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Cognitive Functioning, Immune Functioning, and Disease Progression in Perinatally Infected HIV+ School-Aged Children on Highly Active Anti Retroviral Therapy

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COGNITIVE FUNCTIONING, IMMUNE FUNCTIONING, AND DISEASE PROGRESSION IN PERINATALLY INFECTED HIV+ SCHOOL-AGED CHILDREN ON HIGHLY ACTIVE ANTI RETROVIRAL THERAPY

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This study is one of the only investigations to examine the complex inter-relationships between immune status, cognitive functioning, and disease progression in school-aged, perinatally infected, HIV+ children on HAART over time and is the first to conduct long-term follow-up assessments beyond one year after initiating HAART. Results demonstrated that poorer immune status, as measured by CD4% <25, at the first time point significantly predicted lower PIQ scores and PIQ subtest scores at the third time point, even after controlling for covariates. Results also showed that PIQ scores remained stable over the three time points. Further analyses revealed, however, that PIQ scores significantly declined over time as a function of CD4% category at the first time point. Finally, scores on the PIQ, VIQ, Coding, Picture Arrangement, Symbol Search, and Arithmetic at the first time point were all significant predictors of CDC C classification at follow-up. The clinical relevance of this study and recommendations for future research in this area are also discussed.

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Introduction

Advances in medical treatment, such as the institution of highly active antiretroviral therapy (HAART) and early diagnosis have resulted in prolonged survival and decreased mortality in children perinatally infected with HIV (de Martino et al., 2000; Gortmaker et al., 2001). Consequently, many researchers have noted that pediatric HIV infection can now be considered a chronic disease (i.e., Newell & Thorne, 2004). Recent research has shown that as the use of HAART has increased in HIV+ children; survival rates have also increased (McConnell et al., 2005). Now that HIV+ children are reaching adolescence and adulthood, it is critical to research examine the long-term effects of HIV on their lives.

Neurocognitive impairment is one of the most salient long-term effects of HIV infection in children. Declines in composite IQ scores and specific deficits in attention, memory, processing speed, language, visual-spatial organization, and motor functioning are frequently seen (see reviews in Wachsler-Felder & Golden, 2002 & Willen, 2006). Although multiple environmental factors, such as poverty and prenatal drug exposure, may contribute to neurocognitive impairment in children perinatally infected with HIV, it appears that HIV's impact on Central Nervous System (CNS) development independently contributes to neurocognitive delays (Armstrong, Willen, & Sorgen, 2004). Medical factors such as immune status and HAART may also impact neurocognitive functioning. Poorer immune status has been associated with neurocognitive delays (Brouwers et al., 1996), whereas HAART may prevent further neurocognitive decline or actually restore neurocognitive functioning (Gray et al., 2001). Furthermore, research has shown there is a relationship between poor neurocognitive functioning and disease progression (Pearson

et al., 2000; Llorente et al., 2003). It is clear that understanding the impact of neurocognitive impairment in perinatally infected HIV+ children requires a complex model involving the relationship between neurodevelopment, environmental and medical factors, and disease progression.

There has been a multitude of studies examining neurocognitive functioning in HIV+ children. However, there are very few studies exploring the specific relationships between HAART, neurocognitive functioning, and disease progression in the current population of perinatally infected children who are already receiving HAART. This study is one of the few to examine these important relationships. The main objectives of the study were threefold. The first objective was to determine whether or not perinatally infected HIV+ children receiving HAART display improvement in neurocognitive functioning over time. Secondly, this study explored whether prior immune functioning was predictive of neurocognitive functioning over time. Thirdly, this study examined whether level of neurocognitive functioning was predictive of disease progression in this post-HAART population.

Biology of Pediatric HIV

Transmission

Historically, children have been infected with HIV by receiving blood transfusions or through perinatal transmission from mother to infant during the labor and delivery process. Changes in screening of the blood supply have resulted in most new pediatric HIV transmission occurring via perinatal transmission. Transmission of HIV can occur before delivery (prepartum) via a break in the barrier of the placenta, during

delivery (intrapartum) by the newborn ingesting contaminated maternal blood, or after delivery (postpartum) through breastfeeding (Burns & Mofenson, 1999). Effective treatment of mothers during pregnancy, labor and delivery makes a significant difference in infant HIV-infection rates. If mothers are receiving treatment, the rate of transmission is reduced to 1-2% (Newell & Thorne, 2004). Even though transmission rates have drastically declined, transmission of HIV from mother to child is still a significant risk in mothers who do not receive prenatal care and are unaware of their HIV status. Thus, it is crucial that research examining the long-term effects of perinatally-acquired HIV infection continue.

HIV and The Immune System

HIV affects three branches of the immune system: cell-mediated (T-cell) immunity, humoral (B-cell) immunity, and natural (monocyte and natural killer cell) immunity. HIV primarily affects T-cell immunity as it attaches to a surface membrane receptor of the CD4 cell and infects this cell, leading to CD4 cell death once replication begins. Thus, the quantity of CD4 cells are depleted and the HIV-infected person's immune system is compromised and he/she becomes more susceptible to opportunistic infections such as pneumocystic carinii pneumonia (PCP), cryptococcal meningitis, toxoplasmosis, and candida esophagitis (Kaplan et al., 1987).

In healthy individuals, the ratio between CD4 cells and CD8 is 1.6-2.0 to 1 (Fauci et al., 1983). But since CD4 cells are depleted in those with HIV, CD8 cells are usually elevated and there is a reversal of the CD4 to CD8 ratio. The humoral immune system is affected as well, as HIV causes a deficit in the feedback system between CD4 cells and B cells. Consequently, the humoral immune system cannot adequately mount a response to

HIV. In addition, nonspecific natural immunity, which includes natural killer (NK) cells, is compromised. This part of the immune system is important in immune surveillance against tumor cells and viruses. Since natural immunity is no longer effective in individuals with HIV, these individuals are more susceptible to various forms of tumors and viruses, which usually do not affect healthy people in the population (Antoni & Schneiderman, 1998).

The impact of HIV on these three major branches of the immune system leaves the individuals infected with this disease susceptible to a multitude of various infections, cancers, and viruses that can eventually lead to illness and death. During the asymptomatic stage of HIV infection, wherein the infected individual has not yet developed AIDS-defining opportunistic infections, the disease is still progressing as the viral load increases and the CD4 counts are depleted (Antoni & Schneiderman, 1998). Because the effect of HIV on the immune system is gradual, it is important to discover if there are any mechanisms that may protect against this decline in immune functioning.

Comparison of Clinical Outcomes in Pediatric HIV and HIV in Adults

There are both similarities and differences in the expression of HIV in adults and children. Both populations are required to take large amounts of drugs to manage viral replication and immune functioning. In both children and adults with HIV, the primary target of the virus is the CD4+ mononuclear cell, and because CD4+ cells travel to many tissue sites, HIV can affect many organ systems. Overall, clinical conditions seen in children can overlap with those seen in adults. However, there are important differences in the course of HIV infection between children and adults.

In perinatally infected children, HIV affects developing immune systems and growing organs. Consequently, perinatal HIV infection can result in the development of unique diseases and infections that are not normally seen in the adult HIV population. For example, lymphocytic interstitial pneumonitis (LIP), which is a lung disease, occurs much more frequently (40-50% of infected children) in children with HIV than in adults with HIV (Gonzalez et al., 2000). Also, HIV-infected children are more likely to suffer from frequent and serious bacterial infections that can cause seizures, fever, pneumonia, recurrent colds, diarrhea, and dehydration, amongst other complications (Krasinski et al., 1988). Disease progression may also be accelerated in HIV+ children compared to HIV+ adults because the latency period between HIV infection and the development of AIDS is shorter (Byers et al., 1993; Tovo et al., 1992). Thus, it is important to take these differences in disease progression and expression into consideration when studying children perinatally infected with HIV.

The Effect of HIV on the Central Nervous System in Perinatally Infected Children

HIV not only affects developing immune and organ systems in children, but it also affects a developing CNS. Research has shown that HIV can enter and replicate within the immature CNS early in its infection (Davis et al., 1992). In fact, HIV has been found in the CNS of aborted fetuses of HIV+ mothers as early as 15 weeks of gestation (Lyman et al., 1990). HIV impacts the development of the CNS in perinatally infected children and can result in neurocognitive deficits (Armstrong et al., 2004). Neurocognitive deficits in these children are particularly important to address, as these deficits can directly impact academic functioning (Armstrong et al., 1993). Since

pediatric HIV is now considered a chronic disease, it is imperative that research focus on neurocognitive deficits because adequate academic functioning ultimately affects vocational functioning as these children enter adulthood.

The Neurodevelopmental Model

The impact of HIV on the developing CNS and the resulting neurocognitive deficits are best understood when considered within a neurodevelopmental framework. In their book chapter entitled "HIV and AIDS in Children and Adolescents," Armstrong, Willen, & Sorgen (2004) delineate seven factors that impact neurocognitive deficits in individual children with HIV. These factors are: 1. Medical factors (viral load and CD4 counts) 2. Age of infection 3. Whether CNS damage was an isolated event or a consequence of prolonged CNS disease, 4. Whether and when HAART therapy was initiated, 5. Time interval between CNS damage and assessment of function, 6. Age of child at time of assessment, 7. Neurocognitive abilities the child should have developmentally acquired at the time an assessment is conducted. Taken together, these factors represent components of a complex neurodevelopmental model that elucidates the expression of neurocognitive deficits in HIV+ children. It is clear that each infected child presents with different combinations of these factors, which can influence the development of the CNS. As a result, the clinical neurological and neurocognitive manifestations of impaired CNS development will vary from child to child, based on these factors. Furthermore, neurocognitive deficits can emerge in these children at different time points. Thus, results of serial neurocognitive assessments of these children can vary (Armstrong et al., 2004). In order to capture the emergence of deficits over time, the current study examined serial neurocognitive assessments. Before reviewing the

possible neurocognitive manifestations based on age group, it is important to first review the neurological mechanisms that contribute to impaired CNS development in these children.

Neurological Mechanisms

The exact mechanisms by which HIV affects neurons are unclear. However, some models have been proposed to explain how neuronal cell damage occurs in HIV-infected individuals. HIV's effect on neurons is probably indirect (Mitchell, 2001). HIV is not found in neurons, but rather microglia and brain derived macrophages (Mitchell, 2001). It has been proposed that HIV is carried across the blood-brain barrier by HIV-infected macrophages in peripheral blood (Levy, 1993). HIV-infected CNS macrophages have been identified and these infected macrophages may release toxic factors that may lead to demyelination of neurons (Epstein & Gendelman, 1993) and damage to white matter in the brain (Mintz, 1999; Mitchell, 2001). It is also hypothesized that genetically programmed cell death (apoptosis), is a mechanism by which HIV damages neurons. Certain cytokines that have been shown to promote apoptosis have been found in the cerebral spinal fluid (CSF) of HIV+ patients with encephalopathy (Griffin, 1997). Although the mechanisms by which HIV affects the CNS are not exactly known, it is clear that HIV+ children's CNS is susceptible to damage. The damage to neurons during CNS development can eventually lead to cerebral atrophy, ventricular enlargements, calcifications of the basal ganglia, cerebellum, and subcortical frontal white matter, cerebral atrophy associated with a reduction in white matter, and demyelination (Mintz, 1999). These early changes within the CNS, in addition to other CNS-related events such

as vascular injury and/or secondary infections that can occur during childhood can lead to clinical abnormalities over time (Mintz, 1999; Mitchell, 2001).

Environmental Factors

A variety of environmental factors such as poverty, prenatal drug exposure, maternal education, and changes in caregivers may also contribute to impaired neurocognitive functioning in HIV+ children. There are robust findings indicating that these environmental factors can impact cognitive development in HIV- children (Bornstein & Bradley, 2003; Bradley & Corwyn, 2002; Sameroff, 1998; Sternberg & Grigorenko, 2001). However the impact of these factors on HIV+ children is less clear. Because of HIV's effect on early CNS development, it is difficult to specify the differential effects of environmental factors in HIV+ children. Therefore, it is imperative that research examining neurocognitive functioning in these children includes these factors in their analyses. Ideally, researchers should compare neurocognitive functioning in HIV+ children to HIV- children who are matched on these environmental factors. However, very few studies have examined data in this way (i.e., Gay et al., 1995). Throughout the following review, studies that take into account environmental factors will be noted. Unfortunately, many studies do not describe these factors in their analyses.

Neurocognitive Manifestations

Perinatal vs. Transfusion Transmission

Many studies have examined the neurocognitive effects of pediatric HIV infection. Overall, the results have shown that deficits in neuropsychological functioning exist in this population (Wachsler-Felder & Golden, 2002). It is important to note that the earlier studies examined neurocognitive functioning in both transfusion-infected and

perinatally infected HIV+ children. However, the neurocognitive effects of HIV infection in these two groups vary. As previously described, HIV impacts developing and possibly more vulnerable neural cells in perinatally infected children, with developmental and functional changes occurring in the developing CNS. Because transfusion-infected children do not experience the effects of HIV on the developing CNS in the same way, their neurodevelopmental profile differs from perinatally infected children. Some research has found that the period of time prior to noticeable cognitive decline is longer in transfusion-infected children compared to perinatally infected children (i.e., Cohen et al., 1991). Studies have shown that overall, transfusion-infected children exhibit less severe neurocognitive deficits than perinatally infected children (Englund et al., 1996; Stehbens et al., 1997). Since the neurodevelopmental trajectories for perinatal and transfusion-infected children differ, and the objective of the proposed study is to examine neurocognitive functioning in only perinatally infected children, the subsequent review of the literature will focus on those studies which only examined perinatally infected children. Based on the neurodevelopmental model, neurocognitive deficits can emerge over time and thus, it is important to delineate these deficits by age group.

Infants

Much of the research examining the neurocognitive effects of pediatric HIV has been conducted with infants. Many of the early studies examined neurocognitive development and functioning in untreated or minimally treated perinatally infected infants in their first 24 months of life and compared functioning in these infants to HIV seroreverters, infants who initially displayed HIV antibodies that disappeared, and HIV- infants who have never been exposed to HIV. Overall, these studies found significant

differences in neurocognitive functioning between these groups. The HIV+ groups generally displayed slower cognitive and motor development than the HIV- groups, with specific deficits in language, gross and fine motor, and cognitive development (Aylward et al., 1992; Gay et al., 1995; Nozyce et al., 1994). In one study, these effects were seen even when controlling for prenatal drug exposure (Gay, et al., 1995), indicating that HIV infection contributes to neurocognitive decline above and beyond prenatal drug exposure. These natural history studies confirmed that cognitive impairment exists in untreated or minimally treated infants. This point is important to note in relation to the present study because these findings serve as a comparison to the present study's sample of HAART-treated children.

Children

As infants with HIV are surviving into childhood, more studies are now conducted on children who are preschool and school aged. Severe deficits in global neurocognitive functioning are not seen overall, but functional deficits in areas, such as processing speed, memory, motor skills, visual-spatial and perceptual organization, language development, and executive functioning have been identified (see reviews in Armstrong et al., 2004; Wachsler & Golden, 2002). Based on the literature, it is evident that HIV+ children are susceptible to deficits in most areas of neuropsychological functioning. However, a few recent studies of HIV+ children on HAART have consistently found more specific areas of deficits in visual-spatial abilities, processing speed, fine-motor skills, and aspects of executive functioning (Martin et al., 2005; Smith et al., 2006). Because all of these functions are crucial to success in school, HIV+ children are frequently referred to special education (Mialky et al., 2001). Even though

these functional deficits are subtle, they clearly impact school functioning and research examining the development of these specific deficits over the lifespan is needed.

Adolescents and Young Adults

As children with HIV are entering adolescence and early adulthood, some researchers have hypothesized that perinatally infected adolescents and young adults will exhibit neurocognitive impairment similar to that seen in HIV+ adults (Melton, Kirkwood, & Ghaemi, 1997). These adolescents and young adults can be considered long-term survivors and some of them experienced significant neurological deficits prior to the onset of antiretroviral therapies. As a result, many of them currently display severe cognitive and motor deficits (Mitchell, 2001). There are no major studies examining long-term neurocognitive functioning in this age group and future studies need to focus on this group of survivors and the long-term neurocognitive outcomes of having HIV. In the present study, adolescent participants up to 16 years of age were included.

Assessment of Neurocognitive Functioning in Pediatric HIV

Wechsler Intelligence Scale for Children –III (WISC-III)

A variety of measures have been used to assess neurocognitive functioning in HIV+ children. One of the most common measures used to provide a global estimate of neurocognitive functioning is the WISC (Wechsler, 1991). The WISC-III has been standardized for children aged 6-16 and exhibits "outstanding" reliability (Sattler, 2001). The WISC-III consists of 13 subtests that in turn make up the Verbal Intelligence Scale (VIQ) and Performance Intelligence Scale (PIQ). The VIQ and PIQ together make up the Full Scale IQ (FSIQ). Many studies that have examined neurocognitive functioning have

used the WISC as an assessment tool (i.e., Jeremy et al., 2005; Loveland et al., 2000; Pearson et al., 2000; Raskino et al., 1999). Furthermore, many of the subtests of the WISC-III measure skills in which children with HIV demonstrate deficits in. Therefore, the WISC was also used in the present study as a measure of neurocognitive functioning.

Table 1 is derived from information provided by Sattler's (2001) book entitled "Assessment of Children: Cognitive Applications" and it details the specific functions purported to be measured by each subtest on the WISC-III. As previously stated, there is recent emerging evidence (Martin et al., 2005; Smith et al., 2006) which indicates that HIV+ children in the post-HAART era may experience more significant deficits in visual-spatial, processing speed, fine-motor skills, and areas of executive functioning, which are areas measured by the PIQ subtests. Therefore, the present study focused on analyzing the specific areas of cognitive functioning measured by the PIQ of the WISC-III. Based on initial results further exploratory analyses with the VIQ were conducted when relevant.

HAART and Its Effect on Neurocognitive Functioning

Background

HAART is the most recent and effective treatment for HIV+ adults and children. The Center for Disease Control (CDC) defines HAART as an "HIV treatment regimen consisting of combinations of drugs that have been shown to reduce the amount of HIV virus in a patient's blood." (www.cdc.gov). The NIH Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (2004) recommends HAART for perinatally infected infants, children, and adolescents. These guidelines state that the use

of dual Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs), which are a class of ART, are the "backbone" of HAART in both adults and children. In addition, they recommend the use of a combination of NRTIs along with a Protease Inhibitor (PI), among other possible drug combinations.

The institution of HAART in developed nations in 1996 has led to significant decreases in morbidity and mortality in HIV+ individuals (Palella et al., 1998). This treatment has been very successful and the increased use of HAART with perinatally infected infants and children has led to increased longevity in this population (de Martino et al., 2000). However, successful HAART relies on multiple factors.

Adherence

Adherence to HAART's complex pill-taking regimen is crucial for HAART's success (Arnsten et al., 2001). The NIH Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection also emphasizes that success on HAART requires rigorous adherence to its demanding treatment regimen (2004). Studies have shown that 50% of children who are more than 75% adherent to combination therapies, such as HAART, non-detectable viral loads can be attained (Watson & Farley, 1999). When HIV+ individuals are nonadherent, immune functioning can be compromised, which leads to the development of opportunistic infections and other symptomatology (Llorente et al., 1997). Overall, these studies have shown that roughly 50-52% of children are more than 75% adherent to combination therapies (Albano et al., 1999; Watson & Farley, 1999). It is clear that adherence to combination therapies such as HAART is imperative, but unfortunately not all patients are able to maintain adequate adherence.

Despite the importance of adherence to antiretroviral therapy in treating pediatric HIV, there are only a few studies that examine adherence rates in this population. A literature review conducted by Steele & Grauer (2003) notes there are very few published research studies examining adherence in pediatric HIV. They further state that because of the wide variety of assessment methods used in the thirteen studies they reviewed; it is difficult to draw any general conclusions about adherence in this population. Some researchers in the field maintain that the lack of knowledge about the predictors and correlates of adherence to antiretroviral therapy in children inhibits interventions to improve adherence with HIV+ children (Byrne, Honig, Jurgrau, Hefferman, & Donahue, 2002). It is clear that the study of pediatric adherence to HAART is in its infancy. Due to the lack of research and inconsistent measurements, most studies in the pediatric HIV field do not include measures of adherence in their analyses. This is a major limitation of studies examining neurocognitive functioning in children on HAART. Similar to other studies of neurocognitive functioning in pediatric HIV, the proposed study will not have access to adherence rates either. This is a significant limitation of this study and the relevance of this limitation will be discussed in detail.

Neurocognitive functioning in children receiving HAART

It has been hypothesized that some of the drugs used in HAART regimens (i.e., zidovudine [ZDV]) penetrate CSF and consequently, may provide patients with protection against CNS-related difficulties (Portegies, 1995). ZDV is classified as an NRTI and can be used in HAART regimens. Other HAART medications (protease inhibitors) may not penetrate CSF as effectively (Robertson, 2004). Research examining the effectiveness of various types of HAART medications on improving and/or

preventing neurocognitive decline in children is mixed. Some studies have found that children who receive continuous infusion of ZDV demonstrate improved neurocognitive functioning (Brouwers et al., 1990; DeCarli et al., 1991; Pizzo et al., 1988). But, another study did not find the same improvement when children received ZDV orally (Nozyce et al., 1994). Other studies discovered that combined treatment with ZDV and didanosine (ddI), which is also classified as an NRTI, was more effective in increasing neurocognitive functioning than either drug alone (England et al., 1997; Raskino et al., 1999). It is important to note that ZDV and ddI are not the only NRTIs prescribed with HAART. The effects of other NRTIs (i.e., ritonavir) and protease inhibitors on neurocognitive functioning in children have only very recently been explored.

A recent study conducted by Jeremy et al., (2005) was the first to examine the long-term effects of HAART (antiretroviral therapy containing a PI) on neurocognitive functioning in children who are treatment-experienced. Children in this study (n = 489; aged 4 months – 17 years) had been treated with HAART for at least 16 weeks before entry to the study. Neuropsychological functioning at baseline was significantly poorer than established norms for their age, and children with higher viral load exhibited poorer cognitive functioning. After 48 weeks of HAART, the Vocabulary score of the WISC-III was the only cognitive test to demonstrate significant improvement from baseline. The authors hypothesized that perhaps 48 weeks was not a long enough period to detect neurocognitive improvements in this sample.

Because the current standard care for HIV+ children is HAART, it will be difficult to investigate neurocognitive functioning in children who have never received HAART. Therefore, the Jeremy et al., (2005) study is very important because it examines

neurocognitive functioning in the current population who has already been exposed to HAART. This study provides a foundation for the first objective of the study which was to examine whether or not children receiving HAART displayed improvement in neurocognitive functioning over time.

Further research examining the effect of HAART on neuropsychological functioning in children on HAART is needed. There are no known studies that examine long-term cognitive functioning in children receiving HAART for longer than 48 weeks. As suggested by Jeremy et al., (2005), it is possible that neurocognitive improvements after HAART may appear after 48 weeks. This hypothesis is consistent with the neurodevelopmental model, which proposes that neurocognitive functioning is influenced by a variety of factors and that changes in neurocognitive functioning can emerge at different time points. Based on this model and the previously reviewed research demonstrating that children receiving HAART may demonstrate improvements in neurocognitive functioning, this study examined neurocognitive functioning over time with an average of 1.6 years between the 3 WISC-III administrations.

Neurocognitive Functioning, Immune Functioning, and Disease Progression

Prior research indicates that neuropsychological impairment in HIV+ children is associated with lower CD4+ lymphocyte counts and higher viral loads (i.e., Brouwers et al., 1995; Loveland et al., 2000; Jeremy et al., 2005), and these two markers are associated with increases in disease progression and earlier death (Blatt et al., 1995; Bamji et al., 1996; Phillips et al., 1996; Ullum et al., 1997; Hoots et al., 1998; Palumbo et al., 1998). It is apparent that neuropsychological functioning and immune functioning are

linked. However, there have only been a few studies examining the relationship between neuropsychological functioning, immune functioning, and disease progression in the pediatric HIV population.

One important study examined neuropsychological performance over a period of four years in 333 boys, aged 6-19, with hemophilia who became infected via blood transfusion (Loveland et al., 2000). The authors sought to determine whether declines in immune functioning were associated with changes in neuropsychological performance in this sample. Results indicated that the group with the lowest CD4 counts (average of first two and last two CD4 counts <200) showed the greatest decline in performance on tests of nonverbal intelligence, perceptual skills, nonverbal memory, academic achievement, and language over time. This classification of the sample by CD4 counts takes into account immune functioning at the beginning and end of the four year period, but prior immune functioning was not taken into account. Although there are no known studies that take into account prior immune functioning when exploring neurocognitive functioning, it can be hypothesized that prior immune functioning may be predictive of later neurocognitive functioning, which was the second objective of the present study.

The results of the Loveland et al. (2000) study demonstrate the significance of studying the effect that poor immune functioning may have on neuropsychological functioning. However, the sample examined in this study does not reflect the current pediatric HIV+ population. This HIV+ sample was infected through exposure to blood products at some point during their life. Unlike perinatally infected children, it can be assumed that their CNS developed normally during pregnancy, delivery, and until infection at some point after birth. It is not clear if these results generalize to perinatally

infected children with abnormal CNS development. It is also unclear if the results of this study would differ for children on HAART. Thus, future studies need to examine the relationship between immune functioning and neuropsychological functioning in a more representative sample of the current pediatric HIV population, which is receiving HAART.

Pearson et al. (2000) conducted another important study that examined the usefulness of neuropsychological testing in predicting HIV disease progression in symptomatic HIV+ infants, children, and adolescents after standard biological markers (absolute CD4 counts, plasma HIV RNA load, and age) were taken into account. Ninety percent of the participants in this study were perinatally infected and 92% of the participants had never received anti-retroviral treatment prior to entry into the study. The participants ranged in age from three months to >16 years of age. The authors hypothesized that poorer performance on neuropsychological tests would be associated with a greater risk of HIV disease progression as measured by clinical endpoints (a significant decline in neurocognitive scores, 2 or more opportunistic infections, weight-growth failure, failure of brain growth or cortical atrophy, deterioration in motor functioning, malignancy, or death). Analyses were conducted across age groups, type of treatment, and mode of transmission. Before this study, the clinical endpoints used to determine disease progression in this study had not been used in any other known studies to define disease progression.

Results showed that children with the lowest neuropsychological functioning (IQ<70) at baseline had the highest risk for later HIV disease progression. Baseline neuropsychological functioning did not predict disease progression above and beyond

age, CD4 counts, and viral load. However, week 48 neuropsychological score was a significant predictor of disease progression and remained a significant predictor when it was entered into a multivariate model with CD4 count, viral load, and age. This finding is extremely important, because it is the first study to demonstrate that neuropsychological functioning can contribute significantly to the prediction of disease progression in children, even when absolute CD4 counts and viral load are taken into account.

The authors also examined whether baseline and week 48 verbal and nonverbal ability scores each predicted disease progression. The VIQ and PIQ scores were used to measure verbal and nonverbal abilities respectively, on the WISC-R and WAIS-R. They found that neither baseline nor week 48 verbal and nonverbal scores were significant predictors of disease progression. These results indicate that measures of more specific skills (i.e., VIQ & PIQ) are less sensitive in predicting disease progression than global measures of functioning (i.e. FSIQ scores). In their conclusion, Pearson et al. indicated that their sample size for analyzing the differences between the predictive values of verbal versus nonverbal functioning was limited. Future research needs to examine this question with larger sample sizes, a more focused population, and a more representative sample of the current pediatric HIV population. The present study attempted to examine this question of whether specific skills (PIQ) are sensitive in predicting disease progression.

Clinically, the Pearson et al. study is extremely important because it indicates that serial neuropsychological testing may provide clinicians with information that can assist them in predicting disease progression in HIV+ children. However, because the authors did not differentiate between age groups, type of treatment, and mode of transmission in

their analyses, it is unclear if these results would differ if these groups were analyzed separately. Since the standard treatment for HIV+ children is now HAART, it is not known how these results would differ for children who were exposed to HAART at baseline.

Methodological Problems in the Pediatric HIV Literature

In their extensive literature review of the neuropsychological consequences of HIV in children, Wachsler-Felder & Golden (2002) discuss specific methodological problems that exist in the literature. Overall, methodological problems include limited sample sizes, broad age ranges, different tests, and populations (transfusion-acquired and perinatally-infected), and not addressing practice effects. One of the most important recommendations these authors make is that future studies examine specific age groups with the same tests, so that interpretation is clearer and more accurate. The present study took this recommendation into account and consequently focused only on school-aged children whose IQ was measured by the WISC-III. Future studies should take these methodological suggestions into consideration when examining neuropsychological functioning in children with HIV.

Conclusions

Based on the literature reviewed thus far, it is apparent that more research examining neurocognitive functioning in the current pediatric HIV population, which is primarily perinatally infected and on HAART, is needed. It is currently not known if HIV+ school-aged children on HAART are at risk for cognitive decline, whether immune

functioning is predictive of cognitive functioning, or whether cognitive impairment can predict disease progression in this population. This study attempted to improve upon methodological problems seen in previous studies by focusing on a more specific population in terms of age, mode of transmission and cognitive test used to assess for cognitive functioning. Based on the reviewed literature, the following hypotheses were proposed:

Hypotheses

1. Poorer immune status at the first time point will predict lower subsequent PIQ scores.
2. Overall, PIQ scores will improve over time.
    a. Children with a history of poor immune functioning will not demonstrate improvement in PIQ with HAART.
3. Children with the lowest cognitive functioning will have the greatest risk for disease progression over time.

Methods

Participants

This study utilized data from an already existing IRB-approved protocol entitled, "Neurodevelopmental Effects of HIV in Preschool and School Age Children" led by Dr. F. Daniel Armstrong. This larger study was supported by a Ryan White Title IV grant. Participants in this larger study were a group of perinatally infected HIV+ patients recruited from the Pediatric Special Immunology clinic at the Batchelor Children's Research Institute of Jackson Memorial Hospital. Since the mid-1990s, over 400 of these patients have been administered neurodevelopmental assessments, which include a WISC-III, on a semi-annual basis as a part of their clinical care. The ethnic/cultural background of this population is diverse and includes those who are African-American, of Haitian descent, and Hispanic background. Virtually all participants are of low socioeconomic status.

Participants for this study consisted of a subsample of the larger study's sample of over 400 patients. Inclusion criteria were age to 6 and 16 years, prescription of a HAART regimen for at least 16 weeks, and a minimum of 2 valid WISC-III evaluations since HAART initiation. The shortest interval between WISC-III evaluations was 6 months, with an average of 1.72 years (SD = 0.89) between the first and second evaluation and an average of 1.61 years (SD = 0.52) between the second and third evaluation.

Procedure

In the larger study, a research assistant explains the study and obtains written informed consent from the caregivers of all the children in this cohort. All participants

were informed that obtained information is confidential and that no identifying information will be attached to their responses. Since participants were administered a battery of tests assessing neurodevelopmental functioning on a semi-annual basis, each participant varied in terms of the number and time between neurodevelopmental assessments. Demographic information was obtained through an interview with caregivers. Relevant medical data (described below) was retrospectively gathered from the participants' medical charts.

In the present study, WISC-III scores were obtained from the participants' semi-annual neurodevelopmental assessment report. Demographic information was obtained by examining existing interview forms from caregivers. Relevant medical data was obtained from the child's medical chart and included absolute CD4 counts, CD4%, CD4% category, viral load, undetectable/detectable viral load, CDC classifications, history of encephalopathy, and age at start of HAART. Immune markers were included if they were dated within a six week window period of the administration of the WISC-III.

Measures

Measure of Cognitive Functioning

Wechsler Intelligence Scale for Children – III (Wechsler, 1991): The WISC-III is the intelligence scale for children (ages 6-16) within the Wechsler series, and was the most widely used measure of intellectual functioning in children at the time of data collection. The WISC-III is administered on an individual basis and is a test of intellectual functioning that produces a norm-referenced Full-Scale Intelligence Quotient (FSIQ), as well as a Verbal Intelligence Quotient (VIQ) and a Performance Intelligence

Quotient (PIQ). There are a total of 11 subtests that assess different types of verbal abilities (Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span) and nonverbal abilities (Picture Completion, Object Assembly, Block Design, Picture Arrangement, Coding, Mazes). In this study, Mazes was not administered to participants. The WISC-III has shown to be psychometrically sound (Sattler, 2001). Average internal consistency reliability coefficients are .96 for the FSIQ, .95 for the VIQ, and .91 for the PIQ (Sattler, 2001; Wechsler, 1991). The average internal consistency reliability coefficients for the subtests range from .69-.85. Studies have shown that the WISC-III has satisfactory criterion and construct validity (Sattler, 2001). As previously stated, the current study focused primarily on the long-term PIQ functioning in this population. In this study, the WISC-III was administered to patients on roughly a 1-1 ½ year basis to monitor cognitive functioning over time.

Immune/Medical Measures

Absolute CD4 counts: The CD4 count provides an estimate of the immunologic status of the patient, and therefore, is an excellent marker of the immediate risk of opportunistic infection. Lower CD4 counts indicate faster HIV disease progression. Because absolute CD4 was not normally distributed in this sample, a square root transformation was conducted. The square root transformed absolute CD4 count (sqCD4) was analyzed as a continuous variable.

CD4 Lymphocyte Percentage: CD4 percentage (CD4%) is a marker of disease progression in HIV-infected children. It measures the percentage of CD4-positive T lymphocytes compared with the total number of lymphocytes in peripheral blood. CD4%

is less subject to intrapatient variation and age-related change than absolute CD4 count (Raszka, et al., 1994). CD4% was analyzed as a continuous variable.

CD4% Category (<25 or ≥25): The CD4% category has been used as a clinical marker of health status in HIV+ children. CD4% <25 have been described as immune suppressed, while CD4% ≥25 is in the normal range. In recent studies, it has been useful in classifying children at risk for disease progression (i.e., Resino, et al., 2006). CD4% category was analyzed as a categorical variable.

Viral Load: The viral load test measures the amount of HIV particles in one's peripheral blood. Viral load can help predict how long someone will stay healthy. A higher viral load indicates faster HIV disease progression. Over the course of time, different assays were used for quantifying viral load in the larger study. Since children were not evaluated at the same time, it was not possible to report the specific assay used at each time point. Of all the assays used over time in the larger study, the largest limit of quantification was 400. Values below 400 were replaced by 399. Viral load was not normally distributed, so a natural log transformation was conducted with viral load counts. All analyses in this study used the natural log transformation of viral load (logVL) and logVL was analyzed as a continuous variable.

CDC Classifications: This is a clinical classification of disease status (as opposed to immunological) used in pediatric HIV infection, whereby classification is based primarily on the occurrence of certain signs, symptoms, and illnesses which precipitates deterioration of the immune system (CDC, 1994). To meet criteria for classification, these occurrences must be attributable to HIV infection. The categories are as follows:

N: Not symptomatic – Includes children who have no signs or symptoms considered to be the result of HIV infection, or one mild symptom such as enlarged lymph nodes.

A: Mildly Symptomatic – Includes children with two or more milder conditions such as enlarged lymph nodes/spleen or dermatitis.

B: Moderately Symptomatic – Includes children with conditions such as anemia, bacterial meningitis, cardiomyopathy, and chronic diarrhea.

C: Severely Symptomatic – Includes children with multiple or recurrent serious bacterial infections such as pneumonia, septicemia, and meningitis, or the presence of an opportunistic infection, or cancer.

Statistical Analysis

An alpha level of .05 was used for all statistical tests. For all preliminary analyses, Pearson's correlations were conducted to assess relationships between continuous independent and dependent variables, and potential covariates. Independent samples *t*-tests and ANOVAs were conducted to assess relationships between continuous and categorical independent and dependent variables, and potential covariates. Chi-square analyses were used to evaluate relationships between categorical independent and dependent variables and potential covariates. Descriptions of the overall study population will be reported at the beginning of the Results section. Results of preliminary analyses for each hypothesis will be reported by hypothesis.

Because of the exploratory nature of this study, corrections for Type I error were not made for multiple comparisons. However, attempts were made to minimize

comparisons when possible. For example, further PIQ subtest analyses were not conducted unless significant findings were found at the PIQ index level. Additional steps to minimize Type I error will be discussed by hypothesis. Specific analyses used to test each hypothesis will also be discussed.

Hypothesis #1

It was hypothesized that children with poorer immune status at the first time point would exhibit lower PIQ standard scores at the second and third time points (PIQ2 and PIQ3). This hypothesis was examined by analyzing baseline immune functioning in both a continuous and categorical fashion to determine which measure of immune status was most predictive of PIQ standard scores and PIQ subtest scaled scores. LogVL was chosen as a continuous estimate of immune status at the first time point. CD4% category was chosen as a categorical estimate of immune status at the first time point.

To assess the specific hypotheses concerning the relationships between immune status at the first time point and PIQ2 and PIQ3, hierarchical multiple regression analyses were conducted. Hierarchical multiple regression was chosen because it is possible to examine the change in variance accounted for by each step in the regression equation. Independent variables (logVL and CD4% category at the first time point) that were significantly correlated with dependent variables (PIQ2, PIQ3) were then used as the predictor variables in the hierarchical multiple regression analyses. In order to minimize Type I error, hierarchical multiple regression analyses between independent variables and PIQ2 and PIQ3 subtests were only conducted if the independent variable added significant incremental variance to the prediction of PIQ2 and/or PIQ3. Demographic

variables with significant correlations with PIQ2 and PIQ3 and respective subtests were used as covariates in analyses predicting that respective PIQ or PIQ subtest.

Hypothesis #2

It was hypothesized that children with a history of poor immune functioning would not demonstrate an improvement in PIQ over time. To test this hypothesis, the effects of a categorical measure of immune functioning on changes in PIQ over time were examined by conducting a repeated measures ANOVA with time (PIQ at times 1, 2, and 3) as a within-subjects variable and CD4% category as a between-subjects variable. To minimize Type I error, further exploratory repeated measures ANOVAs were conducted to examine changes in PIQ subtests over time only if significant overall results across PIQ at times 1, 2, and 3 were found.

For all analyses, group x time interactions were examined first to establish whether PIQ scores (or PIQ subtest scores) differ across time as a function of CD4% category. In order to decrease potential Type I error, further simple effects analyses were conducted only when a significant group x time interaction was obtained.

To determine inclusion of covariates, repeated measures ANOVAs were conducted with potential covariates as between-subjects variables and PIQ across the three time points as the within-subjects variables. Results of these analyses are reported in the results section.

Hypothesis #3

It was hypothesized that PIQ standard scores at the first time point (PIQ1) would predict disease progression in HAART-experienced HIV+ children. More specifically, it was hypothesized that lower PIQ1 would be associated with more severe disease

progression as indicated by a CDC classification of category C at time of follow-up. To test this hypothesis, a hierarchical logistic regression analysis was conducted with CDC classification (coded as 0 = CDC classification of N, A, or B categories and 1 = classification of C category) as the categorical dependent variable with relevant baseline covariates entered in Block 1 and PIQ1 entered in Block 2 as predictor variables.

Independent samples *t* tests were conducted between relevant demographic and health-related variables and CDC classification to determine relevant covariates to be entered in Block 1 of the model. Additional independent samples *t* tests were also conducted to explore the relationships between PIQ1 subtests and VIQ1 with CDC classification. Exploratory hierarchical logistic regressions were conducted based on the results of these *t* tests.

Results

Overall Demographic, HIV-Related, and IQ Information

Table 2 reports demographic and HIV-related variables for the overall sample. Table 3 reports demographic and HIV-related variables by time point. Table 4 reports FSIQ, PIQ, VIQ, and subtest standard and scaled scores by time point.

Hypothesis #1

Preliminary Analyses

Pearson correlations were conducted to evaluate relationships between dependent and demographic variables (PIQ2, PIQ3, and respective subtests) and relevant continuous demographic variables (age and months on HAART at second and third time points) to determine the presence of any covariates to include in the regression models. Results revealed no significant relationships between PIQ2, PIQ3, and respective subtests with age or months on HAART at the second and third time points.

Independent samples t-tests were conducted to assess for significant relationships between PIQ2, PIQ3, and relevant subtests and gender and history of encephalopathy. Results revealed that PIQ2, PIQ3, and relevant subtests means did not differ by gender or history of encephalopathy.

One-way ANOVAs were conducted to test associations between PIQ2, PIQ3, and relevant subtests and income level, language, and ethnicity. There were no significant differences in PIQ2 scores across income levels, language, and ethnicity. Further, PIQ3 scores were not significantly different among income level categories.

However, a one-way ANOVA indicated significant differences in PIQ3 across the three ethnic groups F (2, 34) = 4.714, $p<.05$, $eta^2 = 0.22$. Hispanics scored highest on

PIQ3 (M = 95.73, SD = 14.32), followed by Haitian-Americans (M = 94.33, SD = 18.56) and African-Americans (M = 77.26, SD = 18.63). To assess pairwise differences among these ethnic groups, for the main effect of PIQ3, a Tukey follow-up procedure was performed. Results indicated that PIQ3 scores in Hispanic children were significantly higher than PIQ3 scores in African-American children ($p<.05$).

Based on this finding, one-way ANOVAs were also conducted to evaluate differences in PIQ3 subtest scaled scores across the three ethnic groups. Significant differences were found in Block Design scaled scores at time 3 (BD3) and Object Assembly scaled scores at time 3 (OA3) by ethnicity, F (2, 35) = 4.08, $p<.05$, $eta^2 = 0.19$ and F (2, 35) = 11.21, $p<.001$, $eta^2 = 0.39$, respectively. Hispanic children scored the highest on BD3 and OA3 (M = 9, SD = 2.1; M = 10, SD = 2.49, respectively), followed by Haitian-American children (M = 7, SD = 4.58; M = 9.67, SD = 2.08, respectively), and African-American children (M = 5.42, SD = 3.80; M = 5.08, SD = 3.32, respectively). To assess pairwise differences among these ethnic groups for the main effects of BD3 and OA3, the Tukey follow-up procedure was performed. Results indicated that Hispanic children scored significantly higher than African-American children on BD3 and OA3 ($p<.05$). These results are unexpected and possible explanations for this finding will be elaborated in the discussion section.

A one-way ANOVA also indicated significant differences in PIQ3 across the three language groups F (2, 35) = 6.05, $p<.01$, $eta^2 = 0.31$. Bilingual Spanish/English children scored highest on PIQ3 (M = 96.27, SD = 14.06), followed by Bilingual Creole/English (M = 94.59, SD = 17.48) and African-Americans (M = 76.53, SD = 18.64). To assess pairwise differences among the three language groups, for the main

effect of PIQ3, the Tukey follow-up procedure was performed. The results indicated that PIQ3 scores in bilingual Spanish/English children were significantly higher than PIQ3 scores in monolingual children ($p<.05$).

Based on this finding, one-way ANOVAs were also conducted to assess for differences in PIQ3 subtest scaled scores across the three language groups. Results indicated significant differences in Block Design scaled scores at time 3 (BD3) and Object Assembly scaled scores at time 3 (OA3) across language groups, F (2, 37) = 8.48, $p<.01$, $eta^2 = 0.36$ and F (2, 37) = 8.15, $p<.001$, $eta^2 = 0.41$, respectively. There were also significant differences in Picture Arrangement at time 3 (PA3) and Symbol Search at time 3 (SS3) across language groups, F (2, 37) = 3.27, $p<.05$, $eta^2 = 0.21$ and F (2, 37) = 3.28, $p<.05$, $eta^2 = 0.21$, respectively. Bilingual Spanish/English children scored the highest on BD3, OA3, PA3, and SS3 (M = 9.5, SD = 2.12; M = 10, SD = 2.49; M = 9.6, SD = 3.2; M = 9.4, SD = 2.97, respectively), followed by bilingual Creole/English children (M = 7.8, SD = 5.3; M = 8.0, SD = 3.1; M = 8.8, SD = 3.6; M = 9.1, SD = 2.82, respectively), and African-American children (M = 5.03, SD = 3.58; M = 5.33, SD = 3.57; M = 6.6, SD = 4.32; M = 6.62, SD = 3.4, respectively). To assess pairwise differences among the three ethnic groups for the main effects of BD3, OA3, PA3, and SS3, the Tukey follow-up procedure was performed. Results indicated that bilingual Spanish/English children scored significantly higher than monolingual children on BD3, OA3, PA3, and SS3 ($ps<.05$). These results are unexpected and possible explanations for this finding will be elaborated in the discussion section.

It was hypothesized that children with higher logVL at time 1 would perform significantly lower on PIQ2 and PIQ3. Pearson correlations were conducted to determine

the associations between baseline logVL and PIQ2 and PIQ3. Results revealed significant negative correlations between logVL and PIQ2 and PIQ3 ($r = -.26$, $p<.05$; $r = -.43$, $p<.01$), suggesting that children who had higher viral load at the first time point obtained lower PIQ scores at the second and third time points. This result is consistent with the hypothesis.

Hierarchical Regression Analyses of baseline logVL predicting PIQ2 and PIQ3

In the regression predicting PIQ2, PIQ1 was entered in the first block as a covariate to take into account baseline functioning. Baseline logVL was entered in the second block. The results of this regression are presented in Table 5. The overall model significantly predicted PIQ2, $F(2, 69) = 86.12$, $p<.001$, explaining 71.4% of the variance. In the first step of the regression model, PIQ1 was a significant predictor of PIQ2, explaining 70% of the variance ($p<.001$). Baseline logVL did not significantly contribute to the prediction of PIQ2 and accounted for 1.4% of unique variance. This finding is inconsistent with the hypothesis. Because logVL did not add significant incremental variance to the prediction of PIQ2, further hierarchical regressions with logVL predicting PIQ2 subtests were not conducted.

Two separate hierarchical regression models were conducted to determine the relative contribution of baseline logVL in the prediction of PIQ3. As previously stated, both ethnicity and language are significantly correlated with PIQ3. Ethnicity and language are also significantly correlated with each other ($X^2 = 105.74$, $p<.0001$). Due to the collinearity between these two predictor variables, they were not entered together in the same model. Instead, these variables were entered as covariates with logVL in separate regression models predicting PIQ3.

In the first model predicting PIQ3, PIQ1 was entered in the first block as a covariate, to account for baseline PIQ functioning. Ethnicity was entered in the second block and baseline logVL was entered in the third block. The results of this regression are presented in Table 6. The overall model significantly predicted PIQ3, $F(3, 31) = 29.2$, $p<.001$, explaining 73.9% of the variance. In the first step of the regression model, PIQ1 was a significant predictor of PIQ3, and explained 68.2% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 32) = 41.17$, $p<.001$. In this step, ethnicity significantly contributed to the prediction of PIQ3 and uniquely accounted for 3.8% of the variance ($p<.05$). In the third step, logVL did not significantly contribute to the prediction of PIQ3 and only uniquely accounted for 1.9% of the variance. This finding is inconsistent with the hypothesis and suggests that baseline logVL does not significantly contribute to the prediction of PIQ3.

In the second model predicting PIQ3, PIQ1 was entered in the first block, language was entered in the second block, and baseline logVL was entered in the third block. The results of this regression are presented in Table 7. The overall model significantly predicted PIQ3, $F(3, 32) = 33.91$, $p<.001$, explaining 76.1% of the variance. In the first step of the regression model, PIQ1 was a significant predictor of PIQ3, and explained 70.2% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 33) = 46.43$, $p<.001$. In this step, language significantly contributed to the prediction of PIQ3 and uniquely accounted for 3.5% of the variance ($p<.05$). In the third step, logVL did not significantly contribute to the prediction of PIQ3 and uniquely accounted for 2.3% of the variance. This finding is inconsistent with the hypothesis.

Independent Samples t-tests with baseline CD4%< or ≥25, PIQ2, PIQ3, and respective subtests

It was hypothesized that children with baseline CD4<25% would perform significantly lower on PIQ2 and PIQ3. To test this, independent samples t-tests were conducted with baseline CD4 < or ≥ 25% as the grouping variable and PIQ2 and PIQ3 as the independent variables. As was predicted, results indicated that children with baseline CD4 < 25% scored significantly lower on PIQ3 (M = 75.41, SD = 22.33; t = -2.387, p<.05). This finding is consistent with the hypothesis. Contrary to the hypothesis, children with baseline CD4 < 25% did not score significantly lower on PIQ2. Additional independent samples t-tests were conducted with baseline CD4 < or ≥ 25% as the grouping variable and the PIQ3 subtests as the independent variables. Also, consistent with the hypothesis, children with baseline CD4 < 25% scored significantly lower on COD3, OA3, and SS3 (M = 5.29, SD = 2.93; t = -2.94, p<.01; M = 5.35, SD = 4.21; t = -2.14, p<.05; M = 6.24, SD = 3.66; t = -2.28, p<.05, respectively).

Hierarchical regression analyses with baseline CD4 < or ≥ 25% predicting PIQ3, OA3, COD3 and SS3

Similar to the regression models examining the relative contribution of baseline logVL to the prediction of PIQ3 and BD3, two separate hierarchical regression models were also conducted to determine the relative contribution of baseline CD4 < or ≥ 25% in the prediction of PIQ3 and OA3, respectively. As previously stated, both ethnicity and language are significantly correlated with PIQ3 and OA3, and with each other. Due to the potential collinearity between these two predictor variables, they were not entered

together in the same model. Instead, these variables were entered as covariates with CD4 < or ≥ 25% in separate regression models predicting PIQ3 and OA3.

In the first model predicting PIQ3, PIQ1 was entered in the first block as a covariate, as it was significantly related to PIQ3. Ethnicity was entered in the second block and baseline CD4 < or ≥ 25% was entered in the third block. The results of this regression are presented in Table 8. The overall model significantly predicted PIQ3, $F(3, 32) = 38.35$, $p<.001$, explaining 78.2% of the variance. In the first step of the regression model, PIQ1 was a significant predictor of PIQ3, and explained 70.9% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 33) = 46.93$, $p<.001$. In this step, ethnicity did not significantly contribute to the prediction of PIQ3 and uniquely accounted for 3.1% of the variance. In the third step, baseline CD4 < or ≥ 25% significantly contributed to the prediction of PIQ3 and uniquely accounted for 4.3% of the variance ($p<.05$). This finding supports the hypothesis and again indicates the importance of baseline immune functioning in the prediction of PIQ functioning over time.

In the second model predicting PIQ3, PIQ1 was entered in the first block, language was entered in the second block, and baseline CD4 < or ≥ 25% was entered in the third block. The results of this regression are presented in Table 9. The overall model significantly predicted PIQ3, $F(3, 33) = 43.68$, $p<.001$, explaining 79.9% of the variance. In the first step of the regression model, PIQ1 was a significant predictor of PIQ3, and explained 72.7% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 34) = 52.78$, $p<.001$. In this step, language did not significantly contribute to the prediction of PIQ3 and uniquely accounted for 2.9% of the variance. In

the third step, baseline CD4 < or ≥ 25% significantly contributed to the prediction of PIQ3 and uniquely accounted for 4.2% of the variance ($p<.05$). This finding also supports the hypothesis.

In the first model predicting OA3, OA1 was entered in the first block as a covariate, ethnicity was entered in the second block as a covariate, and baseline CD4 < or ≥ 25% was entered in the third block. The results of this regression are presented in Table 10. The overall model significantly predicted PIQ3, $F(3, 32) = 29.28$, $p<.001$, explaining 73.3% of the variance. In the first step of the regression model, OA1 was a significant predictor of OA3, and explained 57% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 33) = 31.53$, $p<.001$. In this step, ethnicity significantly contributed to the prediction of OA3 and uniquely accounted for 8.7% of the variance ($p<.01$). In the third step, baseline CD4 < or ≥ 25% significantly contributed to the prediction of PIQ3 and uniquely accounted for 7.7% of the variance ($p<.01$), providing further support to the hypothesis that poorer baseline immune functioning is predictive of poorer PIQ scores over time.

In the second model predicting OA3, OA1 was again entered in the first block, language was entered in the second block, and baseline CD4 < or ≥ 25% was entered in the third block. The results of this regression are presented in Table 11. The overall model significantly predicted OA3, $F(3, 33) = 29.61$, $p<.001$, explaining 72.9% of the variance. In the first step of the regression model, OA1 was a significant predictor of OA3, and explained 59.7% of the variance ($p<.001$). The second step of the regression model was also significant, $F(2, 34) = 31.08$, $p<.001$. In this step, language significantly contributed to the prediction of OA3 and uniquely accounted for 5% of the variance

(p<.05). In the third step, baseline CD4 < or ≥ 25% significantly contributed to the prediction of PIQ3 and uniquely accounted for 8.3% of the variance (p<.01), which again supports the hypothesis.

In the model predicting COD3, COD1 was entered in the first block as a covariate. Baseline CD4 < or ≥ 25% was entered in the second block. The results of this regression are presented in Table 12. The overall model significantly predicted COD3, $F(1, 37) = 16.76$, p<.001, explaining 44% of the variance. In the first step of the regression model, COD1 was a significant predictor of COD3, and explained 31.2% of the variance (p<.001). In the second step of the model, baseline CD4 < or ≥ 25% significantly contributed to the prediction of COD3 and uniquely accounted for 12.8% of the variance (p<.01). This finding is also consistent with the hypothesis.

In the model predicting SS3, SS1 was entered in the first block as a covariate, language was entered in the second block as a covariate, and baseline CD4 < or ≥ 25% was entered in the third block. The results of this regression are presented in Table 13. The overall model significantly predicted SS3, $F(3, 31) = 8.02$, p<.001, explaining 43.7% of the variance. In the first step of the regression model, SS1 was a significant predictor of SS3, and explained 29.4% of the variance (p = .001). The second step of the regression model was also significant, $F(2, 32) = 8.65$, p = .001. In this step, language did not significantly contribute to the prediction of SS3 and uniquely accounted for 5.7% of the variance. In the third step, baseline CD4 < or ≥ 25% significantly contributed to the prediction of SS3 and uniquely accounted for 8.6% of the variance (p<.05), providing further support of the hypothesis.

Hypothesis #2

Preliminary Analyses

Because PIQ3 scores were significantly correlated with ethnicity and language in the preliminary analyses of Hypothesis #1, ethnicity and language were chosen as potential covariates in the current analyses examining PIQ functioning over time as a function of immune category. To determine whether or not to include ethnicity and/or language in the current analyses as covariates, two separate 3 (group) x 3 (time) repeated measures ANOVAs were conducted to determine if PIQ differed across the three time points as a function of ethnicity or language. Results revealed no significant interactions across time and group for either ethnicity or language ($F(4, 62) = .89$, $p>.4$, $eta^2 = .05$ and $F(4, 64) = 1.74$, $p>.1$, $eta^2 = .09$, respectively). Based on these non-significant findings, ethnicity and language were not included as covariates in analyses for this hypothesis.

Before examining PIQ scores over the three time points as a function of immune category, a one-way repeated measures ANOVA was conducted to determine if PIQ differed across the three time points. PIQ at times 1, 2, and 3 served as the within-subjects variable. Results indicated there were no significant differences in PIQ standard scores across the three time points ($F(2, 70) = .83$, $p>.40$, $eta^2 = .02$). This finding is important to note because it indicates that overall, PIQ does not change over time in this sample.

Repeated Measures ANOVAs Testing PIQ and PIQ Subtests Over Time by CD4% Group

A 2 (group) by 3 (time) repeated measure ANOVA was conducted to test for differences in PIQ scores over time between the CD4% <25 group and the CD4% ≥25

group. The group x time interaction was significant ($F(2, 68) = 3.67$, $p<.05$, $eta^2 = .10$). The simple effect for the CD4% <25 group was significant ($F(2, 32) = 5.4$, $p = .01$, $eta^2 = .25$) indicating that PIQ scores declined significantly over time in children with baseline CD4% less than 25. The simple effect for the CD4% ≥25 group was not significant ($F(2, 36) = .72$, $p>.4$, $eta^2 = .04$).

Exploratory analyses were conducted to examine PIQ subtest scores over time as a function of CD4% group. A series of 2 (group) by 3 (time) repeated measures of ANOVAs were conducted to test for differences in PIQ subtests over time between the CD4% <25 group and the CD4% ≥25 group. For the repeated measure ANOVA testing differences in OA scores over time, the group x time interaction was significant ($F(2, 70) = 6.3$, $p<.01$, $eta^2 = .15$). The simple effect for the CD4% <25 group was not significant ($F(2, 32) = 3.04$, $p = .06$, $eta^2 = .16$). Even though this finding was not significant, it approached significance and an examination of the OA mean scores over time when selecting for children with baseline CD4% <25 shows that OA means appear to decrease over time. The simple effect for the CD4% >25 group was significant ($F(2, 38) = 3.91$, $p<.05$, $eta^2 = .17$), such that OA scores increased significantly over time in children with baseline CD4% greater than or equal to 25.

Five additional 2 (group) by 3 (time) repeated measures ANOVAs were conducted to assess differences in the remaining PIQ subtest scores (PC, BD, PA, COD, and SS), over time between the CD4% <25 group and the CD4% ≥25 group. None of the group x time interactions were significant. Relevant statistics follow by subtest: PC ($F(2, 74) = 1.17$, $p>.3$, $eta^2 = .03$); BD ($F(2, 70) = .39$, $p>.6$, $eta^2 = .01$); PA ($F(2, 36) = .32$, $p>.7$, $eta^2 = .01$); COD ($F(2, 72) = 1.80$, $p>.1$, $eta^2 = .05$); SS ($F(2, 66) = 1.12$, $p>.3$, eta^2

= .03). See Table 14 for means and standard deviations of PIQ and PIQ subtests at times 1, 2, and 3 by CD4% category.

Hypothesis #3

Preliminary Analyses

Independent samples *t* tests revealed that children who were classified in the CDC C category had significantly higher LogVL and significantly lower SqCD4 counts ($t(76) = -1.99$, $p<.05$ and $t(81) = 2.28$, $p<.05$ respectively). Chi-square analyses were also conducted to determine if categorical demographic and health-related control variables were significantly correlated with CDC classification. There were no significant relationships between categorical demographic and health-related control variables and CDC classification. Of all the possible demographic and health-related control variables, only LogVL and SqCD4 counts were related to CDC classification at the $p<.05$ level. Based on these results, baseline LogVL and SqCD4 were entered in the first blocks as control variables in all hierarchical logistic regression analyses predicting CDC classification.

Independent samples *t* tests revealed that baseline PIQ and VIQ standard scores were significantly lower in children who were classified in the CDC C category ($t(80) = 2.06$, $p<.05$ and $t(80) = 2.14$, $p<.05$). Based on these results, and to gain further specificity, independent samples *t* tests were conducted to determine if baseline PIQ and VIQ subtest scaled score means differed by CDC classification. Results revealed that of the baseline PIQ subtests, Coding, Picture Arrangement, and Symbol Search scaled scores were all significantly lower in children who were classified in the CDC C category ($t(80) = 2.18$, $p<.05$; $t(80) = 2.57$, $p<.05$; and $t(80) = 2.69$, $p<.01$ respectively). Of the

baseline VIQ subtests, only Arithmetic score was significantly lower in children who were classified in the CDC C category ($t(80) = 2.73$, $p<.01$). These results support the hypothesis that lower baseline PIQ scores are significantly related to disease progression, as measured by classification of CDC C category at follow-up. Further, exploratory analyses examining the relationship between baseline VIQ standard scores and VIQ subtest scaled scores provide support for the notion that lower baseline PIQ and VIQ are both significantly related to disease progression in HAART-experienced HIV+ children. The implications of these findings will be discussed in the discussion section.

Hierarchical Logistic Regression Analyses Predicting CDC Classification

Six separate hierarchical logistic regressions were conducted, controlling for baseline logVL and sqCD4 and testing baseline PIQ, VIQ, Coding, Picture Arrangement, Symbol Search, and Arithmetic scores as predictors of CDC classification. For the logistic regression with baseline logVL, sqCD4 and PIQ as the predictors of CDC classification at follow-up, there was good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 2.80$, $p = .90$). The overall model was significant ($X^2 = 11.92$, $p<.01$) and explained 14.7% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 69.3%, with 86.4% of CDC classification of N, A, or B category and 45.2% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification. However, after controlling for baseline logVL and sqCD4, baseline PIQ standard scores were significantly related to CDC classification. For every 1 point increase in baseline PIQ standard score, children were 4% less likely to be categorized as CDC "C" at follow-

up (odds ratio [OR] = .96; 95% confidence interval [CI] = .93 - .99, p<.05). This finding supports the hypothesis that PIQ standard score is a significant predictor of disease progression as measured by CDC classification of category C at follow-up and indicates that baseline PIQ standard scores predict CDC classification at follow-up even when controlling for immune-related predictors of CDC classification.

There was a good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 4.65$, p = .70) for the logistic regression with baseline logVL, sqCD4 and Coding as the predictors of CDC classification. The overall model was significant ($X^2 = 10.30$, p<.05) and explained 12.8% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 62.7%, with 79.5% of CDC classification of N, A, or B category and 38.7% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification. However, after controlling for baseline logVL and sqCD4, baseline Coding scaled scores were significantly related to CDC classification. Results indicated that for every 1 point increase in baseline Coding scaled score, children were 17% less likely to be categorized as CDC "C" (OR = .83; 95% CI = .70 -.98, p<.05). These results also support the hypothesis and indicate that specific baseline PIQ subtests also significantly predict CDC classification at follow-up. The specific implications and possible explanations for these results will be further elaborated in the discussion section.

For the logistic regression with baseline logVL, sqCD4 and Picture Arrangement as the predictors of CDC classification, there was a good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 4.07$, p = .77). The

overall model was significant ($X^2 = 12.43$, $p<.01$) and explained 15.3% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 68%, with 79.5% of CDC classification of N, A, or B category and 51.6% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification. However, after controlling for baseline logVL and sqCD4, baseline Picture Arrangement scaled scores were significantly related to CDC classification. Results indicated that for every 1 point increase in baseline Picture Arrangement scaled score, children were 17% less likely to be categorized as CDC "C" (OR = .83; 95% CI = .70 -.98, $p<.05$). These results provide further support to the hypothesis.

There was a good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 13.51$, $p = .10$) for the logistic regression with baseline logVL, sqCD4 and Symbol Search as the predictors of CDC classification. The overall model was significant ($X^2 = 10.82$, $p<.05$) and explained 14% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 62.5%, with 79.1% of CDC classification of N, A, or B category and 37.9% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification. Consistent with the hypothesis, after controlling for baseline logVL and sqCD4, baseline Symbol Search scaled scores were significantly related to CDC classification. Results indicated that for every 1 point increase in baseline Symbol Search score, children were 17% less likely to be categorized as CDC "C" (OR = .83; 95% CI = .71 -.98, $p<.05$).

For the logistic regression with baseline logVL, sqCD4 and VIQ as the predictors of CDC classification, there was a good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 7.65$, $p = .36$). The overall model was significant ($X^2 = 11.28$, $p<.05$) and explained 14% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 70.7%, with 84.1% of CDC classification of N, A, or B category and 51.6% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification. However, after controlling for baseline logVL and sqCD4, baseline VIQ scores were significantly related to CDC classification. Results indicated that for every 1 point increase in baseline VIQ score, children were 4% less likely to be categorized as CDC "C" (OR = .96; 95% CI = .93 -.99, $p<.05$). These results are nearly identical to the results achieved in the first logistic regression with baseline PIQ standard score as a predictor of CDC classification. These similar findings indicate that PIQ and VIQ standard scores are both useful predictors of disease progression in this sample.

There was a good model fit as supported by the non-significant Hosmer and Lemeshow chi-square statistic ($X^2 = 7.68$, $p = .36$) for the logistic regression with baseline logVL, sqCD4 and Arithmetic as the predictors of CDC classification. The overall model was significant ($X^2 = 13.76$, $p<.01$) and explained 16.8% of the variance in CDC classification (Cox and Snell R^2). Overall classification rate for the model with all predictors included was 70.7%, with 84.1% of CDC classification of N, A, or B category and 51.6% of CDC classification of C category correctly classified. Results demonstrated that baseline logVL and sqCD4 were not significantly related to CDC classification.

However, after controlling for baseline logVL and sqCD4, baseline Arithmetic scaled scores were significantly related to CDC classification. Results indicated that for every 1 point increase in baseline Arithmetic scaled score, children were 19% less likely to be categorized as CDC "C" (OR = .81; 95% CI = .69 -.96, $p<.05$). These results are very similar to the results found with the PIQ subtest scaled scores as predictors of CDC classification. It provides further support to the importance of examining the relationship between IQ and disease progression at the subtest level to gain further specificity.

Discussion

The present study systematically examined the complex inter-relationships between immune status, cognitive functioning, and disease progression in school-aged, perinatally infected, HIV+ children on HAART over time. It is one of only a handful of investigations to examine this topic and the first to conduct long-term follow-up assessments beyond one year after initiating HAART. This study's goals were informed by an integrated model of neurodevelopment for children with chronic illness which states that neurodevelopmental functioning in chronically ill children is impacted by the interaction of multiple factors. These include: age of child at time of assessment, type of medical treatment, specific disease progression, and environmental factors (Armstrong, 2006; Armstrong et al., 2004). Based on this theoretical model, the objectives of this study were threefold. The first objective was to determine whether prior immune status was predictive of cognitive functioning at later time points. The second objective was to examine whether these children in this HAART-treated cohort displayed improvements in cognitive functioning over time. The third objective was to investigate whether early cognitive functioning was associated with more rapid HIV disease progression.

Although describing the cognitive functioning of this sample was not a main focus of the study, it is important to note that children performed over one standard deviation below the established norms for their age on the FSIQ, VIQ, and PIQ of the WISC-III at each of the three time points. Across the three time points at least 36% of children performed in the Borderline or Intellectually Deficient categories of PIQ functioning. These results are particularly striking when taking into account the fact that these children were on HAART for an average of 4.5 years (SD = 1.2 years) at the time

of the final assessment. Cognitive impairments in HIV+ children have been well documented in the pre-HAART era (see reviews in Wachsler & Golden, 2002; Willen, 2006). Findings from the present study highlight that cognitive impairment remains a serious concern in school-aged children, even after long-term HAART treatment. This is supported by recent literature which observed similar impairments in cognitive functioning in perinatally infected HIV+ infants and children on HAART (i.e., Jeremy et al., 2005; Kullgren et al., 2004; Lindsey et al., 2007; Noycze et al., 2006). Taken together, emerging evidence indicates that even after long-term HAART treatment, HIV+ children are at significant risk for cognitive impairment overall.

In preliminary analyses, Hispanic children unexpectedly performed significantly better than African-American children on the PIQ, Block Design, and Object Assembly subtests at the third time point. Research on the WISC-III norms across ethnicities has shown that Hispanic children perform better than African-American children on the PIQ. The mean PIQ for Hispanic children is 97.7, while the mean PIQ for African-American children is 88.5 (Prifitera, Weiss, & Saklofske, 1998). These findings are similar to results found in the current study in which the mean PIQ at the third time point for Hispanic children was comparable to the norms for this ethnic group with a mean of 95.7. However, the mean PIQ at the third time point for African-American children was substantially lower than the norm for this group with a mean PIQ of 77.3. Interestingly, no significant differences in immune status, disease progression or family income level were observed across ethnic groups. Other risk factors such as prenatal drug exposure, lower maternal education, malnutrition, or a chaotic home environment may account for ethnic differences in PIQ. One study conducted by Coscia et al (2001) found that aspects

of the home environment (i.e., organization, parental involvement, and play materials) mediated the association between SES and IQ in HIV+ children The present study did not have access to these additional socioeconomic and demographic variables. Therefore, I could not determine the relative contributions of these factors on PIQ scores in African-American children. Future studies need to examine this issue since it appears that HIV+ African-American children are at particular risk for impaired cognitive functioning.

In a related analysis, I observed that bilingual English/Spanish speaking children scored significantly better than monolingual children on PIQ, Block Design, Object Assembly, and Symbol Search at the third time point. There is a body of literature which has demonstrated that bilingual children consistently perform better on tasks measuring executive functioning (i.e., Bialystok et al., 2005). Researchers in this field have hypothesized that the simultaneous management of two languages actually enhances the development of executive functioning in bilingual children (Bialystok, 2001; Rodriguez-Fornells, De Diego Balaguer, & Münte, 2006). This area of research may help explain the current findings. Although the Block Design, Object Assembly, and Symbol Search subtests measure a broad range of nonverbal cognitive skills, all of these subtests require visual organization, abstract conceptualization, and a certain degree of attention and concentration, which are all components of executive functioning. Perhaps the higher PIQ score seen in bilingual Spanish/English children in this sample is reflective of an inherent strength in executive functioning. It is also noteworthy; however, that bilingual status may merely serve as a marker for race/ethnic differences in PIQ in this sample.

Recent research in this area has obtained evidence indicating that the effect of bilingualism is substantially diminished after accounting for SES and ethnicity. A study

conducted by Morton & Harper (2007) demonstrated that when bilingual and monolingual children were matched on SES and ethnicity, they performed similarly on a task measuring executive functioning. They did find, however, that children from higher SES families performed better than children from lower SES families. It is possible that bilingual Spanish/English children in this sample are from higher SES families, which may explain the discrepant scores between these children and monolingual children. The discrepant scores between bilingual Spanish/English children and monolingual children may also be an artifact of the strong correlation between ethnicity and language in this sample. Because of this strong correlation, it is difficult to ascertain whether higher PIQ scores in these children are related to ethnicity, bilingualism, or both of these variables.

Hypothesis 1:

The first hypothesis was supported as poorer immune status, as measured by CD4% <25, at the first time point significantly predicted lower PIQ scores and PIQ subtest scores at the third time point, even after controlling for covariates. This study was the first to thoroughly examine the effect of important continuous and clinically relevant categorical immune markers (logVL and CD4% category) on subsequent cognitive functioning. CD4% category was the most consistent predictor of later PIQ and PIQ subtest scores. Immune suppression, as measured by the CD4 < 25% category at the first time point, significantly predicted lower PIQ, Object Assembly, Coding, and Symbol Search scores at the third time point.

These findings extend the small, but expanding literature examining the relationship between immune markers and cognitive functioning in infants and school-aged children in the post-HAART era. The current investigation is one of only a handful

of studies that have evaluated the longitudinal relationships between early immune markers to later cognitive functioning. Results from a recent longitudinal study indicate that increases in mean CD4% scores in the 6 months prior to cognitive assessment were associated with higher overall cognitive scores (Shanbhag et al., 2005). The authors did not specify which assessment tool was used to obtain cognitive scores in their sample. Lindsey et al. (2000) found that viral load at time of HAART initiation was predictive of lower cognitive scores 24 weeks later. This study collapsed analyses across a variety of cognitive assessment tools. The present study confirms these findings overall and provides further evidence to support the importance of both continuous and categorical measures of immune status as important predictors of cognitive functioning over time.

This is the only known study to find that poor immune status predicts lower scores at the subtest level of the WISC-III. The results indicate that poorer immune status predicts of lower scores on PIQ subtests that are all timed and require the use of one's hands to complete the task. Thus, all of these subtests assess processing speed and fine-motor abilities. In addition to processing speed and fine-motor skills, these subtests also involve visual discrimination and organization, attention, short-term memory, nonverbal reasoning and planning, cognitive flexibility, and abstract conceptualization (Sattler, 2001). As described above, some of these nonverbal cognitive skills are also related to executive functioning. Taken together, these results suggest that these specific neuropsychological functions may be particularly susceptive to HIV.

These results are similar to those of a recent cross-sectional study examining the relationship between CT brain scan abnormalities and WISC-III scores in HIV+ children on HAART (Martin et al., 2005). Although this study was cross-sectional, and therefore

did not examine the predictive value of immune status, the authors found that children with CD4 counts <500 scored significantly lower on the processing speed index of the WISC-III, which includes the Coding and Symbol Search subtests. The present investigation also observed that poorer immune status predicted lower scores on these subtests. Thus, processing speed impairments are clearly associated with poorer immune status. This is consistent with the adult HIV literature, which has also shown that processing speed is one of the most salient neuropsychological deficits in HIV+ adults (Sacktor et al, 1996). Perhaps processing speed and the other related neuropsychological functions assessed by the PIQ subtests are especially susceptible to decrements in immune status. Since processing speed can greatly impact children's academic performance (i.e., ability to take notes, finish assignments, take tests, etc.) and hence, affect their ability to learn effectively, it is extremely important to assess processing speed in HIV+ children and particularly in HIV+ children with poorer immune status.

Hypothesis 2:

Contrary to the second hypothesis, PIQ scores did not significantly increase over the three time points. Instead, PIQ scores remained stable over time, which indicates that HAART may have more of a protective effect in stabilizing cognitive functioning in HIV+ children over time, rather than actually improving cognitive functioning. Numerous studies in the adult HIV literature have shown short-term improvements (up to 2.5 years) in cognitive functioning after initiation of HAART (Ferrando et al., 2003; Robertson et al., 2004; Tozzi et al., 1999). By contrast, recent studies in the pediatric HIV literature have found only limited improvements in cognitive functioning following the initiation of HAART. For example, Jeremy et al. (2005) found slight improvement in

vocabulary subtest scores after 48 weeks of HAART. However, similar to the current study, global measures of cognitive functioning remained stable after 48 weeks. In another investigation, Lindsey et al. (2007) found trends towards improved mental and motor scores in infants after receiving HAART for up to 3 years. These modest increases were also observed in a study conducted by Tamula, Walsek, and Civitell (2003) where, FSIQ scores increased by 6 points in the 6 months after HAART initiation. Building on these findings, it appears that the effects of HAART on cognitive functioning are more robust in infants who are treated at birth. Shanbhag et al. (2005) found that children born in the post-HAART era performed 4.9 points better on general cognitive testing than children born in the pre-HAART era. However, when focusing only on the post-HAART era group, cognitive scores remained stable over time. This finding is also similar to the results of the current study where children who were born in the pre-HAART era were followed around 4.5 years on average. The longer follow-up period is a significant improvement on previous studies, but no long-term increases in cognitive functioning were observed. It may be that minor improvements are seen early on after HAART initiation, but more long-term improvements are not observed.

In sum, the stability in PIQ scores observed in the current study is generally consistent with results from recent longitudinal investigations examining cognitive functioning in the post-HAART era. Cognitive functioning does not appear to markedly improve in HAART-treated HIV+ children who were born in the pre-HAART era. At the same time, it is important to note that stability of cognitive functioning is a crucial improvement from the pre-HAART era where declines in cognitive functioning were well documented in HIV+ children (see review in Wachsler-Felder & Golden, 2002). It

appears that HAART likely has a protective effect on cognitive functioning, possibly by minimizing the viral load in the periphery and hence reducing the amount of infected cells penetrating the CNS (Tamula et al, 2003).

Although overall PIQ scores remained stable over time, analyses revealed that PIQ scores significantly declined over time as a function of CD4% category at the first time point. This result is consistent with the Hypothesis #2a. Children with CD4% <25 at the first time point showed a significant decrease of approximately 5 standard score points on the PIQ from the first to third assessments. In contrast, children with CD4% ≥25 at the first time point showed stable PIQ scores over time. Analyses of PIQ subtests as a function of CD4% category at the first time point demonstrated that children with CD4% ≥25 at the first time point showed an increase of 1.3 scaled score points on the Object Assembly subtest from the first to the third assessments. Overall, results indicate that children who have a history of low CD4% are not able to benefit from the possible stabilizing effects of HAART and appear to be more vulnerable to cognitive decline. Lower CD4% may indicate that a child's HAART regimen is failing, which places them at risk for cognitive decline. Further, children with better immune status at the first time point, as indicated by having CD4% ≥25, showed an increase in Object Assembly over time and stable functioning over time on the PIQ and other PIQ subtests. This study is the only known pediatric study to longitudinally examine cognitive functioning as a function of CD4% category in the post-HAART era.

These findings are also very similar to results obtained when Lindsey et al (2007) examined cognitive functioning over time in the pre-HAART era group. They discovered that infants with immune suppression (also measured by CD4% <25) had lower mean

mental and motor scores than HIV+ infants with CD4% ≥25 and HIV-exposed infants. Although this study did not find that cognitive decline over time was a function of the CD4% category, this study provides further support to the importance of CD4% category as a vital immune marker that differentiates between children who are and are not at risk for cognitive impairment. Based on the current findings and those of Lindsey (2007), it is clear that history of CD4% < 25 is an extremely important clinical immune marker and should be used regularly to identify children who are at risk for cognitive impairment and decline.

There are many possible explanations for why children with a history of immune suppression (CD4% <25) are at greater risk for cognitive decline, despite long-term HAART. In a recent review article, Mitchell (2006) proposes that as HIV+ children survive into adolescence and adulthood, a more slow-progressing form of cognitive impairment may emerge. The decline in PIQ scores within the immune suppressed group of children in the present study may be an example of this slow-progressing cognitive impairment. Mitchell hypothesizes that although HAART has significantly decreased the most profound forms of encephalopathy in adults and children; it may not be as effective in preventing milder forms of cognitive impairment (see Mitchell, 2006 for review). The insufficient ability of various HAART medications in penetrating the blood-brain barrier, which likely results in uncontrolled viral replication in the CNS, and the evolution of HAART resistant mutations among viral quasispecies in the CSF are proposed as possible explanations for a potential slowly-progressing form of cognitive impairment in children. These possible explanations are applicable to the current findings. Perhaps children in the immune suppressed group were not receiving an adequate number of

CNS-penetrating HAART medications, which may elucidate why they experienced a decline in PIQ. Unfortunately, the present study did not have access to the specific types of HAART medications taken by each child, so it was unable to test this hypothesis. HAART failure, as a result of nonadherence is another possible explanation for the findings.

In addition to biological explanations, sociodemographic and environmental factors may help explain the decline in PIQ seen in the immune suppressed group. Although the CD4% groups did not differ by the demographic variables available in the current study, other unavailable variables which are consistently related to IQ, such as quality of home environment, maternal education, prenatal drug exposure, and attachment, may be partially explain declines in PIQ that were observed in the immune suppressed group. It may be that immune suppressed children are actually more susceptible to the effects of these sociodemographic risk factors. For example, in the study conducted by Coscia et al (2001), described above, the impact of quality of home environment on cognitive functioning was stronger for children with more advanced disease, as measured by CD4 counts. The greater impact of the abovementioned demographic risk factors for poorer cognitive functioning in the immune suppressed group may also explain their apparent vulnerability to cognitive decline.

Hypothesis 3:

Finally, the third hypothesis was supported as scores on the PIQ, VIQ, Coding, Picture Arrangement, Symbol Search, and Arithmetic at the first time point were all significant predictors of CDC C classification at follow-up, even after logVL and sqCD4 at the first time point were taken into account. These results are consistent with other

studies which have found neurodevelopmental markers to be significant predictors of disease progression in this population (Llorente et al., 2003; Pearson et al., 2000). However, this is the first study to find that more specific measures of performance and verbal cognitive functioning, rather than global measures are independently predictive of disease progression as measured by CDC classification category. Based on results from this study, for every 1 standard deviation increase on PIQ or VIQ scores at the first time point, children were 60% less likely to be categorized as category "C". Similarly, for every 1 standard deviation increase in subtest scores at the first time point, children were approximately 54% less likely to be categorized as category "C".

There are, however, several important limitations to consider when interpreting these results. First, the exact date of CDC classification was unknown in this study. Therefore, it is possible that in some children an AIDS-defining illness may have occurred early in life, which would have placed them in the "C" category and may explain the strong association with lower IQ scores. One recent study conducted by Smith et al. (2006) provides support to this possible explanation of the findings. The authors compared cognitive functioning in young HIV+ children (<7 years of age) who were classified with category "C" with HIV+ children who were not classified with category "C". They discovered that children who experienced an early-AIDS defining illness (category "C"), demonstrated more cognitive impairment in areas of verbal, perceptual-performance, quantitative abilities, and memory subtests of the McCarthy Scales of Children's Abilities than children who did not experience an early-AIDS defining illness. This study not only helps to explain the relationship between cognitive functioning and CDC "C" category in the present study. Interestingly, it also observed deficits in similar

domains of neuropsychological functioning as did the present investigation. Despite the limitations, these findings build on the results from the previous two hypotheses and indicate that cognitive functioning is a potent marker of disease progression in this population over and above the immune status. Ongoing monitoring of cognitive functioning among HIV+ children can substantially improve the quality of medical care they receive as neuropsychological changes could provide an important early indicator of a failing HAART regimen.

Limitations and Clinical Implications:

There are a number of important limitations to this study, overall. First, measures of HAART medication adherence were not available. Therefore, it is difficult to be confident about the assertions and deductions made about the effectiveness of HAART and its relation to cognitive functioning in this study because the lack of improvement in cognitive functioning seen in this and other studies may also be related to nonadherence. Unfortunately, this is an extremely common limitation in the pediatric HIV literature. In fact, none of the articles studying this literature included measures of adherence. This study also did not take into account the specific medications included in the children's HAART regimens. Even at high levels of adherence, HAART medications vary greatly in their effectiveness to penetrate the CNS. The cognitive decline in immune compromised children in this study may also be related to a lack of CNS-penetrating HAART medications (Mitchell, 2006).

Another important limitation is the lack of a comprehensive measure of socioeconomic status. The present study did not have access to specific family income, maternal education history, prenatal drug exposure, family environment, or other

important sociodemographic variables that are consistently associated with poorer cognitive functioning. Since this study could not statistically control for these variables and did not have access to a demographically matched HIV- control group, it is difficult to ascertain whether the observed cognitive impairments in this population are due exclusively to the effect of HIV.

Despite these limitations, the findings have extremely important clinical implications. First, it reinforces the importance of continued serial neuropsychological assessment throughout childhood, adolescence, and adulthood in this population. Ideally, full neuropsychological batteries should be administered to this population, in order to detect changes in cognitive functioning over time. However, if abbreviated batteries are used, they should minimally include specific measures of processing speed, fine-motor skills, and aspects of executive functioning as it appears from the results of this and other recent studies (i.e., Martin et al., 2005; Smith et al., 2006) that these skills are particularly vulnerable in HIV+ children.

Based on the fact that overall, these children are performing significantly worse than established norms for their age and that children with a history of immune suppression actually show continued decline in the post-HAART era, it is crucial that these children receive early interventions to help improve areas of weakness, such as processing speed, fine-motor skills, memory, and attention. These interventions will not only assist children's learning in school, but may actually help to decrease disease progression.

Overall, this in-depth analysis of the complex relationships between immune status, cognitive functioning, and disease progression in HIV+ school-aged children on

HAART revealed many important results. It is clear that despite extensive HAART treatment; HIV+ children still perform significantly worse than the established norms on IQ measures overall. Additionally, this is the first study to find that children with a history of immune suppression actually demonstrated a decline in cognitive functioning over time, despite extensive HAART treatment. Throughout the analyses, CD4% category (</≥ 25) emerged as a significant clinical marker of immune suppression, which identified children risk for cognitive impairment and decline. Further, it became clear that HIV+ children are particularly vulnerable to specific neuropsychological deficits in the areas of processing speed, fine-motor skills, working memory, and aspects of executive functioning. Lastly, this is one of very few studies which demonstrated the utility of more specific measures of cognitive functioning in predicting disease progression.

Taken together, this study attempted to depict a neurodevelopmental model of HIV by including environmental, disease-specific, and cognitive measures of functioning to better understand the impact of HIV on children in the post-HAART era. The significant findings lend support to the importance of the neurodevelopmental model of chronic illness proposed by Armstrong (2006), confirm existing research and provide new insight into cognitive functioning in HIV+ children in the post-HAART era. HIV+ children are at severe risk not only because of the effect of HIV itself on the CNS, but also because of the myriad sociodemographic, genetic, and disease-specific risk-factors in their lives. It is crucial that future studies examine variables that may modify the relationship between poorer immune status and cognitive impairments. By investigating the role of adherence, sociodemographic variables, home environment factors, and the neuro-protective effects of specific HAART medications future studies will provide more

insight into the pathways that promote long-term maintenance of cognitive functioning in this population. As HIV+ children are surviving into late adolescence and adulthood, it will be important to not only focus on their survival, but also the quality of their lives. Impaired cognitive functioning can greatly impact quality of life, so it is imperative that researchers continue to explore the mechanisms by which these children experience cognitive decline.

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Appendix

Table 1

WISC-III Subtest Descriptions

WISC-III Subtest	Functions Measured
Picture Completion	Visual discrimination, concentration, reasoning, visual organization, long-term visual memory
Information	Memory for habitual, overlearned material, long-term memory retrieval
Coding	Information processing, visual-motor coordination, processing speed, attentional skills, visual acuity, visual scanning and tracking, short-term memory for new learning, cognitive flexibility, fine-motor skills
Similarities	Verbal concept formation, organization, conceptual thinking
Picture Arrangement	Nonverbal reasoning, planning ability, planning, visual organization, temporal sequencing
Arithmetic	Numerical reasoning ability, concentration, attention, knowledge of numerical operations, memory
Block Design	Non-verbal concept formation, perceptual organization, spatial visualization, visual-motor coordination, abstract conceptualization
Vocabulary	Learning ability, fund of information, richness of ideas, memory, concept formation, language development, long-term memory, concept formation, language skills
Object Assembly	Visual organization, visual-motor coordination, visual organization
Comprehension	Social judgment, knowledge of practical information, common/moral sense
Symbol Search	Visual discrimination, visuoperceptual scanning, and processing speed, perceptual discrimination, processing speed, attention and concentration, short-term memory, and cognitive flexibility
Digit Span	Short-term sequential auditory memory and attention, auditory sequential processing, short-term auditory memory, attention, sequencing skills

Table 2

Demographic and HIV-Related Variables for the Total Sample (n=85)

Variable	n	%
Gender		
Boys	49	41
Girls	35	58
Ethnicity		
African-American	47	55
Hispanic	18	21
Haitian-American	15	18
Federal Poverty Guidelines %		
<100%	26	31
101-150%	40	48
151-200%	4	5
201-250%	7	8
Language		
Monolingual	57	67
Bilingual-Spanish	18	21
Bilingual-Creole	8	9
CDC Category		
NO C	50	59
C	34	40
Encephalopathy		
Yes	71	84
No	13	15

Table 3

Demographic and
HIV-related variables

Variable	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Age (years)	84	9.45	2.45	84	11.17	2.57	41	12.27	2.12
Months on HAART	83	22	14.87	83	42.81	16.57	41	55.14	13.80
Viral Load	78	87751.14	180491.7	82	72176.82	141312.5	39	48945.15	131750.4
Absolute CD4+ Counts	83	574.63	356.51	84	572.61	373.06	41	610.15	374.56
CD4 %	83	26.23	12.59	83	25.04	11.60	41	26.29	10.54

Table 4

WISC-III Composite & Subtest Standard Scores by Time Point

	Time 1 (n= 82)		Time 2 (n=81)		Time 3 (n= 39)	
Composite/Subtest	M	SD	M	SD	M	SD
FSIQ	77.52	15.06	78.54	15.82	77.87	19.0
VIQ	77.70	15.64	77.40	15.64	76.10	16.85
Arithmetic	6.56	3.30	6.73	3.15	6.10	2.88
Vocabulary	6.06	2.80	5.56	2.96	5.35	3.12
Comprehension	5.72	3.58	5.54	3.11	4.90	3.3
Digit Span	7.44	3.19	9.0	3.45	7.80	3.3
Information	6.10	2.65	5.90	2.97	5.88	2.99
Similarities	5.76	3.46	6.16	3.63	6.73	3.81
PIQ	81.32	15.22	83.28	16.20	83.46	19.63
Picture Completion	7.49	3.16	8.08	3.03	8.81	3.78
Coding	7.82	3.17	7.81	3.20	6.90	3.25
Picture Arrangement	6.73	3.45	7.34	3.59	7.68	4.33
Block Design	6.59	3.31	6.74	3.21	6.5	3.76
Object Assembly	6.11	3.11	6.51	3.43	6.8	3.84
Symbol Search	7.28	3.44	8.24	3.75	7.62	3.5

Table 5

Hierarchical Multiple Regression Analysis Summary for Baseline LogVL Predicting PIQ2 (N = 72)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.700***	163.12***		
PIQ1	.92	.07	.84***				
Step 2				.714	86.12***	.014	3.4
PIQ1	.90	.07	.82				
LogVL	-1.75	.94	-.12				

***p < .001.

Table 6

Hierarchical Multiple Regression Analysis Summary for Baseline LogVL Predicting PIQ3 (N = 35)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.682***	70.75***		
PIQ1	.96	.11	.83***				
Step 2				.720*	41.17***	.038*	4.37*
PIQ1	.85	.12	.73***				
Ethnicity	4.41	2.11	.22*				
Step 3				.739	29.20***	.019	2.12
PIQ1	.86	.12	.74***				
Ethnicity	3.03	2.27	.15				
LogVL	-2.34	1.58	-.15				

*p < .05. ***p <.001.

Table 7

Hierarchical Multiple Regression Analysis Summary for Baseline LogVL Predicting PIQ3 (N = 36)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.702***	80.23***		
PIQ1	.99	.11	.84***				
Step 2				.738*	46.43***	.035*	4.46*
PIQ1	.88	.12	.74***				
Language	4.40	2.09	.22*				
Step 3				.761	33.91***	.023	3.07
PIQ1	.88	.11	.75***				
Language	3.06	2.16	.15				
LogVL	-2.62	1.50	-.16				

*p < .05. ***p <.001.

Table 8

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting PIQ3 (N = 36)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.709***	82.87***		
PIQ1	.97	.11	.84***				
Step 2				.740***	46.93***	.031	3.91
PIQ1	.89	.11	.77***				
Ethnicity	3.97	2.01	.19				
Step 3				.782***	38.35***	.043*	6.25*
PIQ1	.88	.10	.77***				
Ethnicity	2.78	1.92	.13				
CD4< or ≥25%	8.32	3.33	.21*				

*p < .05. ***p <.001.

Table 9

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting PIQ3 (N = 37)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.727***	93.21***		
PIQ1	.99	.10	.85***				
Step 2				.756***	52.78***	.029	4.10
PIQ1	.91	.11	.78***				
Language	4.02	1.99	.19				
Step 3				.799***	43.68***	.042*	6.97*
PIQ1	.89	.99	.77***				
Language	2.75	1.90	.13				
CD4< or ≥25%	8.61	3.26	.22*				

*p < .05. ***p <.001.

Table 10

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting OA3 (N = 37)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.570***	93.21***		
OA1	.91	.14	.76***				
Step 2				.636***	52.78***	.087**	8.35**
OA1	.72	.14	.60***				
Ethnicity	1.36	.47	.33**				
Step 3				.708***	43.68***	.077**	9.17**
OA1	.76	.12	.63***				
Ethnicity	.98	.44	.24*				
CD4< or ≥25%	2.18	.72	.29**				

*p < .05. **p <.01. ***p <.001.

Table 11

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting OA3 (N = 37)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.597***	51.78***		
OA1	.92	.13	.77***				
Step 2				.646***	31.08***	.050*	4.79*
OA1	.78	.14	.66***				
Language	1.05	.48	.25*				
Step 3				.729***	29.61***	.083**	10.08**
OA1	.80	.12	.67***				
Language	.64	.44	.15				
CD4< or ≥25%	2.31	.73	.30**				

*p < .05. **p <.01. ***p <.001.

Table 12

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting COD3 (N = 39)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.312***	16.76***		
COD1	.55	.14	.56***				
Step 2				.440***	14.14***	.128**	8.24**
COD1	.52	.12	.52***				
CD4< or ≥25%	2.31	.80	.36**				

**p <.01. ***p <.001.

Table 13

Hierarchical Multiple Regression Analysis Summary for Baseline CD4 < or ≥25% Predicting SS3 (N = 35)

Predictor	B	SE B	ß	R^2	F	Δ R^2	Δ F
Step 1				.294***	51.78***		
SS1	.62	.17	.54***				
Step 2				.351***	31.08***	.057	2.81
SS1	.55	.17	.48***				
Language	.92	.55	.25*				
Step 3				.437***	29.61***	.086*	4.75*
SS1	.58	.16	.51***				
Language	.54	.55	.15				
CD4< or ≥25%	2.15	.99	.31*				

*p < .05. **p <.01. ***p <.001.

Table 14

PIQ & PIQ Subtest Means & Standard Deviations
by CD4% Category (n = 36)

	CD4% < 25			CD4% ≥ 25			Group *
	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time
PIQ/Subtest	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	F
PIQ	80.29(19.30)	81.30(21.80)	75.41(22.33)	87.11(14.90)	88.84(14.57)	90.11(15.95)	3.67*
Object Assembly	6.35(3.86)	6.82(4.14)	5.35(4.2)	6.9(2.65)	7.3(3.48)	8.3(3.04)	6.30**
Picture Completion	7.35(4.04)	8.47(3.88)	7.71(4.30)	8.73(3.0)	8.86(2.64)	9.55(3.34	
Block Design	6.35(4.10)	6.12(3.82)	5.41(4.10)	7.5(3.28)	7.35(3.15)	7.3(3.56)	
Coding	8.10(3.73)	6.72(3.36)	5.44(2.91)	8.81(2.77)	8.57(2.92)	7.95(3.10)	
Symbol Search	7.87(3.53)	6.8(4.38)	6.73(3.58)	7.40(2.93)	7.89(4.13)	8.75(3.17)	
Picture Arrangement	5.83(3.59)	6.33(3.97)	6.39(5.32)	7.9(3.63)	8.95(3.23)	9.05(3.03)	

*p<.05, **p<.01