six years of age. The control group consisted of children who were siblings of children with HIV infection. Three were siblings of children with vertically transmitted HIV infection and 7 were siblings of children who acquired HIV through transfusion of blood or blood products. Exclusion criteria for both groups included children with known pre-existing non-HIV-related conditions such as Down syndrome, congenital multiple handicaps, severe prematurity, significant perinatal trauma associated with developmental delays and severe intraventricular hemorrhage. **Table 1** contains descriptive data for the two groups. Age was compared using an independent t-test, all the 2 x 2 tables using Fischer's exact test and all the rest a chi-square.

Twelve of the children were on antiretroviral therapy at the time of assessment. Four children were taking a combination of drugs including a reverse transcriptase

inhibitor and one protease inhibitor. Eight children were receiving a combination of drugs that included only nucleoside analogues. The average number of drugs that the children were taking at the time of assessment was 2 (range 0-4). Four children were receiving regular infusions of intravenous gamma globulin and 6 children were on PCP prophylaxis. **Table 2** contains a number of medical variables that were recorded as part of the children's routine follow-up at the clinic. Viral load were not available for the majority of children at the time of testing.

Table 1. Description of the sample of 14 HIV-positive school age children

	HIV-positive	HIV-negative	P- value
Age ± SD (years)	9.4 ± 2.7	10.2 ± 2.4	0.415
Range	6.3 – 14.2	6.9 – 14.9	
Gender			
Males	4	6	
Females	10	5	0.183
Race			
Black	7	1	
White	5	9	
Other	2	1	0.027
Socioeconomic Status (Family Income)			
$40,000 +	5	6	
$30-39,000	3	3	
$20-29,000	2	1	
$15-19,000	3	1	
Unknown	1	0	0.718
Mothers Intravenous Drug Use	3	0	0.158
English as a Second Language	1	1	0.697
Any foster or kinship care	4	1	0.245

Table 2. Medical variables for 14 children with vertically-acquired HIV-infection.

	Mean ± SD	Reference	N
Height (%ile)	29.4 ± 27.7	50	14
Weight(%ile)	39.4 ± 26.5	50	14
WBC (10^9/L)	5.1 ± 2.4	4.0-10.0	12
Hgb (g/L)	114.5 ± 11.2	120-160	12
MCH (pg)	29.3 ± 4.6	24-31	12
Plt (10^9/L)	263.0 ± 94.9	150-400	12
Lymphocytes (10^9/L)	2.0 ± 1.4	1.5-7.0	12
Polymorphs (10^9/L)	2.0 ± 0.9	1.5-8.0	12
CD4 (λL)	519.7 ± 388.4	500-1000	12
CD8 (λL)	1200.9 ± 1301.9	500-1000	12

Seven of the children had CD4 counts above 500 at the time of assessment. Of the fourteen children, 2 had never had clinical symptoms associated with their HIV infection. Eight children had experienced only non-AIDS defining illnesses and 4 children had experienced both a non-AIDS and an AIDS defining illness. **Table 3** classifies the children into immunologic and clinical categories according to the CDC 1994 guidelines. The types of medical conditions found in this sample were similar to those described in the literature for children with HIV infection. The most frequent medical problems were as follows: recurrent upper respiratory infections (50%), generalized lymphadenopathy (36%), lymphoid interstitial pneumonia (36%) and recurrent oropharyngeal candidiasis (29%).

Table 3. Classification of children according to CDC 1994 guidelines

	Clinical Symptoms		
Signs or Symptoms	**None**	**Mild/Moderate**	**Severe**
Immunologic Categories			
No Evidence of Suppression (CD4 ≥ 500)	1 (N1)	5 (A1/B1)	1 (C1)
Evidence of Moderate Suppression (CD4 200 – 499)	0 (N2)	4 (A2/B2)	0 (C2)
Evidence of Severe Suppression (CD4 ≤ 200)	0 (N3)	0 (A3/B3)	3 (C3)

Procedures

For the purposes of this study, data were obtained from the assessments that provided the longest outcome measure for each child. Seven children had more than one school age assessment, in which case their most recent scores were used. Participants were administered an extensive battery of tests as part of a comprehensive assessment of the child's development. Test administration required 4-6 hours to complete. In the majority of cases, the assessments were completed in two testing sessions conducted in 1 day with a break for lunch between testing sessions. Participants were offered short breaks during the sessions to control for fatigue. Some children did not complete all of the tests because of fatigue or time constraints, leading to a slight variation in sample size across analyses.

The neuropsychological evaluation included the following tests classified according to functional area:

General Intelligence measures: Intelligence measures were obtained using the Wechsler Intelligence Scale for Children (WISC) – Revised or III (Wechsler, 1974). Full scale, Verbal and Performance IQ scores were determined.

Language: WISC Vocabulary, Comprehension and Similarities subtests; Word Fluency (F-A-S and Categories; Gaddes & Crockett, 1975); Test of Reception of Grammar (Bishop, 1982); Expressive One Word Picture Vocabulary Test (Gardner, 1979).

Academic measures: Wide Range Achievement Test, Revised or 3rd Edition (WRAT-3; Wilkinson, 1993).

Memory: WISC Digit Span and Information subtests; Story Recall (Denman, 1984); Rey-Osterreith Complex Figure (Osterreith, 1944; Rey, 1942).

Attention: WISC Arithmetic and Digit Span subtest.

Visual-Spatial Processing and Reasoning: WISC Picture Arrangment, Block Design, Picture Completion and Object Assembly subtests.

Visual-motor speed and coordination: WISC Coding subtest and the Developmental Test of Visual-Motor Integration (Beery, 1989)

Motor: Finger Tapping (Reitan, 1969), Grooved Pegboard (Reitan, 1969), Hand Dynamometer (Reitan, & Davison, 1974).

The degree of neurodevelopmental disability on the IQ scales was classified according to the following criteria (Wechsler, 1974). The children were determined to be functioning at a superior level if their score was 125 or above; high average between 116-124; average if their score was 90-115; low average between 80 and 89; borderline between 70-79; and deficient at 69 and below. On all other tests participants who showed results that deviated from published normal values by approximately 1 standard deviation

or more in either direction were considered above average (+1 SD) or below average (-1 SD) with respect to their level of functioning.

CT Scan Evaluation

Staff neuroradiologists, who were not blinded to the clinical status of the patients, rated the computed tomography (CT) scans for presence and degree of ventricular size, presence of basal ganglia and other calcifications, white matter attenuation and cerebral atrophy. All CT scans were performed on GE 9800 and GE Advantage CT scanners. All patients had unenhanced scans. In addition, enhanced scans were performed if the neuroradiologist considered that the unenhanced scan showed lesions for which enhancement might provide further information.

Clinical Management

Clinical management has been provided to the patients by the same two pediatric consultants since 1988, and the use of antiretroviral therapy is consistent with current standards of care (Working Group on Antiretroviral Therapy, National Pediatric Resource Center, 1998). The patients whose results were used in this study received various antiretroviral drugs and drug combinations consistent with clinical practice at the time of testing.

Data Analysis

Given the sample size and the number of tasks, steps were taken in order to reduce the likelihood of committing a Type I error. In order to reduce the number of analyses conducted when comparing the children with HIV and the controls and when comparing the children with evidence of CT brain abnormalities with children who had normal brain scans, composite variables were created (visual spatial/perceptual organization, verbal, academic, motor, memory, and attention). Each composite was comprised of the measures that would fall into the area of psychological function. *Z*-scores were calculated for each variable using the data for all participants as a whole. For each participant, the mean of the z-scores for each group of tasks was taken as the composite score. Preliminary group comparisons were conducted on the composite scores. Subsequent analyses of each dependent variable individually were conducted, using standard scores, for more exploratory purposes only, and therefore should be viewed cautiously. Independent t-tests were used to draw comparisons between the children displaying abnormal CT scans with children with normal results on the composite measures described above and measures of general intelligence.

Results

Results revealed that no significant differences between children with vertically transmitted HIV and the control group on IQ measures. Both groups had mean intelligence scores in the average range (see Table 4). Seven of the children with HIV

infection had a FSIQ in the Average range, 6 in the low average range and 1 in the deficient range. The one child who showed serious impairments was diagnosed later in life and had not received antiretroviral therapy until an advanced stage of the disease process. In the sibling control group, 3 children had high average intelligence, 6 were in the average range and 2 were in the borderline range.

Mean test scores in all functional areas, except academic achievement, as indicated by standard scores on the WRAT, did not differ significantly from average relative to published norms in both groups (**Table 4**). The mean score for the general population on the reading, spelling and math subtests of the WRAT is 100 (SD = 15). Mean academic scores for both groups fell within the low average range. In our sample, five children with HIV (36%) and 5 control children (50%) experienced specific difficulties in reading, spelling or math as defined by achieving standard scores that were considered to be an indication of borderline or deficient achievement.

Using composite scores to compare performance of children with HIV with the sibling control group indicated that there were no significant differences between the two groups in any area of neuropsychological function. The only difference that approached significance was on the motor composite score (t_{15} = -1.95; p = 0.07). Subsequent analysis revealed that a significant difference existed between the groups on the Hand Dynamometer which provides a measure of gross motor strength (t_{15} = -3.1; p = 0.007) and finger tapping with the dominant hand which provides a measure of fine motor skill and speed (t_{15} = -2.2; p = 0.04).

Table 4. Mean Scores for Areas of Neuropsychological Functioning by School Age Children with Vertically Transmitted HIV Infection and the Control Group

	HIV Positive	N	Control	N	p
General Intelligence					
[1]Full Scale IQ	91.7 (16.1)	14	100.5 (17.9)	11	0.21
[1]Verbal IQ	91.0 (14.5)	14	97.2 (19.5)	11	0.37
[1]Performance IQ	94.4 (18.2)	14	104.1 (15.6)	11	0.17
Academic Achievement					
[1]Reading	85.6 (15.9)	11	87.7 (13.7)	9	0.76
[1]Spelling	89.5 (16.3)	12	86.8 (11.3)	8	0.89
[1]Arithmetic	89.5 (24.7)	13	88.3 (12.9)	9	0.90
Language					
[2]Vocabulary[a]	9.4 (2.7)	14	8.9 (3.8)	11	0.73
[2]Comprehension[a]	8.7 (2.8)	14	10.1 (4.1)	11	0.33
[2]Similarities[a]	8.6 (3.4)	14	10.5 (3.2)	11	0.19
[1]Expressive One Word	95.8 (18.2)	13	100.3 (24.1)	11	0.61
[1]TROG	90.1 (15.1)	10	97. 6 (7.9)	8	0.22
Word Fluency					
[3]FAS	-0.5 (1.4)	12	-0.4 (1.4)	10	0.87
[3]Animal/Food[b]	-0.6 (1.1)	12	-0.7 (1.0)	9	0.99
Memory					
[2]Digit Span[a]	8.1 (2.7)	14	10.2 (2.7)	11	0.10
[2]Information[a]	7.4 (2.8)	14	9.3 (4.1)	11	0.18
Story Recall					
[3]Immediate recall	0.5 (2.4)	12	-0.6 (1.3)	10	0.24
[3]Delayed recall	0.3 (1.9)	12	-0.6 (1.3)	10	0.28
Rey Figure					
[3]Immediate recall	0.4 (1.1)	10	-0.2 (1.5)	8	0.35
[3]Delayed recall	-0.7 (1.1)	10	-0.1 (1.3)	7	0.39
Attention[c]					
[2]Digit Span	8.1 (2.7)	14	10.2 (2.7)	11	0.10
[2]Arithmetic	8.1 (2.4)	14	8.5 (3.2)	11	0.78
Visual Spatial Processing					
[2]Picture Arrangement[a]	8.4 (3.0)	14	10.3 (3.2)	11	0.14
[2]Block Design[a]	9.0 (3.6)	14	11.4 (2.5)	11	0.08
[2]Object Assembly[a]	9.1 (3.2)	14	10.6 (3.1)	11	0.25
[2]Picture Completion[a]	9.4 (3.8)	13	10.7 (2.9)	11	0.35
Visual Motor Speed and Coordination					
[2]Coding[a]	9.0 (4.6)	14	9.6 (2.9)	11	0.69
VMI	90.2 (15.9)	13	102.1 (15.4)	8	0.11
Motor					
[3]Grooved Peg-D	-0.6 (0.3)	8	-0.3 (1.0)	9	0.39
[3]Grooved Peg-N	-0.5 (0.5)	8	-0.2 (0.7)	9	0.38
[3]Finger Tapping-D	-0.3 (1.1)	8	0.8 (0.9)	9	0.04 *
[3]Finger Tapping-N	-0.02 (1.0)	8	0.5 (0.9)	9	0.29
[3]Hand Dynamometer-D	-0.3 (0.4)	8	0.8 (1.1)	9	0.02 *
[3]Hand Dynamometer-N	-0.3 ± 0.4	8	0.9 (1.0)	9	0.007 *

[1]General population mean standard score is 100 ± 15.

[2]General population mean standard score is 10 ± 3

[3]Scores represent z-scores. General population mean is 0 ± 1

[a] Sub-tests of the WISC-III or R.

[b] Z-Score represents the sum of words produced in the categories of animals and foods.

On the Fine Motor tasks, D refers to the dominant hand and N to the non-dominant hand

p significant at the p = 0.05 level.

The one child who showed serious impairments was diagnosed later and had not received antiretroviral therapy until an advanced stage of disease. As a result this child's results were considerably worse than the rest of the group. Therefore, analyses were conducted again, excluding this child, to examine whether some of the difference was arising because of this one set of results. He was not administered all the tests, and thus the results presented in **Table 5** represent a subset of the entire battery. As expected, the results show that differences between the HIV-positive and control groups are diminished.

Table 5. Mean scores for areas of neuropsychological functioning excluding the one child with significant HIV-related impairment.

	HIV Positive	N	Control	N	p
General Intelligence					
[1]Full Scale IQ	95.2 (9.7)	13	100.5 (17.9)	11	0.37
[1]Verbal IQ	94.1 (8.8)	13	97.2 (19.5)	11	0.37
[1]Performance IQ	98.0 (12.8)	13	104.1 (15.6)	11	0.31
Academic Achievement					
[1]Reading	88.8 (12.6)	10	87.7 (13.7)	9	0.88
[1]Spelling	91.1 (7.2)	11	86.8 (11.3)	8	0.56
[1]Arithmetic	95.1 (15.0)	12	88.3 (12.9)	9	0.21
Language					
[2]Vocabulary[a]	9.8 (2.0)	13	8.9 (3.8)	11	0.45
[2]Comprehension[a]	9.3 (1.8)	13	10.1 (4.1)	11	0.54
[2]Similarities[a]	9.2 (2.7)	13	10.5 (3.2)	11	0.32
[1]TROG	93.4 (11.5)	9	97. 6 (7.9)	8	0.40
Memory					
[2]Digit Span[a]	8.6 (2.1)	13	10.2 (2.7)	11	0.13
[2]Information[a]	7.8 (2.2)	13	9.3 (4.1)	11	0.29
Attention[c]					
[2]Digit Span	8.6 (2.1)	13	10.2 (2.7)	11	0.13
[2]Arithmetic	8.7 (1.3)	13	8.5 (3.2)	11	0.81
Visual Spatial Processing					
[2]Picture Arrangement[a]	9.0 (2.3)	13	10.3 (3.2)	11	0.23
[2]Block Design[a]	9.5 (3.1)	13	11.4 (2.5)	11	0.13
[2]Object Assembly[a]	9.7 (2.6)	13	10.6 (3.1)	11	0.42
[2]Picture Completion[a]	10.1 (3.0)	13	10.7 (2.9)	11	0.61
Visual Motor Speed and Coordination					
[2]Coding[a]	9.6 (4.1)	13	9.6 (2.9)	11	0.99

[1]General population mean standard score is 100 ± 15.
[2]General population mean standard score is 10 ± 3
[3]Scores represent z-scores. General population mean is 0 ± 1
[a] Sub-tests of the WISC-III or R.

CT scans were available for all 14 children with HIV. Fifty percent (7) of the children had abnormal scans: brain atrophy was observed in 1, calcification in 1, ventricular enlargement in 4 and white matter abnormalities in 5. It should be noted that each scan could contain evidence of more than one specific abnormality. On the general intelligence measures, children with evidence of CT abnormalities showed similar performance on the Verbal IQ scale as did children with normal CT scans (t_{12} = -0.72; p = 0.48), but the difference for the Performance IQ scale approached significance (t_{12} = -1.7; p=0.11).

Using composite scores to compare performance of children with CT abnormalities with those with normal scans indicated that there were no significant differences between the two groups. The only differences that approached significance were on the visual spatial and perceptual organization composite score (t_{12} = -2.0; p = 0.07). Subsequent analysis revealed that the difference between the groups approached significance in their performance on the Picture Arrangement and Block Design subtests of the WISC (t_{12} = -1.92; p = 0.08 and t_{12} = -1.98; p = 0.07 respectively). Again, excluding the one child who displayed deficient performance on intelligence measures revealed that the difference on visual spatial tasks became less pronounced (t_{11} = -1.7; p = 0.11). **Table 6** shows the mean standard scores the children with and without evidence of CT brain abnormalities on VIQ, PIQ, visual spatial/perceptual organization composite score, picture arrangement from the WISC and block design from the WISC.

Table 6. Neuropsychological function on specific areas according to CT status.

	CT Abnormal (n = 7)	CT Abnormal* (N = 6)	CT Normal (n = 7)
VIQ (Mean ± SD)	88.1 (19.6)	94.5 (11.1)	93.9 (7.0)
PIQ	86.7 (18.9)	93.2 (9.0)	102.1 (14.7)
Visual Spatial Composite	7.4 (3.0)	8.4 (1.8)	10.2 (2.1)
Picture Arrangement	7.0 (2.9)	8.0 (1.3)	9.8 (2.7)
Block Design	7.2 (3.5)	8.1 (2.9)	10.7 (2.9)

* excludes the one child diagnosed with late in life

Pearson correlation coefficients showed that no significant association existed between lower absolute CD4 counts and poorer performance in any area of neuropsychological function. However, the correlation between fine motor skills and absolute CD4 count did approach significance ($p = 0.051$).

Discussion

Previous research on the neurodevelopment of HIV-infected school age children has focussed much of its attention on children who have hemophilia and HIV infection (Loveland et al., 1994; Sirois et al., 1998; Smith et al., 1997; Whitt et al., 1993). Despite small sample sizes, studies have consistently reported no overall impairment in children with hemophilia and HIV infection (Loveland et al., 1994; Sirois et al., 1998; Smith et al., 1997; Whitt et al., 1993). It has also been reported that HIV-positive children with hemophilia and HIV, children with only hemophilia, and their healthy siblings are similar in performance on a wide variety of cognitive, neuropsychological and academic measures (Smith et al., 1997).

Our study included only children who acquired HIV through vertical transmission, with the vast majority (80%) being born to mothers who did not abuse substances during pregnancy. Our results indicate that school-age children with vertically transmitted HIV infection generally do well with respect to their neuropsychological development. The results are consistent with previous results reported by Englund et al. (1996) on a large cohort of antiretroviral therapy-naïve, symptomatic, HIV-infected children. Their results indicated that younger children had significantly higher rates of developmental abnormalities before antiretroviral therapy than did older children, especially with regards to neurologic and cognitive function.

Analyses indicated that there were no significant differences between school age children with vertically transmitted HIV and the sibling control group on measures of academic achievement. Both groups had mean scores on reading, spelling and math that were reflective of low-average performance. Five children with HIV (36%) and 5 of the control children (50%) experienced specific difficulties in reading, spelling or math. In the general population we would expect that 16% of children would perform in the borderline and deficient ranges on measures of reading, spelling and math as assessed by the WRAT. Poorer academic achievement was not a reflection of poor overall general performance in these children because no corresponding deficiencies in language, memory, or visual spatial/perceptual organization abilities were observed. It is not possible to determine whether their academic difficulties reflect specific cognitive impairments or whether they are secondary to other factors. There is a broad array of stressful psychosocial conditions that may influence academic performance in both the HIV-positive and control groups that include poverty, frequent absences from school for

medical reasons, familial/genetic factors and cultural factors. Some of the conditions that are unique to HIV disease are: the multigenerational impact of this infection and the social stigma associated with HIV/AIDS (Lewis et al., 1994; Salter-Goldie et al., 1997).

Despite normal cognitive development, subtle motor impairments were documented in children with HIV infection. This finding is consistent with reports that motor function is compromised early in development in infants with HIV (see chapter 2 of this thesis). Motor impairments have been reported previously in school children with HIV infection. Frank et al (1998) reported that visual motor integration, as measured by the Developmental Test of Visual-Motor Integration, was in the low average range. Our results are the first report of fine motor and motor strength deficits in school-age children with HIV. While both groups fell within the average range the children with HIV achieved lower scores on measures of fine motor skill and motor strength. While fine motor deficits have not been reported in school-age children before, fine motor deficits have been observed in adults with improvements seen with HAART (Sacktor et al., 2000; Tozzi et al., 1999). In addition to these motor skills, impairments have been described in psychomotor skills in adult populations (Heaton et al., 1995; Rourke et al., 1999; White et al., 1995).

The inclusion of CT results complements the collection of data from the neuropsychological evaluations of the participants in our study. Previous research on CT brain scan abnormalities and neuropsychological functioning has been conducted on symptomatic children of different ages who acquired HIV both vertically and through exposure to contaminated blood or blood products without controlling for risk factors other than HIV. In this study, all 14 patients had CT data available. The children who

had CT brain abnormalities, showed a trend toward worse performance on measures that involved perceptual organization/visual spatial skills than infected children without observable brain abnormalities. The exact cause of the observed CT brain abnormalities can not be determined in this type of study. However, it seems reasonable, based on the literature on HIV and the central nervous system, to assume that HIV infection plays a significant role, although other confounding factors, such as maternal drug abuse and co-infections during pregnancy could also influence such abnormalities.

White matter abnormalities were observed in one-third of the children. There are three types of white matter connections (projection, association and commisural) in the central nervous system that develop at different rates and at different times during the developmental process. Complete myelination is achieved first in the projection fibers. For association fibers, myelination will begin later progressing from the region around the central sulcus towards the poles of the parietal, occipital, temporal and frontal lobes. In a similar fashion, the commisural fibers are myelinated at a later period (Dietrich et al., 1988). Thus, the time at which infection occurs would be important, because, under the assumption that connections are most vulnerable when they are being formed, infection early in the developmental process would be damaging to myelination, which is of critical developmental importance. Since children with vertically transmitted HIV are infected *in utero*, during birth or through breastfeeding it would be expected that any disruption in the myelination of important brain structures would produce observable deficits.

Since HIV probably infects the brain shortly after infection, it would be expected that early interference with myelination would affect all three types of white matter connections producing global deficits in functioning. Overall global deficits are

consistently observed in infants (see chapter 2 in this thesis). However, in older children who display seemingly normal performance, interference may occur in more subtle ways thus affecting specific connections producing more defined deficits. School age children may represent a group with slower disease progression that is characterized by lower viral load and better immune status early in life, which may be responsible for the results observed.

A parallel can be drawn with children with hydrocephalus because visual motor weakness has been reported. Hydrocephalus can affect white matter tracts, particularly the corpus callosum and projection fibers near the midline, which connect the hemispheres to the diencephalon and more caudal regions of the brain (Fletcher, et al., 1992). Several studies have shown that children with hydrocephalus have significantly better verbal abilities than visual-spatial abilities (Fletcher, et al., 1992; Thompson, et al. 1999). In a study of school-age children with achondroplasia (ACH), a common dwarfing condition associated with central nervous system anomalies including hydrocephalus, results revealed as a group, intelligence was in the average range (Thompson, et al., 1999). However, some children with ACH obtained scores well below normal, as evidenced by the large standard deviations on several tasks. These included the group average scores in spelling, writing, arithmetic and visual-spatial perception. We observed similar results in our group on measures of academic achievement and visual-spatial abilities. Further, the group of children who had observable abnormalities on CT scored significantly worse on measures of visual-spatial and perceptual organization abilities than did those children with normal scans.

Overall, our results were consistent with those presented by Tardieu et al (1995). Two-thirds of the children in their study were showing normal academic performance at a mean age of 9.12 (SD = 2.13). Further, our results indicated that children with CT abnormalities performed worse on visual spatial tasks than did children with normal CT results. Tardieu et al (1995) reported that children with vertically transmitted HIV infection experienced greater visual spatial impairment than the population used for standardization of tests. These consistent results may reflect the fact that the two samples were similar in their degree of maternal separation (26% and 27%) and the number of mothers from Africa and the West Indies. Also, the number of mothers reporting the mode of infection as heterosexual contact in an endemic area was 51% in the Tardieu study which is consistent with our sample in which the percentage of women whose risk factor for acquiring HIV was heterosexual transmission in an endemic area was 50%. The results indicating that the majority of children were showing normal academic performance in our sample may occur because of improved antiretroviral therapy but this has yet to be investigated in a pediatric population.

Our results contrast those reported by Papola and colleagues (1995). In the Papola study, 56% of 90 school age children, with presumed vertically transmitted HIV infection, displayed functioning in the borderline range or lower, with 50% demonstrating significant language impairments. Further, over half of the children (63%) were referred for placement in special education. The language impairment finding may arise from 50% of the children being Hispanic and English may not have been their first language. Further, a large number of children (62%) were not living with a biologic parent(s). Lastly, the sample was recruited predominantly from the Bronx in New York City and no

information was recorded about maternal drug use or socioeconomic status which may have influenced the results. Other studies of children with HIV from this and similar urban areas have revealed high rates of maternal drug use and poverty (Chase et al., 1995; Epstein et al., 1986; Nozyce et al., 1994).

Maternal substance abuse is an important consideration when investigating cognitive development in children because children perinatally exposed to a number of drugs are at risk for developmental delay. In the literature, there exists controversy as to the extent of the deficits observed which range from overall cognitive impairment to subtle deficiences in certain domains of functioning. Reports have documented reliable decrements in cognitive development that are subtle (Koren, et al., 1996; Lester, et al., 1998; van Baar & de Graaf, 1994). Substance abuse research has documented clinically significant levels of language delay in both expressive and receptive tasks (Chasnoff, 1998). The presence of clinically significant language impairments in children following maternal substance abuse further reinforces the need to try and reduce the rate of maternal substance abuse in a research cohort used to investigate neuropsychological function in children with pediatric HIV infection.

Our results do not indicate the presence of a specific language impairment in the presence of stable overall cognitive functioning as was observed by the Wolters group (1997). However, some similarities do exist between the two studies. In our study, mean group standard scores on both measures of receptive and expressive vocabulary were within normal limits. In the Wolters et al. (1997) study, for the 17 children with the 24-month follow-up, measures of receptive vocabulary were consistently within normal limits over time. However, on measures of expressive language, results were consistently

within a low-average range. The results from the school-age children contrast with what was reported in a group of preschool children followed at HSC. In the preschool cohort, a specific weakness was noted on a measure of receptive vocabulary. The reason for the differing results may be accounted for by the use of different tests to provide a receptive language measure. The PPVT is a receptive vocabulary measure whereas the TROG is a more a measure of receptive grammar.

This study has some limitations that need to be considered when interpreting the findings. One such limitation is the small sample size. All of the standard deviations are large and therefore the results need to be interpreted with some caution. Secondly, our control group consists of children whose siblings contracted HIV through both vertical transmission and the transfusion of blood or blood products. The gender and racial composition of the two groups was different; however, in the group with HIV no significant differences between males and females or between children of different races were observed. Such differences could not be explored in the control group due to small sample size. Thirdly, continuing changes in the standard of clinical care for these patients meant that children were on different antiretroviral therapies at the time of their neuropsychological evaluation. The literature on antiretroviral therapy and cognitive function in adults indicates that the use highly active antiretroviral therapy can improve neuropsychological outcome (Ferrando et al, 1998; Tozzi et al, 1999).

With advances in research and clinical practice, pediatric HIV infection is changing from a terminal disease to a chronic illness with children living longer and healthier lives. Thus, future studies should focus on longitudinal follow-up of school-aged children infected with HIV in an effort to describe further the developmental process

and profile of this group of children. With such efforts, health professionals will be able to provide optimum medical, educational, psychosocial and rehabilitative services to patients and their families. Further research needs to be conducted on the antiretroviral drugs and their ability to penetrate the CNS in these children and potentially delay, prevent, or reverse HIV-related CNS involvement. Research on antiretroviral drugs and the CNS should also seek to identify any drug side effects that may be associated with therapy. Our current understanding of drug effects and the CNS is limited and primarily based on literature on adults living with HIV. Future studies should also focus on prospectively identifying other markers, for example viral load and other immunological prognostic markers that may indicate the onset of neurodevelopmental delay. This would have an important implication for both therapeutic and preventative efforts. The academic and functional deficits that were observed in this study highlight the need for flexible academic programs for these children. Visual-spatial and perceptual organization deficits may undermine certain aspects of academic achievement such as early handwriting, conceptual mathematics, and map usage. Educational professionals aware of individual vulnerabilities can arrange for remediation or compensation in the classroom setting. Lastly, it is important that future studies look at identifying the educational and vocational needs of school-age children and adolescents that should have a remedial, therapeutic and preventative focus.

General Discussion

This present research provides a description of cognitive and motor development in a cohort of Canadian children with vertically transmitted HIV infection. The neurological sequelae associated with HIV infection in this population implicate various areas of neurological functioning, as assessed by neurospychological and neuroimaging evaluation, which can account for the range of deficits that were observed in the children. The research findings suggest that several neuropsychological domains are affected during the course of viral infection. Specifically, difficulties in overall intellectual functioning, receptive language, visual-spatial skills, motor skills, and adaptive/behavioural functioning were observed.

Due to the cross-sectional nature of the research, the small sample sizes, and other potential confounds, the results need to be interpreted with a certain degree of caution. Like previous research, ours was not free from the potential confounds outlined in the introduction. It must be understood that HIV infection within a family is associated with complex psychosocial issues that may affect developmental functioning, and in that respect, our group is not unique. While we more effectively controlled for maternal drug abuse, rates of maternal separation, and English as a Second Language, the analysis did include data from children born to drug abusing mothers, living in kinship or foster care and whose primary language was not English. It is important to keep in mind that there is great heterogeneity in the pediatric HIV population.

One of the strengths of the present study is the fact that the neurocognitive evaluation of the infants, preschoolers and school age children assessed a wide range of

abilities known to be vulnerable to the effects of HIV. Each test battery included an age-appropriate test that provided a composite measure of general cognitive function. Attaining global measures of cognitive function is important because previously it has been shown that scores on these measures have been associated with measures of disease progression and neurological status in children with HIV infection (Brouwers et al., 1995). Understanding that a general measure of cognitive function may mask the separate effects of HIV on individual domains of functioning, tests were included in the battery that comprehensively assessed as many areas of neuropsychological functioning as possible. It was expected that subtle deficits would be apparent in specific areas of function based on previous research. This approach was particularly important in the preschool and school-age children with HIV infection because we expected that they would tend to exhibit less severe CNS manifestations than infants.

The current research provides insight into the developmental functioning of children with vertically transmitted HIV infection at three distinct points in time. Our results for the infant cohort were consistent with previous research, as our data present evidence that, as a group, the infants are more adversely affected by HIV infection than older children as indicated by abnormalities in development and immunologic disease indicators. Further, those children who live to the preschool and school- age stages experienced a better developmental course with more subtle deficits observed. To date, little research exists exclusively on children between the ages of 3 and 6 years. Our results indicate that preschool children are doing generally well with respect to neuropsychological function. In the preschool and school-age cohorts, our results indicated that with early treatment with antiretroviral therapy children with vertically transmitted HIV infection show many area of cognitive functioning within the normal range. The relative

weakness that was observed in receptive language function is a new finding and warrants further investigation. At school-age, despite normal cognitive development, subtle motor impairments were documented. This finding is consistent with reports that motor function is compromised early in development in infants with HIV. Our results are the first to report fine motor and motor strength deficits in school-age children with HIV.

It is hoped that this thesis provides a balanced view of the impact of the disease on children with vertically transmitted HIV infection. In some cases, particularly among the infants and children in an advanced stage of viral infection, severe impairments in neuropsychological functioning across most domains were observed. It is also known that HIV-associated encephalopathy and certain opportunistic infections, consequent to an immunosuppressed state as a result of HIV infection, are also capable of producing similar consequences. By contrast, there were a number of children who appeared not to be affected by HIV infection according to measures of general cognitive function. However, detailed neuropsychological evaluation of these children revealed a different picture with children showing subtle but clinically important deficits across selective domains including language function, visual spatial abilities and academic achievement. Finally, a third group of children emerged from the overall population, those who remain asymptomatic for years with no corresponding neuropsychological difficulties or neurological infarcts despite the fact they occasionally experience varying degrees of immunosuppression.

These results have confirmed the contributions of neuropsychology to the scientific understanding of the disease, and the applications of these findings to the rehabilitative and diagnostic process are of importance. Neuropsychology has complemented advances in

neuroradiology, specifically the use of CT and MRI, because neuropsychological evaluation can assess the consequences of brain dysfunction on development. As our results indicate, many children do not display the clinical and immunologic signs of severe immune suppression and many have unremarkable brain scans. Many of the preschool and school-age children appeared not to have any complications from the infection at the time of assessment. Further, in the school-age cohort, the children with HIV infection showed very similar performance to a group of uninfected school-age siblings. These results are positive for both the patients and their families. However, when these seemingly unaffected children underwent neuropsychological evaluation, subtle deficits in selected domains of cognitive functioning were observed. It remains to be seen how these subtle deficits resolve or evolve with further development in this group.

The infant results correspond well with what has been previously reported in the literature confirming the existing findings that early delays in neurodevelopment are observed in HIV-infected infants born to HIV-positive mothers. Overall, for the preschool and school-age children our results are positive and encouraging. The results indicate that as a group the children are generally performing well with respect to their cognitive development. Some specific deficiencies were noted on an individual case by case basis. Since previous research in the area of neuropsychology and pediatric HIV/AIDS has yielded contrasting results and has been conducted in the United States and Europe, this research will provide the patients and families tangible results on what is happening in Toronto. Considering all the complex and difficult issues that arise as a result of HIV infection within a family these results are positive and should be viewed as such. When discussing these results in relation to populations across the country, some caution should be used. The demographic composition of HIV-positive children varies

across the country and the issues that arise in one population may indeed be specific to that sample; thus, generalizations must be made with caution.

The results should also not be used to generalize a developmental trajectory for children with vertically transmitted HIV infection. This research is not a longitudinal study rather it is three distinct cross-sectional studies. There are similarities across the three studies, firstly, all the children with HIV acquired the infection through vertical transmission and were followed at the Hospital for Sick Children in Toronto. Secondly, the control children in the infant and school-age studies were affected by HIV. They were either born to a positive mother or had a HIV-positive sibling. However, there are differences that require the results be interpreted with caution and as distinct cohorts. The studies were cross-sectional and the children were not followed longitudinally. At different ages, different developmental milestones are reached and the tests administered were in many cases age-specific. Further, some of the tests such as the Bayley Scales of Infants Development stipulate that the test should be used as an indicator of development at a defined point in time rather as an predictor of future outcome. Lastly, in working with children with HIV there is an inherent selection bias because it is only possible to study the children who have survived to a certain age. Young, sick infants will die and older children will become clinically ill and may not receive neuropsychological testing. Just as importantly, some of the psychosocial issues will be different for children of different ages. For these reasons the studies should be viewed as distinct cohorts rather than an indictor of developmental progression in children with HIV infection.

Directions for Future Research

Neuropsychological research in childhood HIV disease is still in its infancy and much work lies ahead. Future research investigating the neurocognitive functioning in pediatric HIV

disease needs to focus on examining long-term cognitive functioning throughout the disease process and across developmental stages. The lack of research employing longitudinal investigations is unfortunate because cross-sectional research can only provide us with a description of the effects of the disease process at a specific point in time revealing little about its long-term impact. Further, while previous research in the area has reported between-group differences it has largely ignored within-group variation. For this reason, future research should attempt to examine the within-group effects that are associated with HIV infection. For example, are specific markers for long-term survival associated with particular neuropsychological variables in asymptomatic children? In such a case, could these markers be used to determine when to intervene to maintain functioning consistent with an asymptomatic state?

Understanding that a great deal of heterogeneity exists in the pediatric HIV population, it would be advantageous for future investigation to attempt to control for, as best they can, other confounding factors, such as maternal drug abuse and English as a Second Language. In Canada, collaboration amongst the Canadian Pediatric AIDS Research Group across the country in longitudinal prospective research would be beneficial. Through such a pursuit, a large sample could be recruited allowing for more stringent exclusion criteria. Further, it would then provide a better indication of the developmental experience of Canadian children with HIV/AIDS rather than an experience of the children followed in Toronto. Previous research conducted in the USA has demonstrated that evaluation of neurocognitive functioning in a population of children with HIV infection can be achieved in a multicenter setting with good results. Previous psychosocial research has been conducted with a national focus in Canada and a multicenter study involving programs across the country could only benefit our understanding of the developmental consequences of pediatric infection in Canada.

It is important to keep in mind that recent advances in research and antiretroviral treatment are gradually changing HIV infection from a terminal disease to a chronic illness in which children infected at birth are living healthy, functional lives well into adolescence. Thus, the investigation of long-term survivors of pediatric HIV infection is necessary to understand the effects of the disease and treatment in these children. In doing this, the focus should continue to involve a multidisciplinary, family-focused team to identify the medical, educational, rehabilitative and psychosocial services that most appropriately meet their needs.

Future research should also focus on the uninfected siblings of children with HIV infection. The siblings are affected by the presence of HIV within the family but have been described as the forgotten members of the family, whose psychosocial needs often go unmet (Mellins & Ehrhardt, 1994). Such children may end up "orphaned" by the disease and will be the long-term survivors of the disease. Neuropsychological assessment will provide an insight into their level of cognitive functioning and will also provide a proper control group for children with HIV. By sharing the same environment as children with HIV and dealing with many of the same complex issues they provide a comparison whereby the true effects of the disease may be noticed.

Lastly, much of the existing research on antiretrovirals and their ability to penetrate the CNS has been done in adults. It is also widely accepted that the CNS is probably the most important sanctuary site in HIV-infected individuals. The presence and replication of HIV within the CNS is an important issue, especially for children, where the infection is occurring in an immature nervous system. Our research, along with previous reports, has shown that many infected children have a broad range of neurological and neuropsychological deficits. As a result, some important questions that need to be answered are; is it possible to suppress viral

replication within the CNS as successfully as has been observed systemically? Which drugs should be used for this purpose and how should their efficacy be measured?

In conclusion, this area of research is in its relative infancy and there is a lot of work still to be done. Our studies have provided a good first step in describing the developmental experience of a group of Canadian children living with HIV/AIDS. It is only a first step though. Researching the neuropsychological function of these children is important and can play an integral role in developing preventative and rehabilitative programs for the children. Through understanding the deficits and CNS abnormalities that may be caused by pediatric HIV infection, we can work to improve treatment options and quality of life for children living with HIV/AIDS.

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Appendix 1

Preschool composites comparison of children with normal CT scans vs. children with CT abnormalities.

Perceptual Processing: $t_{12} = -0.390$; $p = 0.703$

Verbal: $t_7 = 0.132$; $p = 0.898$

Attention: $t_{11} = -0.237$; $p = 0.871$

Visual Spatial: $t_{12} = -0.059$; $p = 0.954$

Motor: $t_9 = -0.281$; $p = 0.785$

Adaptive function: $t_7 = -0.858$; $p = 0.703$

School-age composites: comparison between children with vertically transmitted HIV infection vs. the HIV negative comparison group

Fine motor: $t_{15} = -1.951$; $p = 0.07$

Verbal: $t_{17} = -1.016$; $p = 0.324$

Academic: $t_{17} = -0.121$; $p = 0.905$

Memory: $t_{14} = 0.442$; $p = 0.665$

Visual spatial: $t_{21} = -1.725$; $p = 0.099$

Visual motor: $t_{19} = -1.135$; $p = 0.270$

School-age composites: comparison between children with HIV who have normal CT scans vs. children with HIV who had abnormal brain scans

Motor: $t_6 = -0.305$; $p = 0.770$

Memory: $t_7 = 0.721$; $p = 0.494$

Academics: $t_9 = 0.307$; $p = 0.766$

Verbal: $t_7 = 0.285$; $p = 0.784$

Visual Spatial: $t_{12} = -2.0$; $p = 0.07$