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Contributions of Disease Severity, Psychosocial Factors, and Cognition to Behavioral Functioning in Youth Perinatally Exposed to HIV

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By

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I dedicate this dissertation to the families and children who are affected by HIV. May we as a field continue to commit research to finding a cure. And now the music begins to play…

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Abstract

Study Objectives: Perinatal HIV infection has been linked to problems in both behavioral functioning (BF) and cognitive functioning (CF). The differential impact of psychosocial and disease-related factors on CF and BF has been described, but synthesis of findings has been difficult due to methodological differences. Utilizing structural equation modeling (SEM) analysis, our study investigated the individual and combined contributions of psychosocial factors on CF and BF in youth with perinatal HIV infection (PHIV) and those HIV-exposed but uninfected (PHEU), and examined the role of disease related-factors among PHIV youth. It was also determined whether CF was a mediator of the relationship of disease severity and psychosocial factors with BF.

Methods: Child and caregiver psychosocial interviews and age-standardized assessments of CF and BF were administered to participants enrolled in the Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study (PHACS) network, a prospective longitudinal study examining the long-term effects of HIV and its treatment. Preliminary exploratory factor analyses were used to identify latent variables reflecting clusters of predictors, in order to establish four parsimonious SEMs: child-assessed BF, and caregiver-assessed BF in PHIV and PHEU youth.

Results: Participants included PHIV (N=231) and PHEU (N= 151) youth; 47% male, 62% black, 27% Hispanic; mean age at entry was 10.9 years. Among PHIV youth, most were well controlled (median CD4%, 34%; HIV plasma RNA values <400 copies/ml., 75%); 24% had a prior AIDS diagnosis (8% with encephalopathy). Youth demonstrated CF within the low average range (Wechsler mean Full Scale IQ= 86.8, *sd*= 15.1) and BF t-scores within average range

(Behavioral Assessment Scale for Children, 2nd ed. (BASC-2) mean caregiver reported t-score= 50.2, *sd*= 10.8; child reported t-score= 45.9, *sd*=8.5).

SEM results indicated that higher levels of *Caregiver Stress* and *Family Emotional Stress* predicted higher (worse) BF scores in PHIV and PHEU youth. *Caregiver Educational Opportunity* (reflecting IQ, education, and income) and two disease severity variables, *Late Presenter* and *Better Past HIV Health* were significant predictors of youth CF. Higher child CF was associated with significantly lower (better) caregiver-reported BF in both PHIV and PHEU. *Caregiver Educational Opportunity* predicted caregiver-reported BF in PHEU youth. Results of mediation analyses suggested that among PHEU youth, the effect of *Caregiver Educational Opportunity* on caregiver-assessed BF was mediated by CF. Among PHIV youth, both *Better Past Disease Severity* and *Caregiver Educational Opportunity* mediated the effects of CF on caregiver-assessed BF. No significant direct relationships between disease severity variables and child-assessed BF were found.

Conclusions: Using a novel statistical approach, the deleterious impact of caregiver and family stress was identified on BF among youth affected by HIV, suggesting that the impact of compounding stressors may negatively influence the BF of PHIV youth more than the disease itself. Expected associations of HIV disease severity factors and previous disease status with CF among PHIV youth reinforce the importance of early antiretroviral treatment of HIV to reduce the risk of cognitive impairment. These results communicate the need for evidence-informed child, caregiver and/or family support to diminish behavioral risk among youth living with and affected by HIV.

CHAPTER 1

Statement of the Problem

Despite recent advances in medical treatment, the Human Immunodeficiency Virus (HIV) continues to affect the neurocognitive and adaptive functioning of infants, children, and adolescents. Today, more than 34 million people worldwide are living with HIV, with young people aged 13–29 accounting for 39% of all new infections (Centers for Disease Control [CDC], 2011).In the United States, these figures are even more startling for ethnic minority populations who often face additional economic, social, and financial barriers to both preventative healthcare and adequate sex education. As reported by the CDC (2003), African American and Latino children represent 82% of all current pediatric Acquired Immunodeficiency Syndrome (AIDS) diagnoses, but only 25% of the general non-HIV US population. African American adolescents account for 65% of diagnoses of HIV infection reported among persons aged 13–24 years (CDC, 2009).

HIV is a retrovirus that significantly weakens a patients' ability to combat disease by attacking the Cluster of Differentiation- 4 (CD4) cells responsible for protecting the immune system from opportunistic infection. The loss of CD4 cells significantly decreases immunity, thus making the body more susceptible to disease. Subcortical-frontal areas of the brain are often negatively impacted due to a compromised immune system, resulting in decreased attention and concentration, psychomotor slowing, reduced speed of information processing, executive dysfunction, and verbal memory impairment (Bartlett & Ferrando, 2004; Heaton et al., 2004).

In addition to the neurocognitive effects of the disease, comorbid behavioral problems such as impulsivity, hyperactivity, and difficulties attending to and focusing on stimuli have been described in the literature (Chernoff et al., 2009;Gadow et al., 2012; Mellins et al., 2011; Nozyce

et al., 2006; Wolters, Brouwers, Moss, & Pizzo, 1994). Perinatally-acquired HIV-positive (PHIV+) infants, children, and adolescents are at a particular risk for behavioral problems due to the direct effects of HIV infection on brain structures involved in the regulation of emotion, behavior, and cognition (Bachanas et al., 2001), as well as home environmental factors associated with perinatal infection (Landau, Meyers, & Pryor, 2006; Smith et al., 2012). In the United States, most PHIV+ children are born in large, urban environments to families with multiple daily life stressors including family discordance and instability, poverty, maternal drug and alcohol abuse, and low parental education (Elkington, Bauermeister & Zimmerman, 2010; Smith et al., 2006). Each of these environmental factors has been associated with poor behavioral and cognitive outcomes in childhood and adolescence (Bauman, Camacho, Silver, Hudis, & Draiman, 2002; Havens & Mellins, 2008; Lester et al., 2006).

HIV can be transmitted by blood (which contains the highest concentration of the virus), semen, vaginal fluids, and breast milk. Infants born to HIV+ mothers may be more susceptible to infection if the mother has a high viral load, additional sexually transmitted diseases, and vaginal delivery (Adjorlolo-Johnson et al., 1994; John & Kreiss 1996; Peckham & Gibb, 1995). Due to the combined effects of comprehensive treatment, newborn screening, and prevention counseling, the transmission rate of HIV has declined 89% since its highest levels in the mid-1980s (CDC, 2009). Although the rates of transmission have decreased significantly, infants continue to be perinatally infected. In a large surveillance study conducted by the CDC (2009), of the 10,834 children who were diagnosed with HIV when they were younger than 13 years, 9,522 (88%) acquired HIV perinatally.

Treatment of HIV

Highly active antiretroviral regimens (HAART), a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), are widely used to suppress viral replication and inhibit the aggressive progression of HIV (Gardner et al., 2002; Sackoff &Shin, 2001) The HAART regimen has had a profound impact on the HIV/AIDS epidemic in the U.S. as it significantly lowers the level of active virus to undetectable levels. Because of advances in treatment, HIV is no longer considered a terminal illness but rather is considered "…a chronic disease with complex medical management required for long term positive outcomes" (Landau, Meyers, & Pryor, 2006, p. 871).In order to decrease the progressive effects of the retrovirus, treatment must begin early. The current standard of care is to test all babies born to HIV-positive (HIV+) mothers using ribonucleic acid testing (RNA testing or viral load testing) in order to identify HIV infected infants within the first weeks of life (Constantine & Zink, 2005). This prenatal information allows for immediate initiation of the HAART regimen in order to stop the progression of the disease. However, the detection of viral loads requires that the mother is both aware of her HIV status and is currently receiving adequate prenatal treatment in which newborn screening is a routine component of prenatal care (Sansom, Jamieson, Farnham, Bulterys, & Fowler, 2003).

Even with the introduction of antiviral retrotherapies such as HAART and AZT, infants from communities that have been historically disenfranchised (e.g., poor and African-American) continue to be born with HIV. In a national surveillance study, Peters and colleagues (2003) found that, of those infants born with HIV, 18% of infected mothers received no prenatal care, 29% had prenatal care but were not tested for HIV before delivery, and 9% had HIV diagnosed during pregnancy but did not receive antiretroviral treatment.

To truly understand the cause of the racial and socioeconomic disparities inherent to the disease, practitioners and theorists must move beyond individual level factors and examine larger contextual systems that serve as potential barriers for adequate medical care. By solely examining only the molecular basis of HIV and neglecting to understand the macrosystem, current research is contributing to what Farmer and colleagues (2006) call the "desocialization of scientific inquiry" (p.1686). Desocialization continues to plague the current medical system, as physicians may not feel responsible for intervening with HIV on a structural level, and view macro-level changes as the responsibility of politicians and other public policy makers, instead exclusively focusing their energies on individual lifestyle factors. Both Shannon and colleagues (2008) and Farmer and colleagues (2006) suggest that structural forces inherent in contemporary society are the key derivation of all epidemic diseases and by not intervening at the structural level, medical professionals are neglecting to take into account the environmental and macro-level forces responsible for the continued racial and social disparity inherent in epidemiology of HIV.

Rhodes et al. (2005) define those structural variables that increase an individual's likelihood of acquiring HIV as their "risk environment" (p.85). This concept is closely linked to Galtung's (1969) definition of "structural violence", later described by Weigert (1999) as the economic, political, legal, religious, and cultural structures that serve as barriers preventing individuals or communities from resilience over adversity and acquiring their full potential. Applied to the healthcare system, structural violence is comprised of institutional racism, stigmatization and toxic environments inherent in the existing macrosystem that prevent underserved disenfranchised populations from receiving both comprehensive and affordable healthcare, thus continuing the spread of HIV in low-SES African Americans in urban centers

(Farmer et al., 2006). Structural violence is often associated with biological consequences, thus, redefining HIV as a disease with a *biosocial* origin. Therefore, effective treatment and intervention must take into account the interplay of socialization and biology so that therapies remain sustainable within the population.

Lane and colleagues (2004) applied the conceptual framework of structural violence to examine the risk environments contributing to the disparate rates of HIV among African American women living in a large urban center in the Northeast. Upon examining the ecology of the HIV transmission longitudinally, Lane and colleagues found three ecologic pathways responsible for HIV transmission including community rates of infection, concurrent partnerships, and increased vulnerability. These pathways were then divided into specific risk-promoting environments including disproportionate incarceration rates of African-American men, segregation, socially toxic neighborhoods, and limited access to sexually transmitted disease services, a skewed sex ratio whereby women outnumber men, stigmatization of homosexuality and increased sales of douching products known to increase risk of HIV transmission. Lane et al. conclude that the accumulation of risk environments inherent within the three ecological pathways increases African-American women's exposure to HIV. Yet in order to establish effective treatment and decrease the transmission of disease, medical professionals must be educated that risky individual-level behaviors take place in social contexts in which structural violence impedes sexually responsible behavior.

Cognitive and Behavioral Sequelae of HIV

In addition to its impact on the immune system, HIV is known to directly attack the central nervous system, with effects ranging from mild to severe (Heaton et al., 2004). The consequences of this infection are more devastating for PHIV+ infants because children's

neurological systems are still developing in utero (Landau, Meyers & Pryor, 2006). These infant neurological indicators are called HIV-Associated Minor Cognitive Motor Disorder (MCMD) and HIV Encephalopathy (Bartlett & Ferrando, 2004; Heaton et al., 2004), which involves impaired brain growth, motor dysfunction, developmental delays, and the loss of developmental milestones (Landau, Meyers & Pryor, 2006). Subclinical functional impairment deficits are often observed as early as 4 months, long before other physical and immunity-related markers of HIV, and if left untreated can develop into later global delays in neurocognitive development evidenced in childhood, adolescence, and adulthood (Woods et al., 2009). In addition to increased HIV infection risk, infants born to HIV+ mothers may be at an increased risk for later mental health problems (Brouwers, Belman & Epstein, 1991; Castellon et al., 2006) and delayed psychomotor development (Mellins, Levenson, Zawadzki, Kairam, & Weston, 1993).

Although the use of HAART has also had a positive impact on the incidence of HIV-associated neurocognitive disorders and encephalopathy, PHIV+ infants who continue to receive limited or no postnatal care consistently demonstrate poorer neurocognitive outcomes (Willen, 2006). HAART has also increased the lifespan of children infected with HIV, thus providing researchers an opportunity to investigate the longitudinal impact of HIV on neurocognitive abilities of PHIV+ adolescents and adults (Smith et al., 2012). Limited existing longitudinal assessment of intellectual functioning of PHIV+ children has documented significant declines in test scores associated with encephalopathy, and subsequent increases in scores after antiretroviral treatment that exceed the magnitude and rate of interval change expected by practice effects (Wolters, Brouwers, & Moss, 1995).

Neurocognitive functioning is often investigated through the use of standardized assessments of intelligence in order to compare PHIV+ children's cognitive profiles to the

national sample or age-matched controls. The developmental and cognitive deficits associated with PHIV+ have been well documented in the literature including specific impairments in mental and motor development in infants and toddlers (Chase et al., 2000), expressive language, attention, perceptual motor abilities, and motor function in school-aged children (Wolters, Brouwers, Moss, & Pizzo, 1995). Additional difficulties with abstraction, executive functioning, learning, attention, working memory, and verbal ability dysfunction have been noted in adulthood (Heaton et al., 2004).

Existing literature suggests cognitive abilities in the low average to average range, with a mean verbal IQ of 85, a mean performance IQ of 90, and the mean full-scale score of 86, with specific deficits in areas such as working memory and executive functioning (Nozyce et al., 2006; Smith et al., 2012). These cognitive skills also affect late reading ability, which has been demonstrated to be an average of one standard deviation below the national mean (Colegrove & Huntzinger, 1994).

In addition to documentation of neurodevelopmental deficits associated with HIV, comorbid adaptive behavior problems such as impulsivity, hyperactivity, and difficulties attending to and focusing on stimuli are well described in the literature (Mellins et al., 2011; Nozyce et al., 2006; Wolters, Brouwers, Moss, & Pizzo, 1994). Emotion and behavior difficulties can range from mild symptoms to psychosis (Landau, Meyers & Pryor, 2006), placing PHIV+ children at a higher risk for psychiatric hospitalizations during childhood and early adolescence (Gaughan et al., 2004).

For children diagnosed with advanced stages of encephalopathy, autism-like behavior has been noted including marked social isolation, diminished goal-directed behavior, apathy, flat affect, and impaired social-emotional expressiveness (Landau, Meyers, & Pryor, 2006; Pulsifer

& Awylward, 2000; Wolters, Brouwers, Moss & Pizzo, 1995). In non-encephalopathic children, several studies have noted behavior associated with attention-deficit/hyperactivity disorder (ADHD) including impulsivity, hyperactivity, and difficulties attending to and focusing on stimuli (Mellins et al., 2011; Nozyce et al., 2006; Smith et al., 2012).

The comorbid behavioral conditions observed in the PHIV+ population have been supported by advances in neuroimaging which have found HIV involvement in the neurologic function of the frontal cortex, basal ganglia, and connecting structures in the central nervous system (CNS) associated with regulation of attention and behavior, areas problematic in children diagnosed with ADHD (Mialky, Vagnoni, & Rutstein, 2001). In addition, as seen in the neurocognitive manifestations of the illness, HAART has had a significant impact on ameliorating the progression of maladaptive behavior. Brouwers and colleagues (1995) found that after 6 months of antiretroviral treatment, the encephalopathic patients exhibited a significant decline in autistic and depressed behaviors. These behaviors appear to reflect direct effects of the virus on the CNS since they were associated with encephalopathy and improved after treatment with an antiretroviral agent that crossed the blood-brain barrier.

Researchers have become interested in identifying the biologic, environmental and psychosocial factors associated with poor cognitive and adaptive functioning in order to establish a model of HIV impact. Smith and colleagues (2012) examined the impact of disease severity on cognitive and adaptive functioning in a multisite cross-sectional analysis of perinatally HIV-infected and HIV-exposed youth. Youth and caregivers completed the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) and the Adaptive Behavior Assessment System, Second Edition (ABAS-II, Harrison & Oakland, 2003). Using linear regression, Smith and colleagues found that overall mean scores on measures of cognitive and

adaptive functioning were in the low average range across perinatally-infected youth with and without AIDS-defining illness and perinatally HIV-exposed but uninfected youth. No statistically significant differences between groups were observed in adaptive functioning.

After adjusting for covariates, mean full-scale IQ scores were significantly lower for the perinatally-infected HIV+ youth with AIDS defining illness cohort (M = 77.8) than the perinatally-infected HIV+ youth with no previous AIDS defining illness (M = 83.4) and the HIV exposed but uninfected youth. (M = 83.3). No statistically significant differences were observed among any of the groups in any of the domains within the cognitive assessment. The lower cognitive performance observed in the HIV+ with AIDS-defining illness was found to be primarily attributable to a prior diagnosis of encephalopathy. Particular findings regarding the discordance in cognitive and adaptive functioning are of interest to the proposed study. Smith et al. found high rates of agreement between cognitive and adaptive functioning across all HIV infected and exposed subgroups including those with a CDC Class C (AIDS) event. The highest rate of discordance was found for the HIV+/C group, who demonstrated cognitive but not adaptive functioning impairment relative to the other participant groups (p<.01). Smith et al.'s (2012) findings uniquely contribute to the literature by examining *both* the behavioral and cognitive impact of HIV in a large pediatric sample.

Rationale for the Proposed Study

Although a preponderance of extant literature suggests that mental health conditions and neurocognitive deficits are related to both disease severity and psychosocial factors (Gadow et al., 2012), very little is known regarding which of the psychosocial and disease related variables have the greatest impact on the outcomes observed in youth perinatally exposed to and infected with HIV, which may be due to the inherent complexity of the disease. The direct effects may

damage the functioning of the CNS and result in varying degrees of developmental dysfunction and comorbid behavioral conditions. In addition, exposure to HIV among children often occurs in the context of psychosocial factors that pose equal or greater risks to a child's development. Most PHIV+ children in the US experience a variety of environmental factors including familial chronic illness, loss, family disruption, poverty, parental drug use, and social stigmatization that may directly or indirectly influence their behavioral functioning.

Because of these reasons, previous studies have faced significant challenges including small sample sizes, poor statistical design, and an absence of an age-matched control group (Smith et al., 2012), thus significantly limiting generalizability of findings. In addition, many studies were performed in the context of clinical drug trials that may significantly limit important environmental and contextual information that may be examined in natural history studies (Smith et al., 2006).

At this time, no existing study has attempted to comprehensively investigate the complex relationship among disease severity and psychosocial factors and their impact on cognitive functioning (CF) and behavioral functioning (BF) as the exact pathways and directionality of these relationships remain unknown. Building upon the findings of Smith et al. (2012), the purpose of this study was to evaluate a structural equations modeling (SEM) approach to understand the complex inter-relationships between home environment, caregiver characteristics, psychosocial characteristics, and CF on behavioral outcomes. Founded in the extant literature, theory and research, specific paths have been drawn in order to establish a conceptual model of impact and to determine the extent to which the theoretical model is supported by the data (See Appendix A). As evidenced in the exogenous measurement model, both the latent concepts of disease severity and psychosocial are comprised of specific variables that have been found to

have a significant effect on both CF and BF. A correlation has been explicitly drawn between psychosocial and disease severity suggesting a hypothesized synergistic and co-varying relationship. Two separate paths have been drawn from psychosocial and disease severity to CF functioning, suggesting that each latent variable uniquely predicts CF. A mediational relationship has been drawn such that CF mediates the relationship between both environmental and disease severity factors and behavioral functioning. In the endogenous measurement model, the latent variable of behavior has been defined as both the internalizing and externalizing index scores on the *Behavioral Assessment System for Children* (BASC-2; Reynolds & Kamphaus, 2004). Paths from disease severity factors to behavior and environmental stressors to behavior have been included to compare the direct and indirect effects.

This study addressed the following research questions in order to evaluate a structural equations modeling (SEM) approach to understand the complex inter-relationships between home environment, caregiver characteristics, psychosocial characteristics, and CF on behavioral outcomes: Do disease severity markers correlate with psychosocial factors? What is the association between psychosocial factors and both cognitive functioning and behavior? What is the association between disease severity markers and both cognitive functioning and behavior? How does cognitive functioning mediate the relationship between disease and psychosocial factors and behavior? Overall, how do behavioral and cognitive profiles differ between perinatally HIV-infected youth and perinatally HIV-exposed but uninfected youth?

It was hypothesized that disease severity immunologic variables and psychosocial factors would demonstrate a robust correlation. Further, it was hypothesized that both psychosocial factors and disease severity would be associated with both behavior and CF, but that CF would mediate the relationship between disease severity and psychosocial factors and behavior.

Finally, it was hypothesized that the cognitive and behavioral profiles of PHEU and PHIV+ children would not differ due to similar psychosocial factors such as SES, living with birth caregivers, parental education, single parent home, parent mental health and parental employment.

CHAPTER 2

Literature Review

Understanding the role of perinatal HIV infection in influencing cognitive and behavioral functioning (BF) is a complex process of disentangling the biologic effects of HIV from other psychosocial factors. Brouwers, Belman and Epstein (1991) describe these disease-related and psychosocial factors as the direct and indirect effects of HIV. Direct effects are those central nervous system (CNS) abnormalities evidenced by neuropathic and neurobiologic changes that affect both neurocognitive functioning and adaptive behavior. Indirect effects are described as the psychosocial and socio-contextual variables associated with living with HIV. Although the cognitive and psychosocial sequelae of HIV are well described in the literature, limited consensus exists regarding the *origin* of these deficits necessary to develop a theory of impact.

This chapter will provide a description of HIV and its impact on the CNS, outline both the direct and indirect effects of HIV on both neurocognitive functioning and behavior, and review the current literature regarding proposed theories of impact (See Appendix A).Articles included in the literature review were published in peer-reviewed journals in the past 30 years, at the height of the AIDS crisis, to the present literature, which has incorporated the use of *f*MRI technology and a renewed focus on both environmental and structural factors responsible for HIV transmission. Overall findings as well as methodological strengths and weaknesses will be discussed.

HIV and its Direct Effect on the Central Nervous System

Before reviewing the impact of HIV on both CF and BF, it is necessary to describe how HIV disrupts the neurologic functioning of the CNS. Immediately upon exposure, HIV quickly crosses through blood brain barrier (BBB) via a "Trojan Horse" mechanism comprised of

infected monocytes and lymphocytes (Hult, Chana, Masliah, & Everall, 2008). From here, the virus continues to infect the monocyte-macrophage and lymphocyte cells, which disrupts the functioning of the temporal and parietal cortices. Additional structural and functional impairments, most notably the basal ganglia, have been found in HIV-infected patients, which has the most demonstrated neurotoxic effects. This specific neurodegeneration has been implicated as the primary source of the neurocognitive impairment associated with HIV (Moore et al., 2006). Because subcortical-frontal areas of the brain are most often negatively impacted, this results in potential decreased attention and concentration abilities, psychomotor slowing, reduced speed of information processing, executive dysfunction and verbal memory impairment (Bartlett & Ferrando, 2004; Heaton et al., 2004).

These neurodegenerative symptoms may manifest differently in children who have been perinatally affected (Violari et al., 2008). Complications related to CNS impairment may be more apparent as perinatally impacted children who may not have the appropriate T-cell, B-cell, or cytokine necessary for an immunologic response. Early CNS infection has been associated with more intensive neurologic involvement including the loss of previously acquired intellectual and motor milestones and developmental delay (Coplan et al., 1998; Pearson et al., 2000; Poirier et al., 2003; Whitt et al., 1993).

HIV and its Direct Effect on Cognitive Functioning

Direct effects are defined as the central nervous abnormalities evidenced by neuropathic and neurodialogic changes that influence neuropsychological functioning (Wolters, Brouwers, Moss & Pizzo, 1995). In patients with HIV, the brain is the second most frequently infected organ after the lungs (Masliah, DeTeresa, Mallory & Hansen, 2000) and has been documented by clinicians since the first known cases of HIV in the United States (Antinori et al., 2007;

Woods, Moore, Weber & Grant, 2008). Before the introduction of HAART in 1996, patients experiencing neurocognitive impairment were often significantly impacted, resulting in permanent brain damage, psychosis, and AIDS-related dementia (Navia, Jordan & Price, 1986). Despite medical advances and the initiation of HAART, mild neurologic disease continues to be observed in approximately 30% of persons with asymptomatic HIV infection and about 50% of individuals with AIDS (Heaton et al., 1995; Valcour, Sithinamsuwan, Letendre & Ances, 2011).

In order to investigate HIV-related neurocognitive effects, the AIDS Task Force of the American Academy of Neurology (AAN; 1991) was founded during height the AIDS crisis, and was responsible for establishing nomenclature and diagnostic guidelines for classifying the neurologic complications of HIV infection, now called HIV Associated Neurocognitive Disorders (HAND). AAN initially described two levels of disturbance including HIV-associated dementia (HAD) with motor, behavioral/psychosocial, or combined features; and minor cognitive motor disorder (MCMD). Patients with HAD demonstrated at least two neurocognitive impairments that negatively affected activities of daily living, abnormal motor or maladaptive psychosocial functioning. MCMD was less severe presentation of HIV-associated neurocognitive impairment and was defined as deterioration in at least one neurocognitive or behavioral area.

These original diagnostic descriptions were amended by an NIH working group (Antinori et al., 2007) who redefined research diagnostic categories of HAND, identifying HIV-associated dementia (HAD) as the most severe form of injury, mild neurocognitive disorder (MND) , a milder form of impairment that still impacts daily activities of living and a new category termed asymptomatic neurocognitive impairment (ANI) to recognize individuals with minor impairments evidenced on neuropsychological testing but who continue to demonstrate functional limitations.

In addition, the new guidelines provided by the NIH working group organize comorbid CNS complication as "incidental", meaning that the patient has a remote history of engaging drug use or other behaviors is unlikely to have residual cognitive effects, "contributing", meaning that an individual has engaged in neurocognitive risk behaviors within one year and is exhibiting clear signs of HIV-related cognitive decline, and "confounding", meaning that the individual is acutely impacted by neurocognitive risk behaviors (Antinori et al., 2007).

Cognitive Sequelae of HIV

Significant research has been dedicated to investigating the pathogenesis of immunologic markers of HIV, but the mechanisms responsible for cognitive impairment remain unknown and widely disputed in the current literature (Biggar et al., 2000; Mellins et al., 2009; 2011). The synthesis of these findings may also be difficult due to additional physiological deficits such as hearing loss (Laughton et al, 2013) and other gross and fine motor deficits (Govender et al. 2011) that may confound existing CF assessment scores. Most often, the presence of cognitive dysfunction is determined by the assessment of at least five areas of CF known to be affected by HIV infection (e.g., attention, working and episodic memory, executive functions, sensoriperception and language) using a performance-based cognitive battery and interpreted using demographically-appropriate normative data (Lyon, McCarter, & D'Angelo, 2009). In more recent work, the use of functional magnetic resonance imaging (*f*MRI) has allowed researchers to examine brain activity and neuronal activation by detecting associated changes in blood flow (Chang et al., 2001). HIV+ patients often receive neuropsychological assessment to update their annual cognitive profile as it provides unique information regarding pediatric HIV disease progression and assists physicians in predicting long-term outcomes in pediatric patients (Pearson et al., 2000).

The following section will review the extant literature regarding the specific cognitive sequelae related to the direct impact of HIV CNS impairments and review a key study that has directly investigated the impact of HIV on a specific cognitive function. The subsequent section will review the extant literature that has focused on the *direct* effect of immunologic severity on CF. As demonstrated by the literature in the last 25 years, specific insult to the fronto-parietal and basal gyrus areas of the brain has resulted in a unique cognitive profile of patients with HIV, including deficits in attention, working memory, episodic memory, executive functions, spatial processing and language. It is important to note that many of reviewed studies contain adult participants, which reflects the general dearth of pediatric HIV literature regarding the developmental neurocognitive sequelae of the disease.

HIV and its Direct Effect on Specific Areas of Cognitive Functioning

Attention

Attention is one of the well-documented functional impairment associated with the cognitive sequelae of HIV in adults and has been demonstrated to increase in magnitude with disease severity (Grant et al., 2005; Hardy & Hinhn, 2002). In beginning stages of HIV disease, basic attention/concentration in patients reflects the non-infected individuals (Reger et al., 2002; Willen, 2006), but for those with perinatally-acquired HIV or more advanced stages, deficits continue to become apparent both with age and disease severity. Specific deficits include automatic attention processes that are necessary during cognitive tests requiring controlled processing (Hardy & Hinhn 2002). This attention profile has been linked to decreased fronto-parietal activation (Chang et al., 2004) and may impact activities of daily living that require sustained attention and memory including driving (Marcotte et al., 2006) and medication adherence (Abaasa et al., 2008).

Chang and colleagues (2001) evaluated the neural correlates of attention and working memory deficits in adult male patients with HIV and their matched controls on a sequential letter-number sorting task. *f*MRI technology allowed the investigators to examine the brain regions activated during each task and were mapped on the brain surface. Results suggested that patients with HIV demonstrated greater brain activation blood oxygenation levels on dependent signal changes in the front-parietal regions compared with control subjects while performing the identical tasks ($p<.05$). For the simpler tasks, patients with HIV showed greater activation in the parietal regions ($p<.01$). For more difficult tasks, patients with HIV showed greater activation additionally in the frontal lobes ($p<.01$). Additionally, HIV+ participants were 23% slower on the most difficult task ($p<.0001$). Chang concluded that these task-dependent activation patterns may be due front-parietal brain injury observed in patients with HIV, resulting in decreased ability to modulate attention.

Working Memory

Because fronto-parietal dysfunction impacts attention and working memory similarly (Woods et al., 2009), patients with HIV have also demonstrated significant difficulties with both visual and verbal working memory tasks (Bartok et al.. 1997; Farinpour et al.. 2000; Martin et al., 2007). The impact of HIV on working memory is often global and includes insult to the patient's short-term memory storage, information maintenance across time delays, or immediate memory manipulations (Martin et al., 2001).

Stout and colleagues (1995) examined the working memory of 147 HIV+ men and their matched controls using the Reading Span Test and the Digit Span subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987). Pairwise comparisons suggested that symptomatic HIV+ subjects were impaired relative to HIV− control subjects on the Reading

Span subtest ($F(3,166)=2.80$, $p<.05$) with even mildly symptomatic HIV+ groups exhibited a trend toward impairment ($p<.05$). Significant group effects were also found for both the Digit Span Forward (F (3,179) =3.12, $p<.05$) and Digit Span Backward (F (3,179) =2.59, p=.05). Mildly symptomatic HIV+ groups exhibited a trend toward impairment ($p<.05$).Additional correlations suggested a strong correlation between neurological dysfunction and working memory tests ($p<.001$). Stout et al.'s results indicate that deficits in working memory are apparent in HIV-infected individuals with more significant impairments than in individuals with less symptomatic HIV.

Episodic Memory

Episodic memory dysfunction has been estimated to as affect as many as 60% of patients with HIV (Rippeth et al., 2004) and is one of the key indicators of the onset of HAND (Carey et al., 2004; Gongvatana et al., 2007). Similar to both attention and working memory, episodic memory is highly dependent on frontal systems. Patients with HIV have demonstrated a unique episodic memory profile that is characterized by dysfunctional strategic encoding abilities, retrieval of future intentions and difficulties with free recall on verbal word lists and visual design tasks (Carey et al., 2006; Delis et al., 1995). HIV infection is associated with frequent episodic memory complaints as it relates to activities of daily living, such as driving and remembering to take medication consistently (Marcotte et al., 2006; Woods et al., 2007).

Castelo, Sherman, Courtney, Melrose and Stern (2006) investigated the integrity of hippocampal-prefrontal circuitry during episodic encoding in patients with HIV. Using *f*MRI techniques, Castelo and colleagues observed changes in blood oxygenation level-dependent (BOLD) signal in HIV+ participants and matched control subjects while during an episodic encoding task in which patients viewed novel or repeated stimuli. Subjects also completed the

National Adult Reading Test (NART: Nelson & Willison, 1991) a neuropsychological measure of attention and memory. HIV+ demonstrated significantly lower verbal IQ ($p<.01$). A repeated measures analysis of variance was conducted to examine the proportion of responses for each item, revealing a main effect of response level (F (4, 23) =10.48, $p<.001$) and a trend toward interaction of disease status and response level; (F (4, 23) =2.54, $p<.067$). Additional chi-square tests suggested that the HIV+ group differed in response accuracy on both repeated and novel picture tasks ($p<.001$).

*f*MRI scans revealed that the HIV group demonstrated significantly reduced signal intensity changes in the right posterior hippocampus, right inferior frontal gyrus, and left lingual gyrus ($F(1,26)=4.47$, $p<.05$). Additionally, the HIV group exhibited more activity within lateral frontal and posterior parietal regions, suggesting a functional alteration of the hippocampal-prefrontal regions during episodic encoding in HIV-positive patients (F (1, 26) =3.502, $p<.05$). Castelo and colleagues' (2006) findings extended the existing theoretical consensus, suggesting that HIV may influence both the fronto-striatal circuits and hippocampal system.

Executive Functioning

Executive functioning is defined as a group of higher-order cognitive functions involved in problem solving, goal-directed behavior and self-direction (Mega & Cummings, 1994). As reviewed in the memory and attention literature, intact executive functions are heavily reliant on the frontal cortex as well as the basal ganglia (Stuss & Levine, 2002). Compared with other cognitive areas such as attention and memory, relatively fewer studies have examined the underlying component cognitive processes of executive dysfunction in HIV (Woods et al., 2009), but the importance of understanding executive functioning is apparent. A study by Dawes and

colleagues (2008) found that executive functioning impairments were the most central cognitive impairment across all of the observed neurocognitive impairment profiles.

An early study by Sahakian and colleagues (1995) investigated the cognitive impairments in both HIV+ males and their matched controls using computerized neuropsychological tests from the CANTAB battery. The CANTAB battery assessed the patients' visuospatial memory, attention and executive function. Results suggested that both the asymptomatic and the symptomatic HIV+ subjects demonstrated impairment in the areas of executive functioning including pattern recognition ($F(2,55)= 3.27$, $p<.05$), spatial working memory, ($F(2,55)=4.65$, $p<.01$) the Tower of London task ($F(4,96)=2.7$, $p<.05$) and attentional shift-setting ($F(2,46)=8.37$, $p<.05$) but unimpaired on verbal fluency on the NART and spatial span. Sahakian and colleagues' findings were particularly important as they both supported the existing literature regarding the role of fronto-parietal dysfunction in executive functioning and demonstrated that the cognitive deficits associated with HIV are present even before the onset of clinical symptoms.

Spatial Perception

Additional investigations have examined selected aspects of spatial cognition, defined as the ability to detect, understand, manipulate, and integrate visual stimuli in the context of its environment (Woods et al., 2009). Unsurprisingly, many of these studies also noted that deficits occur in spatial abilities that rely heavily on the fronto-parietal networks. Particular dysfunction has been noted in egocentric spatial tasks including both covert orienting and perceptual span (Woods et al., 2009).

Olesen, Schendan, Amick and Cronin-Golomb (2007) compared the performance on mental rotation and hierarchical pattern perception in HIV+ men and their age-matched controls.

In a mental rotation task, two objects appear in different orientations and examinees are asked if they are identical to each other or mirror images. On a hierarchal pattern perception task, target letters are presented in a hierarchal manner and attention must be cued to either the letter-or global level. Additional neuropsychological measures were included to examine visuospatial ability including the Standardized Road-Map Test of Direction Sense (Money, 1976), The Hooper Visual Organization Test (Hooper, 1983), the Benton's Judgment of Line Orientation test (JLO; Benton, Varney, & Hamsher, 1978) and The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983).

Olesen and colleagues (2007) found that on both the MR and HPP tasks, HIV+ participants demonstrated significantly longer reaction time ($p<.001$) and more errors ($p<.001$). Significant differences were found on both the Roadmap Assessment ($p<.01$) and the JLO ($p<.01$). Taken together, results suggest that HIV is associated with significant impairment in the parietal-dependent visuospatial tasks, a different finding than both Chang et al. (2001) and Castelo et al. (2006).

Language

Verbal fluency is perhaps the most widely studied aspect of expressive language (Iudicello et al., 2007) and one of the most prominently affected cognitive features of HIV infection in children (Wolters et al., 1995). Verbal fluency impairment is estimated to occur in approximately 40% of the HIV+ population (Rippeth et al. 2004). Specific HIV-related verbal fluency deficits include impairment in specific search and retrieval from lexicosemantic memory stores, which may be reflective of the fronto-parietal dysfunction (Woods et al., 2004).

Evidence of language development insult may be apparent early in development. Coplan and colleagues (1998) compared the language development in infants and young children with

HIV infection to exposed but uninfected controls using the Early Language Milestone Scale (Coplan, 1993; ELM-2). The authors found that global language scores were significantly lower for subjects with HIV infection (M = 89.3), compared with uninfected subjects (M= 96.2; p<.05, Mann-Whitley U test). In addition, subjects with HIV infections scored more than two standard deviations below the mean on the ELM-2 on at least one occasion and continued to demonstrate a deterioration of language functioning.

Recent work has demonstrated a renewed interest in the receptive language abilities of HIV+ patients. Brackis-Cott, Kang, Dolezal, Abrams and Mellins (2009) compared the receptive language ability, word recognition skills, and school functioning of older school-aged children and adolescents perinatally HIV infected and perinatally exposed controls. Participants completed several language measures including the Peabody Picture Vocabulary Test, Third Edition (PPVT-III; Dunn & Dunn, 1959) and the Reading Subtest of the Wide Range Achievement Test, Third Edition (WRAT-3; Wilkenson & Robertson, 2006). Caregivers were interviewed regarding demographic characteristics and current academic placement. Brackins-Cott and colleagues found that HIV-positive participants scored lower than exposed controls on both the PPVT-III (M=83.8 vs. 87.6, t=*2.21*, p<.05) and on the WRAT-3 (M=88. 2 vs. 93.8, t=2.69. p<.01). HIV immunologic status remained significantly associated with PPVT-III and WRAT-3 standard scores after adjusting for other demographic variables.

Taken together, research investigating the cognitive sequelae of HIV provides a unique cognitive profile for both infected and exposed children and adults. Across all of the reviewed studies, the fronto-parietal region and the basal gyrus have been widely implicated as the primary areas of neurodegenerative impact. Both *f*MRI studies and standardized cognitive assessments such as the Wechsler series have been utilized extensively and have demonstrated rich findings

regarding the specific cognitive areas of impact. Alternatively, very few of the reviewed studies have demonstrated a causal relationship between CNS damage and cognitive outcomes. This lack of demonstrated causality may be due to the limited inclusion of other environmental variables that may serve as either protective or risk factors for cognitive outcomes.

In addition, although both Violari and colleagues (2008) and Coplan and colleagues (1998) suggest that neurodegenerative symptoms may manifest differently in children who have been perinatally impacted and may demonstrate more intensive neurologic damage, very few studies have examined direct effects of the HIV+ CNS on cognitive outcomes in children, a significant gap and important area for intervention development and resiliency work.

HIV and its Indirect Effect on Cognitive Functioning

A strong emphasis has been placed on the investigation of CNS mechanisms responsible for the neurocognitive degeneration in the HIV population, but recent attention, primarily from the developmental literature has begun to examine the surrounding environmental stressors that may also account for lower cognitive functioning. Hochhauser, Gaur, Marone and Lewis (2008) describe these stressors as "environmental neurotoxins" (p. 693), and include family dysfunction, socio-emotional functioning, chronic poverty and limited emotional support in their definition. This may be why Landau, Meyers and Pryor (2006) describe HIV as a "family condition" (p. 877). Biographical profiles suggest that HIV+ families face numerous daily stressors including poverty, limited education, psychological and physical manifestations of their own illness, further placing their child at risk for poor cognitive development independent of current HIV serostatus (Brown & Lourie, 2000; Landau, Meyers & Pryor, 2006; Sherwen & Boland, 1994).

Home Environmental Stressors

As early as the Harlow rhesus monkey studies (Harlow & Zimmerman, 1959), developmentalists have identified the relationship between environmental deprivation and its impact on intelligence. In animal models, indigent environments have been associated with impaired hippocampal functioning, important for both cognitive and emotional functioning (van Praag, Kempermann & Gage, 2000). For both healthy and at-risk children, the home environment may account for a significant proportion of the variance in CF (Bradley et al., 1989; Brooks-Gunn, Klebanov, & Duncan, 1996). For families preoccupied with daily crises, the lack of toys, attachment experiences and teaching opportunities has been inextricably linked to both reduced IQ scores (Bradley et al., 1989) and may account for 33-50% of the decreases in academic performances for children in poverty (Korenmann, Miller & Sjaasted, 1995).

In pediatric patients with CNS insults, the home environment may be especially important. Bradley and colleagues (1993) found that for pre-term infants and children with traumatic brain injury, the association between the home environment and CF varied as a function of the child's CNS integrity. These specific environmental aspects and their associations with CNS factors may explain the variability in CF of children with HIV infection. Protective mechanisms such as an enriching home environment, secure attachment and parental health may promote appropriate cognitive development in children with HIV and the stressors in these areas may in turn serve as risk factors for later cognitive dysfunction (Coscia et al., 2001).

Hochhauser, Gaur, Marone and Lewis (2008) investigated role of environmental risk factors, parental stress on IQ in HIV+ pediatric sample. Hochhauser and colleagues collected indicators of environmental risk including caregiver demographics, stability of child's schedule, number of children in home and changes in home occupants and combined into one global risk score. Using Pearson product correlations to examine the relationship between environmental

risk, CD4 count, and IQ, results indicated a significant positive correlation between CD4 and IQ (r=.25, p<.05), with higher levels of immunocompetence predicting higher IQ scores. However, when subjects were dichotomized between high and low environmental risk groups, only the relationship between CD4 and IQ was significant in the high environmental risk group (r=.48, p<.01). The authors suggested that the HIV envelope protein-gp120 might only be toxic to the fronto-parietal region under conditions of high stress but not low stress, thus moderating the relationship between HIV and IQ.

Coscia and colleagues (2001) investigated the effects of the home environment, socioeconomic status (SES), and health status on CF in a sample of children with HIV infection. Self-reports of home environment including play materials, parental involvement, variety of stimulation, and parental attitudes toward the provision of a cognitively stimulating environment were completed by caregivers. CF was assessed using the McCarthy Scales of Children's Abilities (MSCA; McCarthy, 1972), the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler, 1989) and the Wechsler Intelligence Scale for Children–3rd Edition (WISC-III; Wechsler, 1990). Participants ' medical charts were reviewed for information pertaining to disease severity factors. Coscia and colleagues found that SES was significantly correlated with home environment, $r2$=.32, F (1, 41) = 18.9, p< .001, and with child IQ, *(standardized coefficient*= .18, F (1, 41) =8.9, p< .05). Home environment was significantly associated with IQ after controlling for SES, *(standardized coefficient*=.13, F change= 7.3, p< .001). Taken together, health status and home environment accounted for 63% of the variance in IQ scores, suggesting that home environment acts as a moderator of the relationship between HIV and IQ.

Institutionalized children provide researchers with the unique opportunity to directly examine the role of low resource settings, social deprivation and its impact on later cognitive and socio-emotional development (Bos et al., 2011). In an international study of institutionalized children, Dobrova-Krol, van Ijzendoorn, Bakermans-Kranenburg, and Juffer (2010) compared the physical and cognitive development of HIV-infected children in both a family and institution with similar disease severity. Rearing environment was assessed using the Early Childhood HOME Inventory, a measure of quality and quantity of stimulation (Bradley et al., 1993). Measures of disease severity and development included CD4 counts, diurnal salivary cortisol sampling, and measures of physical growth including height, weight and head circumference. Cognitive ability was measured using the Dutch SON-R (Tellegen & Laros, 1993), a test of nonverbal intelligence including visual-spatial abilities and abstract reasoning.

Preliminary analyses suggested that both groups of HIV-infected children had lower supine length at birth than their uninfected counterparts, with a significant difference between uninfected family-reared children and HIV-infected institution-reared children ($p < .01$). Cognitive performance on the SON–R of the uninfected family-reared children was in the average range ($M = 98.94$, $SD = 19.59$), while performance of HIV-infected family-reared children was in the borderline deficiency range ($M = 79.07$, $SD = 16.90$). Performance of the uninfected institution-reared children ($M = 69.73$, $SD = 21.28$) and HIV-infected children ($M = 64.00$, $SD = 8.59$) fell in the range of mental deficiency.

Additional multivariate analyses were conducted to examine the difference between the groups as a function of the rearing environment and HIV status. Significant overall effects were found for rearing environment, $F(3, 44) = 10.23$, $p < .01$, and for HIV status, $F(3, 44) = 3.01$, $p < .05$. Subsequent ANCOVAs demonstrated main effects for rearing environment and HIV status

for both height and cognitive performance and a higher than the environment of HIV-infected family-reared children on the Physical Environment subscale, ($F(1, 27) = 24.11$, $p < .01$ (d =1.94), and the Variety subscale, $F(1, 27) = 8.23$, $p < .01$ (d =1.11), and significantly lower on the Acceptance subscale, $F(1, 27) = 13.31$, $p < .01$ ($d = 2.84$). Correlations were computed between the HOME subscales and SON–R scores. For the whole group of HIV-infected children, higher SON–R scores were related to more Language Stimulation ($r = .54$), and more Acceptance ($r = .42$). For HIV-infected family-reared children higher SON–R scores were related to more Language Stimulation ($r = .50$). For HIV-infected institution-reared children, higher SON–R scores were related to higher total HOME scores ($r = .66$).

Taken together, the impact of environment (home v. institutional) on cognitive performance was greater than the impact of HIV infection suggesting that family care, even if in deprived environments, was found more favorable for children's physical growth and cognitive development, thus serving as a moderator of relationship between HIV status and IQ.

Familial Health Stressors: Drug and Alcohol Exposure

Regardless of HIV status, drug and alcohol exposure has a well-documented deleterious effect on child cognitive development. Perinatally acquired HIV+ children may be at greater risk within families with a history of drug abuse, who may have initially acquired HIV through injection of illicit substances placing their unborn child at an increased risk for low birth weight, poor intrauterine growth, neonatal infections and chorioamnionitis (Nair et al., 1993).

Tassiopoulos and colleagues (2010) evaluated the prenatal substance use in a cohort of HIV+ parents and their PHEU children. The authors found that substance use was reported by 29%; the most common substances reported were tobacco (18%), alcohol (10%), and marijuana (7.2%). Substance use was more common in the first trimester (25%) than the second (17%) and

third (15%), suggesting that even though there is a decrease, substance use is still a persistent issue within HIV+ families. In utero drug exposure can have a severe impact on not only the development of the fetus but also the cognitive development child later in life including a 7-point decrement in IQ (Streissguth, Barr & Sampson, 1994), significant difficulties with sustained attention (Richardson, Conroy & Day, 1996) and a lower likelihood of achievement of IQ above the normative mean (Singer et al., 2004).

Because of the behavioral profile associated with HIV (see following section), perinatally acquired HIV+ youth may be more susceptible to persistent alcohol use that in turn, impacts CF. Green, Radu, Saveanu and Bornstein (2004) examined the potential effect of parental alcohol use on CF and its interaction with HIV. Both HIV+ subjects and controls were given a battery of neuropsychological tests assessing verbal reasoning, reaction time, intelligence, memory, and dexterity. The relationship between past alcohol abuse or dependence and neuropsychological performance was examined by using analysis of variance (ANOVA). The authors found a significant main effect for history of alcohol abuse on the summary impairment rating ($F(1,76)=4.9$. $p<.04$). Further analysis of the individual neuropsychological measures suggested significant effects for alcohol use history on measures of verbal reasoning ($F(1,76)=4.8$, $p<.05$), auditory information processing ($F(1,76)=5.92$, $p<.05$), reaction time for both the dominant ($F(1,76)=5.35$, $p<.05$) and non-dominant hand ($F(1,76)=8.82$, $p<.01$), and verbal IQ ($F(1,76)=8.21$, $p<.01$). Significant effects for HIV status were observed on measures of delayed recall ($F(1,76)= 4.6$, $p<.05$), total learning ($F(1,76)=5.64$, $p<.05$, and dexterity for both the dominant ($F(1,76)=5.70$, $p<.05$) and non-dominant hand ($F(1,76)=5.72$, $p<.05$). Consistent with previous findings (Fein Fletcher, & Sclafani, 1998), these results suggest that HIV infection and

a previous history of alcohol abuse have independent effects, that when combined have deleterious consequences for CF.

Recent theoretical attention to the role of the environmental stressors and its impact on CF provides more information regarding the complex relationship between immunologic severity factors and environmental neurotoxins. Taken together, the results of the reviewed cognitive literature suggest that although there has been substantial attention given to the establishment of a clinical profile, little is known regarding the exact origin of the cognitive deficits evident in HIV+ populations. Additionally, many studies relied on small sample sizes and did not take into account the role of development, as many studies contained both children and adult participants.

Behavioral Sequelae of HIV

In addition to cognitive impairment, patients may also exhibit maladaptive functioning that may be due to comorbid cognitive delays (Wolters, Brouwers, Moss, & Pizzo, 1995). Patients with HIV have a higher prevalence of mental health problems compared to surveys of the general population (Malee et al., 2011) and are additionally at increased risk for psychiatric hospitalizations during childhood and early adolescence (Gaughan et al., 2004). Large-scale studies have demonstrated that many children with HIV demonstrate apathy, depressed or flat affect, social isolation, lethargy, anehedonia, anxiety, hyperactivity and impulsivity (Bauman et al., 2002; Dorsey et al., 1999; Forehand et al., 2002; Landau, Meyers & Pryor, 2006; Mellins et al., 2011; Nozyce et al., 2006; Wolters et al., 1994).

As noted in the review of the cognition literature, although there has been significant theoretical attention dedicated to the behavioral profile of HIV+ children and adults, the comorbid environmental and disease-related risk factors make it difficult to establish causal relationships between HIV and behavioral outcomes as it is influenced by both direct and

indirect factors. Due to this difficulty, the understanding of the behavioral sequelae of HIV is still in its infancy and far behind the existing knowledge regarding HIV and its impact on the CNS and CF.

A literature review by Scharko (2006) suggested that, to that date, only *eight* studies have examined the behavioral profile of HIV+ children and the existing studies are often plagued with both small sample sizes and rudimentary statistical designs (Smith et al., 2012). Although difficult to accomplish, the examination of mental health needs in this population is important because emotional and behavioral problems may affect disease status and illness adjustment (New, Lee & Elliott, 2007) and provide interventionists with windows of opportunity to improve health related quality of life (Mellins, Kang, Leu, Havens, & Chesney, 2003).

As described previously many, HIV+ children and adolescents face multiple risks to their mental and BF including direct effects of viral infection of CNS, prenatal drug and alcohol exposure, poverty, unstable home environment and parental illness. Because of this, 25% of parents of HIV+ children report behavior problems (Bachanas et al., 2001), with the most common reported behavioral concerns including psychosomatic complaints (28%), learning difficulties (25%), hyperactivity (20%), impulsivity (19%), conduct problems (16%) and anxiety (8%; Noycze et al., 2006). In addition, PHIV+ children are more likely than healthy controls to receive psychotropic medication and behavioral treatment (Chernoff et al., 2009).

HIV and its Direct Effect on Behavior

The direct CNS effects of HIV may affect neuropsychological functioning and the child's ability to perform everyday behavioral skills, especially in areas of working memory, attention, executive functioning and verbal comprehension. Animal models with fronto-parietal, basal

gyrus or hypothalamic brain damage demonstrate poor emotion control, increased aggression, impulsivity and limited emotional sensitization (Vuilleumie & Pourtois 2007).

An early study by Brouwers and colleagues (1995) investigated the effect of white matter abnormalities on neurobehavioral dysfunction in children with HIV and their age matched controls. A computed tomography scan and a Q-sort measure of behavior were provided to pediatric participants and their parents. Using stepwise linear regression, significant correlations were found between overall behavioral severity rating and overall and component CT scan (r from .22 to .55, $p<.05$), suggesting that across both groups increases in behavioral severity was correlated with increased white matter abnormalities. Additional significant positive correlations were found for depressed and autistic-like behavior ($r=.47$and .45, $p<.01$). In younger children, a positive correlation was found between increased nonsocial behavior and CT scan ($r=.37$, $p<.05$). Finally, the degree of ventricular enlargement was associated with ratings on the apathetic/withdrawn and self-stimulating behavior scales ($r=.38$ and .41, $p<.05$).

In a more recent study, Misdrahi and colleagues (2004) examined the psychiatric problems encountered in children with HIV and its relationship to the severity of infection. The authors investigated mental health disorders, neurological disorders and presence or absence of progressive encephalopathy. The most frequent diagnoses were major depression (47%) and ADHD (29%). However, only major depression was significantly associated with the results of the clinical neurological abnormalities found on the neuroimaging profiles ($p<.01$). No association was found between ADHD and the CNS impairments. In addition, the percentages of CD4 lymphocytes were close to zero for more than 80% of children presenting with psychiatric complications. Misdrahi and colleagues concluded that psychiatric complications should be

regarded as a factor of disease severity due to the finding of concomitant low percentage of CD4 lymphocytes.

Behavioral sequelae associated with HIV impairment may be particularly responsive to effective treatment and intervention (Levy et al., 2004). Wolters, Brouwers, Moss and Pizzo (1994) assessed the effects of HIV infection and zidovudine (AZT) on the adaptive behavior of HIV+ children and found that after 6 months of AZT, communication, daily living and socialization demonstrated significant improvement ($p<.001$).

The neuronal mechanisms impacted by CNS degeneration may affect cognitive functioning, which in turn may increase the likelihood for impulsive and depressive behavioral profiles noted in the reviewed literature. However, research investigating the behavioral impact of HIV is still within its infancy. Existing studies have almost exclusively relied on broad scale behavioral assessments and attempted to link these findings back to anomalies observed on *f*MRI scans or medical chart reviews with limited in-depth discussion regarding the origin of these maladaptive behaviors.

HIV and its Indirect Effect on Behavior

The environmental stressors associated with behavior problems have been proposed by some as even more potent mediators in HIV-infected children than HIV infection itself. (Mellins et al., 2003; Noycze et al., 2006). As described previously, the majority of HIV+ children in the United States confront daily life stressors including poverty, trauma, and family disruption, which each independently serve as risk factors for poor behavioral outcomes.

Mellins and colleagues (2003) examined the natural history of 307 children born to HIV+ mothers. Caregivers completed parent behavioral rating scales annually, beginning when the children were 3 years old. Data were also collected on prenatal drug exposure; child age, gender,

and ethnicity; caregiver relationship to child; and birth complications. Multivariate analyses comparing the HIV-infected children with perinatally exposed but uninfected children from similar backgrounds failed to find an association between either HIV status or prenatal drug exposure and poor behavioral outcomes. The strongest correlates of increased behavioral symptoms were demographic characteristics including caregiver relationships and income level, suggesting that unlike previous studies which found the imperative role of HIV infection and prenatal drug exposure, other biological and environmental factors are were the only significant contributors toward later behavior problems ($p<.05$).

In a follow-up study, Mellins and colleagues (2008) examined the effect of maternal HIV infection, as well as other individual, family, and contextual factors on the mental health of inner-city, ethnic minority early adolescents. Individual interviews were conducted regarding youth depression, anxiety, externalizing and internalizing behavior problems using the Child Depression Inventory (CDI; Kovacs, 1992) and the trait scale of the State Trait Anxiety Inventory-Child version (STAI-C; Spielberger,1994).Contextual predictors included the mother's age, ethnicity, income, employment, and whether they lived with a partner. Maternal mental health was assessed using the Beck Depression Inventory (BDI: Beck, 1987) and the trait scale from the adult STAI (Spielberger, 1987). Maternal and child support was assessed with parent and child interviews.

Using a multiple regression analyses, Mellins and colleagues (2008) found that the HIV status of mothers alone did not predict youth mental health. Older youth age was significantly related to depression ($r= .17$, $p<.05$). Youth victimization was related to depression ($r= .30$, $p<.001$), anxiety ($r=.19$, $p<.01$), internalizing disorders ($r=.25$, $p<.001$) and externalizing disorders ($r= .28$, $p<.001$). Household income was associated with depression ($r=-.14$, $p<.05$)

anxiety r=-.18, $p<.01$ and internalizing disorders ($r=.27$, $p<.05$).Maternal physical health was associated with depression ($r= .19$, $p<.01$), anxiety ($r=.20$, $p<.0$), internalizing problems ($r=.17$, $p<.05$) and externalizing problems ($r= .19$, $p<.01$). Maternal depression was associated with depression, ($r=.15$, $p<.05$), anxiety ($r=.24$, $p<.001$) internalizing problems $r=.36$, $p<.001$), and externalizing problems ($r=.27$, $p<.001$). Similarly, maternal anxiety was associated with pediatric anxiety ($r= .20$, $p<.01$), internalizing problems ($r= .29$, $p<.001$) and externalizing problems ($r=.23$, $p<.001$). These results suggest a unique combination of individual, maternal demographic factors account for the primary behavioral manifestations of HIV.

As discussed previously, very little research has exclusively focused on the environmental factors responsible for maladaptive behavior associated with HIV. Many of the existing knowledge is borrowed from other medical conditions including fetal alcohol syndrome (Steinhausen & Spohr, 1998), postnatal cocaine addiction (Frank et al., 2001) who are at increased risk for HIV transmission, making the interpretation of these findings particularly difficult.

Direct and Indirect Models of Cognitive and Behavioral Functioning in PHIV+ samples: Simultaneously Examining Direct and Indirect Effects

Although environmental and disease-related factors may independently have neurotoxic effects on CF, both HIV and environmental stressors are also correlated with each other, thus creating a nidus of cognitive vulnerability that may be exacerbated by the effects of HIV infection on the brain and its relationship to comorbid environmental stressors. The robust relationship between immunological factors and environmental stressors forms an iterative cycle of risk, whereby continued environmental stressors perpetuate and increase disease severity markers, further affecting CF. However, as described by Scharko (2006) and Smith et al. (2012),

very few studies have attempted to simultaneously examine direct and indirect factors of cognitive and behavioral impairment. Investigators are becoming more aware of the need to use multiple observed variables to better understand the complex interaction of environmental and disease-related factors inherent to the diagnosis and their longitudinal impact in HIV patients (Bryan, Schmiege, & Broaddus, 2006). Work by Howland and colleagues (2000, 2007) and Nozyce and colleagues (2006) has taken into account the complex intricacies between direct and indirect effects of HIV on behavior and cognition.

Howland and colleagues (2000) evaluated the association of negative stressful life events experienced over 12 months and the risk of moderate to severe immunosuppression among children and youth infected with HIV in a longitudinal study of 618 HIV-1-infected children who participated in the Pediatric Late Outcomes Study. Severity of immune suppression was indicated by the CDC HIV classification syndrome and negative life events were categorized as none, one, or greater than one. Multiple logistic regressions were estimated to assess the relationship of negative life events and immune suppression at outcome, controlling for baseline measures of immune suppression, continuous CD4 count, negative life events, age, race/ethnicity, gender, primary caretaker, education level of caretaker, and acquired immunodeficiency syndrome status. Howland and colleagues found that more than one negative life event was associated with an increased risk of immune suppression (odds ratio [OR]: 2.76; 95% confidence interval [CI]: 1.44, 5.31), controlling for baseline CD4 count, total life events, and other covariates. These results suggest that negative stressful life events increase the risk of children with HIV infection having impaired immune function.

In a follow-up study, Howland and colleagues (2007) conducted a cross-sectional analysis to determine if negative life events occurring in the previous 12 months were associated

with increased risk for poorer health related quality of life in the Pediatric Late Outcomes Study. General health measures including measures of symptoms and perceived distress were included with the assessment of behavior problems using the Behavior Problems Index (Peterson & Zill, 1986).

Multivariate logistic regression analyses suggested that children with higher behavior problems scores were more likely to report a change in housing ($p<.01$) or a family member being sick ($p<.01$). Children with higher depressive symptom scores were more likely to report a family member being hospitalized ($p<.01$) or sick ($p<.01$). As found previously, total number of negative life events was significantly associated with health-related quality of life. For each additional reported negative life event, there was an increase in the odds of behavior problems ($p<.01$; [OR] 1.26, 95% CI 1.13-1.41). In conclusion, Howland et al.'s (2007) results suggest that negative life events further burden families already coping with HIV, which may serve as an additional risk factor for later behavior problems.

Simultaneously Examining Cognitive and Home Environment Factors

In a final study, Nozyce and colleagues (2006) investigated the behavioral and cognitive profile of HIV+ children and their resulting *f*MRI scans. Over 200 HIV+ children were assessed for behavioral, developmental and CF. Behavioral Functioning was examined using the Connors' Parent Rating Scale (Connors, Sitarenios, Parker & Epstein, 1998). CF was assessed with the WISC-III. Children's neurological functioning was assessed through computer tomography and magnetic resonance imaging.

Nozyce et al. (2006) found that *all* children included in the sample had a mean FSIQ below the mean score of 100 in the general population ($p<.001$). As found previously, behavioral assessment results suggested that children with HIV demonstrated higher ratings of somatization,

learning problems, hyperactivity, conduct and anxiety problems and scored less than established population means on verbal *(M*=85), performing *(M*=90) and FSIQ *(M*= 86). Additional correlations were conducted between baseline neuropsychological evaluations and behavioral problems. Children with a higher WISC-III IQ were significantly less likely to exhibit behaviors associated with ADHD. Hyperactivity was more frequent in children with a WISC-III score below the general population mean ($p<.01$).

Similar to Misdrahi colleagues' (2004) findings, no association was found between CF or behavior and cortical atrophy, white matter abnormalities, focal mass lesions or basal ganglia classification. Exploratory findings suggested that children living with their biological parents were less likely to be described as having a conduct problem, hyperactivity or a learning problem. In conclusion, Nozyce and colleagues (2006) suggest that behavioral and cognitive abnormalities persistent in the existing literature are likely multifactorial and must be investigated in depth in future studies.

Summary

The Human Immunodeficiency Virus (HIV) is a retrovirus that over time, if untreated, significantly weakens a patients' ability to combat opportunistic infection. HIV infection affects multiple organ systems, including the central nervous system. Subcortical-frontal areas of the brain are often negatively impacted, potentially resulting in decreased attention and concentration, psychomotor slowing, reduced speed of information processing, executive dysfunction and verbal memory impairment (Bartlett & Ferrando, 2004; Heaton et al., 2004). Neurologic/cognitive dysfunction can manifest itself over a wide range of severity, from mild, asymptomatic dysfunction, to severe progressive encephalopathy. The American Academy of Neurology (Antinori et al., 2007) defines this neurocognitive degeneration as HIV-Associated

Minor Cognitive Motor Disorder (MCMD) and HIV Encephalopathy. In addition to neurocognitive impairment, patients may also exhibit maladaptive functioning that may be due to co-morbid cognitive delays. Patients with HIV have a higher prevalence of mental health problems compared to surveys of the general population (Malee et al., 2011) and are additionally at an increased risk for psychiatric hospitalizations during childhood and early adolescence (Gaughan et al., 2004). Both externalizing and internalizing behavior problems have been noted in the literature including depression, anxiety, hyperactivity and impulsivity (Wolters et al., 1994; Dorsey et al., 1999, Bauman et al., 2002; Forehand et al., 2002; Mellins et al., 2011; Nozyce et al., 2006).

In their conclusions, many studies suggest that investigations solely examining the direct or indirect effects of HIV may not comprehensively tap into the complex and enmeshed relationship between environmental stressors inherent to the population impacted by HIV in America and disease-related immunologic variables. Investigators are becoming more aware of the need to use multiple observed variables to better understand the complex interaction of environmental and disease-related factors inherent to the diagnosis and their longitudinal impact in HIV patients (Bryan, Schmiege and Broaddus, 2006).

Statistical designs that allow the investigator to test and estimate causal relations may begin to address the limited theoretical cohesion regarding causal pathways and propose models of impact existing in the current literature. Building upon the findings of Smith et al. (2012), the current study explored the role of both psychosocial factors and illness severity on cognitive and behavioral functioning in order to establish a model of clinical and research impact.

Until now, many studies have heavily relied on the use of logistic, linear and multiple regression techniques within a multi-site database (see Malee et al., 2011; Mellins et al., 2012;

Smith et al., 2012) that have yielded limited theoretical cohesion regarding causal pathways and proposed models of impact. Although the establishment of large databases has significantly contributed to the existing knowledge regarding the cognitive and behavioral sequelae of the disease, the exact pathways and directionality of these relationships remain unknown. Structural equation modeling will allow the investigators to examine the mediating role of both full scale IQ (FSIQ) and encephalopathy and extend previous findings as models of impact in both HIV-infected and HIV- exposed cohorts can be simultaneously investigated and compared (See Appendix A). The current study contributes to the existing literature by providing investigators with important information regarding the role of disease severity and psychosocial factors and its relationship to the cognitive and behavioral sequelae of the disease.

CHAPTER 3

Method

Participants

Recruitment. Participants were recruited as part of the Pediatric HIV/AIDS Cohort Study (PHACS; National Institutes of Health; 2009) a network of physicians and faculty from Harvard University, the National Institute of Children's Health and Human Development (NICHD), and 15 co-funding institutes. PHACS is responsible for collecting patient data to examine the long-term safety of fetal exposure to prophylactic antiretroviral (ART) chemotherapy and the effects of perinatally acquired HIV infection in adolescents.

More specifically, the data for the proposed study were obtained from the Adolescent Master Protocol (AMP: Allison, Hazra, Hoffman, & Rosario, 2008) of the Pediatric HIV/AIDS Cohort study. The AMP was originally developed to examine cognitive and behavioral changes over time including medication adherence, family and social function, and high-risk behaviors (e.g., illicit drug and alcohol use). Additional data including language and hearing, glucose and lipid metabolism, body composition, bone mineralization, and the clinical course of the Human Papilloma Virus (HPV) have been collected in order to trace the course and development of the disease.

The AMP protocol is one of two multi-study centers supported through the National Institute of Health (NIH) sponsored PHACS. Prior to implementation of AMP, sites in the PHACS network must have the protocol approved by their local institutional review board and must register with the Date and Operations center for the AMP study at Harvard School of Public Health.

Once accepted, clinical staff members were made aware of the eligibility criteria of the AMP study. Potential participants were identified and referred to the clinical research team. The chief staff member contacted the potential participant in order to provide an overview of the study to see if they were interested in participating. Once a patient was determined eligible for the study, permission via parental consent or assent was acquired. Prior to enrollment, patients receive a patient identification number through the Data Management Center (DMC) through PHACS. Once accepted in into the AMP study, all participants engaged in study visits at six months, 1 year, 2 years, 2.5 years and 3 years on study then once a year after.

Access to PHACs Dataset. In order to gain access to the PHACS Adolescent Master Protocol data, the author was required to work closely with the NIH PHACs Scientific Leadership Group (SLG). Approximately one year prior to the data analysis, the author worked collaboratively with NIH mentorship (called the Working Group; WG) to develop a Study Capsule (SC), a brief description of the proposed research with objectives. The SC was presented to the SLG for acceptance and was fully approved in June 2013. After receiving approval from the SLG WG, the study moved to Concept Sheet (CS)development, which provided additional information and detail as it relates to the study design, the data analysis plan, sample size calculations, and proposed budget. The Concept Sheet was fully approved June of 2014 for the full analysis, dissertation and manuscript development. Throughout the development of the SC, CS and dissertation, the author was required to participate in bimonthly phone conferences with both the WG and SLG and meet with the WG biannually at the NIH spring and fall PHACs conferences in Bethesda Maryland in order to track progress towards project completion. Upon completion of the study, the author was required to present the findings at the annual NIH Leadership Retreat in Potomac Maryland in March of 2015.

Description. Patients in the AMP protocol include infected HIV youth (HIV+) (*n*=358) and perinatally exposed but uninfected youth (PHEU; *n*=200). Youth were enrolled in 15 AMP sites in urban areas of the United States including Puerto Rico. To be included in the HIV+ cohort, patients were required to have documentation of perinatal HIV as described in their medical record, be between the ages of 7 and 16, be currently engaged in medical care in which ART chemotherapy data are available, and be aware of their current medical status. Patients were not included if HIV was acquired through blood products, sexual contact and intravenous drug use as documented by their medical record, and/or were currently unaware of their status. In the PHEU cohort, patients were required to be currently uninfected by HIV but born to an HIV-infected mother as documented in their medical record, and between the ages of 7 and 16.

The eligible study population for this study included all AMP youth participants who had CF evaluated via the WISC-IV or the WAIS at the 3 year AMP visit (e.g., week 144), and who have a subsequent parent and child BASC assessment of behavioral functioning conducted within two years of the WISC/WAIS assessment. As of September 1, 2014, 382 subjects met these criteria and are included in the study population. Of the total 678 enrolled in AMP (see Table 1), 296 subjects (43%) were excluded from the analysis (See Table 1). The majority of these (n=182, or 62%) did not have a CF assessment at the year 3 visit, and an additional 100 youth had a CF assessment but did not have both a parent and child BF assessment done (47 had neither, and 53 were lacking one or the other). Ten subjects had both the parent and child BASC done, but it was not within 2 years after the WISC. Finally, four subjects were confirmed to have an invalid assessment of either CF or BF after team review (see Figure 1). A higher percentage of the 451 PHIV youth were excluded than among the 227 PHEU youth (48% vs. 33%). A total of 382 subjects with valid cognitive and behavioral assessments were included in the study

population. A summary of the background demographic and psychosocial characteristics for the eligible subjects is provided in Table 2, overall and by cohort. The subjects were on average about 11 years old at entry, just over half female, and primarily Black.

Measures

The following section provides readers with a description of each of the exogenous and endogenous latent variables and their related factors selected from the PHACs Adolescent Master Protocol (AMP). Measures that have been historically examined to investigate the progression of a patients' HIV diagnosis were selected as primary indicators of disease severity (see literature review). Demographic measures that were indicative of potential structural barriers to adequate treatment and resilience were selected as key measures of psychosocial factors (for additional information regarding measures, see Appendix B).

Exogenous (Independent) Variables: Better Past Disease Severity Markers.

Nadir CD4 percentage. The Nadir CD4 cell count is defined as the lowest CD4 cell count percentage measured after HIV infection (less than 200 cells per ml of blood) and is measured through blood assays. Low CD4 count indicates a high risk of disease progression. As continuous value and grouped: 0-14%, 15-24%, >=25%

Age (in years) at Nadir CD4 percentage. Age is operationalized as the age in years in which the lowest Nadir CD4 percentage was recorded. The younger the age at which the lowest CD4 count was recorded, the more progressive and aggressive the HIV disease.

Age (in years) at HAART initiation. Age is operationalized as the age in months at which *HAART* began. The earlier the age in which *HAART* treatment began, the more controlled the disease.

Peak VL (log10). The peak viral load (Peak VL) is the highest recorded amount of retrovirus in blood plasma measured through blood assays. Classified into quartiles <50,000, 50-99,000, >100,000, >250,000

Age (in years) at Peak VL. Age is operationalized as the age in years at which highest amount of retrovirus was recorded in blood plasma or viral load.

CDC Class C Disease. (yes/no). As defined by the Centers for Disease Control, Class C disease is considered the most symptomatic class of HIV, described as AIDs- defining illness.

Encephalopathy. (yes/no).Diagnosis of encephalopathy abstracted from medical chart data and physician diagnosis.

Present Disease Severity Markers (at time of BASC/entry into the study)

CD4% at Entry. The Nadir CD4 cell count is defined as the lowest CD4 cell count percentage measured after HIV infection (less than 200 cells per ml of blood) and is measured through blood assays at entry into the study. Low CD4 count indicates a high risk of disease progression. As continuous value and grouped: 0-14%, 15-24%, >=25% which will be coded as both a continuous and categorical variable

Viral Load at Entry. Viral load of retrovirus at entry into the study, described as ribonucleic acid (RNA) copies per ml of blood plasma (log 10) as measured through blood assays. Classified in categories as <400 vs. >400, and as < 400, 401-10,000, 10,001-100,000, >100,000)

ARV Regimen at Entry. Antiretroviral therapy (HAART) and protease inhibitor (PI) present at entry. Categorical variable: HAART with PI, HAART without PI, Non-HAART ARV, not on ARV.

Exogenous (Independent) Variables: Psychosocial Factors

Psychosocial

Caregiver Marital Status. Caregiver Marital status included current family structure including single parent, both parents and/or other relative/caregiver.

Relationship to Caregiver This variable includes information regarding current living situation including recorded adoption, foster care placement, living with birthparents or other family member (such as grandparents)

Total number living in household. Current number of people living in household

Total Number supported by Household Income. Calculated variable of household income divided by number of family members.

Low Income. Annual household income, categorical: <$20,000, >$20,000

 # Negative Life Events Number of negative life events experienced by the child including home trauma, abuse, frequent moves, family addiction and sudden death of a family member.

 # Stressful Life Events Number of stressful life events reported from the caregiver-reported QOL form

Caregiver

High School Graduate. Dichotomized as less than or greater than high school completion

Caregiver IQ. Information regarding parent's IQ as measured by a standardized assessment such as the WASI.

Caregiver Mental Health Problem. A*ny* mental health disorder as identified on the Client Diagnostic Questionnaire (screening measure)

 # Drugs used in the Last 6 months. Information regarding parent's current and previous use of illicit substances as measured on the CDQ

Any PCRI Problem. Assessment of parent's attitudes towards their children and their behavior as assessed on the Parent-Child Relationship Inventory (PCRI).

Endogenous (Outcome) Variables

Cognitive Functioning. The *Wechsler Intelligence Series: Scale for Children, Fourth Edition* (*WISC-IV*; Wechsler, 2003) and *the Wechsler Adult Intelligence Scale, Fourth Edition* (*WAIS-IV;* Wechsler, 2008) are measures of intelligence and will be used in the proposed study as the primary endogenous indicator of current CF. Both the *WAIS-IV* and the *WISC-IV* were selected as it demonstrates high reliability and validity (Wechsler, 2003), have been used widely for research and clinical practice with HIV+ children and adolescents (Kapetanovic, et al., 2010; Lyon, McCarter, & D'Angelo, 2009; New, Lee,& Elliott, 2007; Tardieue al.,1995; Wood et al., 2009), and was standardized on 2200 children in proportion to their distribution in the U.S. census (Wechsler, 2003).

The *WISC-IV* is comprised of 10 core subtests yielding scores that reflect ability in four domains of CF including verbal comprehension (VC), perceptual reasoning (PR), working memory (WM), and processing speed (PS). This information is particularly helpful in tracking the neurocognitive deficits related to encephalopathy including significant challenges in processing speed and perceptual reasoning (Lyon, McCarter, & D'Angelo, 2009). Raw scores attained are converted into age-normed standard scores for each index and combined to produce a full-scale intelligence quotient (FSIQ).The norm-referenced mean for the FSIQ and each domain composite score is 100, with a standard deviation (*SD*) of 15.The proposed study examined all four domain scores as well as the FSIQ in order to establish a comprehensive model of cognitive impact. Although indices may vary substantially, full scale IQ as measured by the WISC-IV was selected as the primary measure of intelligence as it a more valid representation of one's cognitive abilities than a single score or index individually examined.

Behavior. The *Behavioral Assessment System for Children* (BASC-2; Reynolds & Kamphaus, 2004) is a norm-referenced, standardized assessment completed by parents, students and teachers designed to facilitate the differential diagnosis and classification of a variety of behavioral, emotional, social, and adaptive functioning disorders in children and was used as the primary endogenous indicator of current adaptive behavior. The BASC-2 has been used widely in both research and clinical practice for children and adolescents with HIV (Bachanas et al., 2001; Chenneville et al., 2010; Elliott-DeSorbo, Martin & Wolters 2009; Malee et al., 2011), has demonstrated reliability and validity (Reynolds & Kamphaus, 2004), and has been standardized with a sample that closely matched the matches the 2001 U.S. Census including demographics related to gender, race/ethnicity, and clinical or special education classification (Reynolds & Kamphaus, 2004). All forms of the BASC-2 are written in both English and Spanish.

The BASC-2 is comprised of five behavioral indices including internalizing and externalizing problems, school problems, behavior problems, and adaptive behavior (see Appendix C). Raw scores attained are converted into age-normed standard scores for each index. Scores that fall in the clinically significant range suggest a high level of maladjustment. Scores that fall in the at-risk range suggest a developing behavior problem that may not be severe enough to require formal treatment. This study examined the five behavioral indices assessed in the BASC-2 to establish a comprehensive profile of behavioral functioning.

Data Analysis /Procedure

Structural equation modeling (SEM), a combination of exploratory factor analysis and multiple regression (Schumacher & Lomax, 2010; Ullman, 2001), was used to examine the relationship between observed variables and their latent factors, and to further investigate the impact of the exogenous variables on the endogenous variables (see Measures section).

Exploratory factor analyses within the measurement model was utilized to test the reliability of the observed variables and to examine the extent of interrelationships and covariation among the latent constructs. In order to examine the potential mediating effects of IQ, a series of regression analyses was conducted for paths between the endogenous and exogenous variables. To compare CF and BF between PHEU and PHIV+ youth, three models were initially proposed but expanded to four models following the exploratory factor analysis (see Chapter 4).

SEM was selected as the primary analysis as it allows the researcher to (a) define variables as latent constructs, (b) test the influence of multiple observed indicators which improves understanding and assessment of variables, (c) test multiple hypotheses simultaneously, and (d) develop and test a theoretical model of research and clinical impact, all within a complex multivariate regression. In addition, goodness of fit indices allows researchers to examine the overall "fit" of the model to the dataset (Schumacher & Lomax, 2010). In order to establish overall model "fit," path coefficients between the variables must be significant and the goodness of fit indices must indicate an overall fit of the model to the data.

SEM allows the researcher to further investigate the mediational effect of CF on behavior. As described by Baron and Kenny (1986), variables are considered mediators when the independent variable is a significant predictor of the mediator variable, the mediator variable is a significant predictor of the outcome variable, and there is no significant relationship between the independent variable and the outcome variable when the mediator is introduced into the model.

There are two models incorporated into SEM, the measurement model and the structural model. The measurement model depicts the relationships between the latent variables and the observed variables (Klem, 2000). The structural model depicts the direct and indirect effects of latent variables on each other (Klem, 2000). Within this study, disease severity and psychosocial

factors and their measured variables are considered exogenous, or independent factors, as those constructs that exert an influence on other constructs under study and are not influenced by other factors in the quantitative model (Schreiber et al., 2006). The endogenous or dependent factors which are affected by one or more of the other latent variables (Klem, 2000) includes both the mediating variable of CF (IQ) as measured by the *WISC-IV* and the dependent measure of behavior (*BASC-2*) including internalizing and externalizing behavior problems. Error terms (or residual variation) are also included in the model as it describes the discrepancy between the indicators and latent concepts (Kaplan & George, 1995; see Figures 2-7).

Parameters, measures of direct effects, variances, and covariances are also included within the structural model to establish statistical power. According to Bentler and Chou (1987), 5 to 10 cases are needed per parameter in order to establish adequate statistical power and reliable results. As this study includes 382 participants, there were significantly more than 10 cases per parameter suggesting sufficient power for the data analysis.

Once power is estimated, model specification must occur. As described by Schumacher and Lomax (2010), model specification is the process in which the researcher uses all available relevant theory, research, and information to explicitly establish the theoretical model. Specification requires determining every relationship and parameter in the model that is of interest including direct effects, variances, and covariances, with the goal of determining the best possible (implied) model and its fit to the true model. The current study was strongly grounded in theoretical research and extends the findings of Smith et al... (2012) that indicated a strong connection between the proposed theoretical model and its covariance matrix.

After model specification occurs, the theoretical model must be identified prior to estimation of parameters. Model identification depends on the designation of parameters as

fixed, free, or constrained. A model is considered under-identified if one or more parameters may not be uniquely determined because there is not enough information in the variance-covariance matrix. A model is considered just identified if all of the parameters are uniquely determined because there is just enough information in the variance-covariance matrix. A model is over-identified when there is more than one-way of estimating a parameter because there is more than enough information in the variance-covariance matrix.

After constructing the hypothesized model (see Figures 2 and 3), the number of estimated parameters was calculated and compared to the number of data points, thus providing evidence for model identification. The proposed model was determined to be over-identified as it had more sample moments than parameters to be estimated thus suggesting positive degrees of freedom. As evidence for the 3-indicator model of identification (Bollen, 1989), the proposed model has three latent variables and within those variables each had at least three indicators per variable, a necessary but not sufficient condition for the 3-indicator model identification (Bollen, 1989).

As noted previously, the goal of SEM is to equate the proposed covariance matrix and the observed covariance matrix reflecting underlying theory. In order to test this goal, measures of fit are needed to examine the model that best represents the data (Schumacher & Lomax, 2010). Chi-square is a global test of the fit of an entire model and is historically reported but is often sensitive to large sample sizes and may unnecessarily reject the proposed model. In addition to chi-square, a variety of fit indices were selected to assess model fit including Goodness of Fit (GFI), with an *a priori* cutoff of .90 (Bentler & Bonett, 1980; Diamantopoulos & Siguaw, 2000; Fabrigar, Wegener, MacCallum, & Strahan, 1999) and Standardized Root Mean Square Residual

(SRMSR) with good fit obtaining values less than .05 (Byrne, 1998; Diamantopoulos & Siguaw, 2000).

The GFI statistic was selected as it is a maximum likelihood estimation of model of fit and provides information regarding the proportion of variance that is accounted for by the estimated population covariance and was selected as it is also sensitive to more parsimonious models (Bollen, 1990).The SRMSR represents the square root of the differences between the residuals of the sample covariance model and the hypothesized covariance model (Hooper, Coughlan & Mullen, 2008) and was selected as it is sensitive to sample size (Byrne,1998).

Two popular incremental fit indices, the Comparative Fit index (CFI) and the Normative Fit Index (NFI) were also included for model fit, with a proposed cut-off of .90 for both (Bentler & Bonnet, 1980; Hu & Bentler, 1999). The CFI was included as a measure of model fit in this study as it takes into account sample size (Byrne, 1998) and performs well even when sample size is small (Bentler & Bonett, 1980). The NFI was selected as it also performs well using more parsimonious models such as the proposed model (Hooper, Coughlan & Mullen, 2008).

CHAPTER 4

Results

Descriptives

The purpose of this study was to evaluate a structural equation model (SEM) as an approach to understand the complex interrelationships between home environment, caregiver characteristics, psychosocial characteristics, and CF on BF. In addition, among youth with perinatally acquired HIV, a separate analysis was conducted to evaluate the joint effects of HIV disease severity (as reflected by both past severity and baseline measures) along with the aforementioned environment, caregiver, and psychosocial measures on both CF and behavioral outcomes. CF is included in the SEM as an intermediate outcome, which in turn affects behavioral outcomes. The baseline demographic, psychosocial, and HIV disease severity measures were anticipated to have both direct effects on BF and indirect effects as mediated through their impact on CF.

A summary of the background demographic characteristics as specified in the concept for the 382 eligible subjects is provided in Table 2, overall and by cohort. The subjects were on average about 11 years old at entry (*sd*=2.49), just over half female, and primarily black or African-American. Psychosocial and environmental information for the participants can be found in Table 3. Disease-related information can be found in Table 4. CF and BF descriptive data by cohort can be found in Tables 5 and 6. Although a single caregiver status variable was proposed, two separate indicators have been included: the relationship of the caregiver to the child (both biological parents, single biological mother, single biological father, other relative, or other non-relative) as well as the marital status of the primary caregiver. For the factor analysis, both types of single biological parents have been combined into a single category, and the separate/divorced

category would be combined with the widowed category for sufficient numbers in each group. The caregiver WASI has been classified as discussed to include a "not done" category, as well as <70, 70-<85, and 85+. However, a very low percentage of caregivers were in the lowest (<70) category, so it was combined this with the <85 category for the factor analysis and subsequent SEM. Several measures from the caregiver CDQ were included, based on programmed (rather than site-reported) summaries of overall and individual mental health problems. Both measures of illicit drug use and abuse were included as possible covariates. The number of drugs used was reported in the last 6 months. The stressful life events measures were added based on the caregiver-reported QOL form. Finally, several measures of parent-child relationship have been included based on the PCRI (Gerard, 1994), including four of the seven possible composite scores (for support, involvement, communication, and limit setting) as well as two overall indicators. An indicator of any problem was modified to reflect whether any of the above four PCRI domain scores was non-missing and below 40. Any indicator of any *serious* problem was based on whether any of these four scores was below 30.

For the caregiver IQ assessment by WASI, caregiver mental health by CDQ, life events checklist, stressful life events measure and PCRI measure, the first available assessment was used as a "baseline" predictor. The PCRI was generally completed at week 24 (the 6-month AMP visit). If the first assessment for either of these was after the date of the week 144 WISC/WAIS assessment, it was not included as a predictor given the need for predictors to be measured prior to outcomes. However, because the caregiver WASI was generally only completed once, and is considered representative of caregiver cognitive status, later caregiver WASI assessments were also considered; it turned out that all caregiver WASI assessments that were completed were done prior to the child WISC at Week 144.

The HIV and antiretroviral (ARV) related characteristics of the PHIV youth are shown in Table 4. These measures include both indicators of past HIV disease severity (nadir CD4%, nadir CD4 count, peak viral load (VL), CDC Class C status reflecting a past AIDS defining condition, and HIV-related encephalopathy diagnosis prior to entry), as well as current measures at study entry. In addition, CD4 and viral load measures at the time of the WISC assessment are summarized in this table. For the measures of past HIV disease severity, the ages at nadir CD4% and peak VL were also included. In terms of ARV-related characteristics, the age at initiation of any ARV and age at first reported highly active antiretroviral treatment (HAART) were also included.

Exploratory Factor Analysis Factor analysis is often utilized to evaluate clustering among predictors and potentially reduce the number of variables such that the remaining constructs are more parsimonious, more representative of the observed data and explain a significant portion of the variance. As the purpose of the current study was to build a conceptual model, the factor analysis selected was exploratory in nature, meaning that maximum likelihood conditions was used to generate an underlying theory regarding the effect of disease severity, psychosocial and cognitive factors on behavioral functioning.

Matrix of association. Standard factor analysis relies on three core statistical assumptions regarding the observed variables: (a) they are continuous, (b) they are normally distributed, and (c) they are linearly related to one another (van Driel, 1978). As the following model contains dichotomous, nominal, ordinal and continuous predictor variables, several correlation matrices were utilized. If both variables were ordinal (e.g., greater than 10 levels), a polychoric correlation was calculated. A tetrachoric correlation was calculated when both variables contained within the factor were dichotomous. If one variable was ordinal and the other

continuous, a polyserial correlation was calculated. If one variable was dichotomous and the other was continuous, a biserial correlation was calculated. If both variables were continuous, a Pearson correlation was calculated (for list of continuous variables, see Appendix B). The exploratory factor analysis was then conducted on the resulting correlation matrices. Therefore, squared multiple correlations (SMC) have been reported as prior communality estimates.

Factor extraction. In order to account for common variance and create a more parsimonious structural equation model, the principal axis factoring (PAF) extraction was selected. PAF replaces correlation matrix *r* with estimates of reliability so that communality coefficients replace error variance utilizing multiple regression.

Rotation. In order to maximize loadings of variables onto each latent concept, an oblique varimax rotation was performed when applicable (i.e., when more than one factor was extracted), as it was assumed that factors were correlated.

Factor Analysis on the Endogenous Variables: Cognitive Functioning and Behavioral Functioning

Results: Cognitive Functioning

All domains of CF assessed on both the WISC and the WAIS across the PHEU, PHIV and overall sample exhibited moderate correlations (*standardized coefficient*=.21-.52; see Table 7). These results in combination with the calculated eigenvalues suggest that a single factor ("cognitive functioning") could continue to be retained. Table 7 and 8 demonstrates the final communality estimates from the EFA, the percentage of variance in the observed variable accounted for by the retained factors. All domains load highly on the single factor (all loadings > 0.40) across the PHEU, PHIV and overall sample. *Processing Speed* exhibited slightly lower

correlations than all other cognitive domains and has the lowest communality; indicating that Factor 1 only accounts for 39% of the variability in processing speed.

Results: Behavioral Functioning

Pearson correlations among BASC-C and BASC-P domains are provided in Table 9a-b and the SMC is provided on the diagonal of each group. Based on the obtained factor pattern and resulting eigenvalues, two factors were retained: the BASC parent-report (denoted as BASC-P) loaded highly onto one factor and the BASC youth self-report (denoted as BASC-C) loaded highly on the other factor. Interestingly, the PHIV sample and the PHEU sample demonstrated paradoxical results, meaning that for the PHIV sample, the BASC-P domains load highly on Factor 1 and the BASC-C domains load highly on Factor 2. In contrast, for the PHEU group, the opposite results were obtained, suggesting that the BASC-C domains load highly on Factor 1 and the BASC-P domains load highly on Factor 2. This would suggest that, among the PHIV youth, the factor representing the parent viewpoint (BASC-P domains) accounts for more of the common variance in the observed variables than the factor representing the child viewpoint (BASC-C domains); and that the opposite is true for the PHEU youth.

Results of the factor analysis were suggestive of two distinctive factors for both the child and parent versions of the BASC. Because of these findings, it was decided that the full SEM model would be separated into *four* models with the parent and child version of the BASC serving as two different endogenous variables.

Factor Analysis on the Exogenous Variables

Due to the initial instability of the model resulting in Heywood cases, the model was broken down and examined in two separate analyses: HIV Disease Severity and Psychosocial factors. Again, squared multiple correlations were used as prior communality estimates in all

analyses. The principal factor method was used to extract factors, followed by an oblique varimax rotation.

HIV Disease Severity Variables

Even after examining the factors as two separate analyses, the factor analysis continued to yield a singular matrix (Heywood case), which is often due to high correlations and/or too many indicator variables. Upon closer inspection, it was found that CDC Class C and Encephalopathy have almost perfect correlation ($r > 0.98$), which is parallel to what is often found in clinical practice as many patients whose HIV diagnosis is at Class C (highly symptomatic) often experience abnormal brain function (encephalopathy). In addition, all treatment variables (HAART with PI', 'HAART, no PI', 'Other ARV', 'No ARV') were highly correlated, therefore a dichotomous ARV group at entry variable was established (combined 'HAART with PI' and 'HAART, no PI' versus 'Other ARV' and 'No ARV').

Results from the newly identified 3-factor model and 4-factor models are shown in Table 10. Although the scree plot suggested that 5 factors should be retained, only the first four factors accounted individually for >10% of the variance. Alternatively, because only one variable loads highly on Factor 4 in the 4-factor model, the 3-factor model was selected as most appropriate. In the 3-factor model, the age variables and log Peak VL load highly on Factor 1, Nadir CD4% and encephalopathy load highly on Factor 2, and the entry variables (log RNA at entry, CD4% at entry, and on HAART at entry) load highly on Factor 3.

Psychosocial Variables

As evidenced in the disease severity variables, the factor analysis for the psychosocial variables also yielded a singular matrix and/or Heywood case. Closer inspection suggested that singular matrices resulted when there were more than one indicator variable within a set was

included in the analysis (e.g. if "Caregiver WASI <85" and "Caregiver WASI not done" were both included) and when there were nominal variables. Therefore, nominal variables were dichomitized such that the *Caregiver Relationship* to child was included as *"Biological caregiver" ("Single mother", "Single father", "Both parents" vs. "Other relative" and "Non-relative")*. Marital status of caregiver was included as *"Married/widowed" ("Married" and "widowed" vs. "Divorced/separated" and "Single, never married").* Caregiver WASI was included as "Confirmed score < 85" ("< 85" versus "85+" and "Not done").

Results from the PHIV only, PHEU only, and overall analyses are shown in Tables 11a-c. Results from a 2-factor, 3-factor, and 4-factor model are presented for each group. The proportion of variance explained by each factor suggested retaining 4 factors. The scree plot also suggested retaining 4 factors for the PHIV and PHEU groups (the scree plot from the overall analysis showed an elbow at 1 Factor). Because only two variables were loading on some of the factors (and only one variable loading on Factor 4 among the PHEU group), 3-factor and 2-factor models were also assessed.

EFA provided a strategic method to reduce and identify the number of observed variables that most adequately capture each latent factor prior to conducting the structural equation analysis. This is traditionally described by Anderson and Gerbing (1988; pp. 411) as the "two-step approach to structural modeling." Because the initially proposed model is strongly rooted in existing literature, only minimal modifications to the endogenous structural model were necessary. Upon conclusion of the EFA, *a priori* exogenous latent concepts were re-identified so that their notations adequately captured the aspects of observed variables. Within the Disease Severity variables, "*Better Past Disease Severity*" remained the same and "*Present Disease Severity*" was re-identified as "*Disease Severity at Entry*". Results of the EFA supported a 3-

factor model, so an additional factor, identified as "*Late Presenter*", youth who did not display significant manifestations of their disease until a later age, has also been included. Significantly more modifications occurred regarding the Psychosocial variables. "*Psychosocial Factors: Demographic*" was re-identified as "*Home Environment*" a term that more adequately captures the included variables. "*Psychosocial factors: Caregiver*" was broken into two factors, "*Caregiver Stress*" and "*Caregiver Educational Opportunity*" again supporting the results of the EFA which suggested a 3-factor model.

Results: Structural Equation Models

As described in the prior results of the EFA, the two originally proposed models (see Figures 2-3) have been expanded to four separate models (see Figures 4-7). In line with the research questions, results have been divided into two sections: Perinatally HIV infected (PHIV+: Models One and Two) and Perinatally Exposed/Uninfected (PHEU: Models Three and Four). Found within each section are the results from *both* the child-assessed BF (BASC: YSR; Models One and Three) and the caregiver-assessed BF (BASC: PRS; Models Two and Four).

Results: Perinatally HIV infected (PHIV+: Models One and Two)

Perinatally HIV-Infected (PHIV+) model fit. In addition to the r^2, absolute (SRMR), parsimonious (RMSEA) and incremental (Bentler CFI) fit indices were selected *a priori* to examine how the hypothesized model fit the resulting data. The SRMR is an absolute measure of fit. A value less than .08 is generally considered a good fit (Hu & Bentler, 1999). The RMSEA is a parsimonious measure of fit. A value of less than .07 is generally considered to be a good fit (Steiger, 2007). The Comparative Fit Index (CFI: Bentler, 1990) is an incremental index of fit and values for this statistic range between 0.0 and 1.0 with values closer to 1.0 indicating good fit.

Model one: perinatally HIV-infected (PHIV+) youth: youth assessed behavioral functioning. The SRMR for the child-assessed PHIV+ model (Model One) is .0814, indicative of a fit approaching significance. The RMSEA for Model One is .0800, indicative of a weak fit. The Bentler CFI for the Model One is .613, suggesting a moderate fit to the data.

Model two: perinatally HIV-infected (PHIV+) youth: caregiver assessed behavioral functioning. The SRMR for the caregiver-assessed PHIV+ model (Model Two) is .0818, indicative of a fit approaching significance. The RMSEA for Model Two is .0826, indicative of a weak fit. The Bentler CFI for Model Two is .641, suggesting a moderate fit to the data.

Additional model indices were examined to potentially improve model fit, but none were found to be substantiated in theory or were inappropriate (i.e. adding a correlation between an exogenous and an endogenous error term). It is important to interpret the results of the fit indices with caution, as the purpose of the proposed model was to establish a theory of impact and not merely fitting an existing theory to collected data (Hooper, Coughlan, & Mullen, 2008).

Covariances Between Exogenous Predictors

Model One: Perinatally HIV-infected (PHIV+) Youth: Youth assessed behavioral functioning. Several significant covariances were found between exogenous predictors (Disease Severity and Psychosocial variables), thus providing important findings for research question 1 (Do Disease Severity markers correlate with Psychosocial factors?). Correlated with four other predictors, a significant covariance was found between *Disease Severity at Entry* and *Late Presenter* (β =-.38, *t*=-4.54) and *Better Past Disease Severity* (β=.29, *t*=3.24). *Disease Severity at Entry* was also uniquely correlated to two psychosocial factors including *Home Environment* (β=-.18, *t*=-1.96) and *Caregiver Stress (*β=.-.251, *t*=-2.25). *Caregiver Stress* was also highly correlated with both *Disease Severity* and Psychosocial factors including *Better Past Disease*

Severity (β=-.35, *t*=-3.43) and *Home Environment* (β=.425, *t*=4.03). For all covariance matrices, see Appendix D a-k.

Model Two: Perinatally HIV-infected (PHIV+) Youth: Caregiver assessed behavioral functioning. Similar to Model One, several significant covariances were found between exogenous predictors (Disease Severity and Psychosocial variables) for the Perinatally HIV-infected (PHIV+) Youth: Caregiver Assessed Mental Health Model (Model Two). *Disease Severity at Entry* continued to be a powerful covariate, significantly correlating with *Late Presenter* (β= 2.06, *t*=-4.03), *Better Past Disease Severity* (β=3.49, *t*=2.85) and *Caregiver Stress* (β= .41, *t*=-2.06). In addition to correlating with *Disease Severity at Entry, Caregiver Stress* also correlated with both *Better Past Disease Severity* (β=.30, *t*=-2.69) and *Home Environment* (β=.009, *t*=1.5). For all covariance matrices, see Appendix Da-k.

Factor Loadings: Endogenous Variables

In both Model One and Two, all cognitive indices significantly loaded onto the cognitive functioning factor at $p < .001$, with correlation coefficients between .69 and .83 (i.e., moderate-strong associations). It is important to note that the indicator variables were expected to predict the latent variables, because the indicator variables were all subscales of FSIQ that comprise the CF latent concept (see Table 12).

Model One: Perinatally HIV-infected (PHIV+) Youth: Youth assessed behavioral functioning. In the Perinatally HIV-infected (PHIV+) Youth: Youth assessed BF Model (Model One), all observed behavioral indices significantly loaded onto the observed BF variable at the $p<.001$ level, suggesting strong associations between the observed variables and the latent concept. Correlation coefficients were between -.66 and .89 (i.e., moderate- strong association). The negative *Personal Adjustment* loading is not surprising as *Personal Adjustment* is reverse-

scored on the BASC, meaning that *lower* scores indicate *poorer* behavioral function and an *increased* risk for clinical impairment. Again, it was expected that indicator variables would significantly predict the latent variables, as the subscales of the BASC comprise the "BF" latent concept.

No significant path was evidenced between CF and Child-Assessed BF, indicating that an increase CF does not directly predict a significant decrease in youth-assessed BF, although the negative non-significant correlation demonstrates this inverse relationship.

Model Two: Perinatally HIV-infected (PHIV+) Youth: Caregiver assessed behavioral functioning. In the Perinatally HIV-infected (PHIV+) Youth: Caregiver Assessed BF Model (Model Two), all observed behavioral indices significantly loaded onto the observed BF variable at the $p<.001$ level, again suggesting strong associations between the observed variables and the latent concept. Correlation coefficients were between .78 and .83 (strong association). The negative *Adaptability* loading is not surprising as like the *Personal Adjustment* score in the child-assessed BASC, it is reverse-scored, meaning that *lower* scores indicate *poorer* adaptability and an *increased* risk for clinical impairment. Again, it was expected that indicator variables would significantly predict the latent variables, as the subscales of the BASC comprise the BF latent concept.

Unlike Model One, a significant path was evidenced between CF and Caregiver-Assessed BF (*standardized coefficient*= -.29 (.109), $p<.01$) suggesting that the higher a child's CF, the lower clinical levels of caregiver-reported behavior.

Factor Loadings: Exogenous Variables: Models One and Two

As both perinatally infected (PHIV+) models are from the same population and only differ regarding the assessment of BF (caregiver vs. youth), findings will be presented simultaneously (see Table 12).

Disease Severity: *Late Presenter.* In Model One, all factors significantly loaded onto the Disease Severity latent concept (all *p*'s <.001). Correlation coefficients were between -.50 and .85 (i.e., moderate/strong association). This was also evidenced in Model Two, with all factor loadings significantly loading onto the Disease Severity latent concept (all *p*'s <.001). Correlation coefficients in Model Two were between -.5 and .84 (i.e., moderate/strong association).

Better Past Disease Severity. In Model One, all factor loadings significantly loaded onto the *Better Past Disease Severity* latent concept (all *p's* < .001*).* Correlation coefficients were between -.81 and .56 (i.e., moderate/strong association). Again, the negative correlations found are not surprising as if a youth had tested positive for CDC classification and HIV-related encephalopathy prior to study entry, the more significant their Better Past Disease Severity. The results of Model One only varied slightly from Model Two, in which all factor loadings significantly loaded onto the *Better Past Disease Severity* latent concept (all *p's* < .001*)* and correlation coefficients were between -.81 and .55 (i.e., moderate/strong association).

Disease Severity at Entry. Interestingly, only two significant correlations were found, CD4% at entry and RNA VL at entry, both at the *p*<.001 level (i.e., moderate correlation coefficients between -.56 and .79). All treatment variables (HAART w/PI, HAART w/out PI and other ARV) were not significantly predictive of *Disease Severity at Entry*. These results were similarly reflected in Model Two in which only CD4% at entry and RNA VL were significant the *p*<.001 level and with moderate correlation coefficients between -.55 and .80. Again, all

treatment variables (HAART w/PI, HAART w/out PI and other ARV) were not significantly predictive of disease severity at entry.

Psychosocial Variables. ***Home Environment.*** With the exception of one factor in Model One (# drugs used in the last six months p=-.06), all standardized weights within the measurement model were significant at the $p < .05$ level, with standardized regression weights ranging from -.75 to .56, suggesting that with the exception of number of drugs used in the last six months, all standardized regression weights demonstrated moderate associations. In Model Two, *all* standardized weights within the measurement model were significant at the $p < .05$ level, with standardized regression weights ranging from -.72 to .57 (moderate associations).

Caregiver Stress. Again, all standardized weights within the measurement model of Model One were significant at the $p<.01$ level with positive correlation coefficients ranging from .25 to .46. These results were also significant for Model Two, in which all standardized weights were significant at the $p<.001$ level, with positive correlation coefficients ranging from .28 to .47.

Caregiver Educational Opportunity. All standardized weights within the measurement model of Model One were highly significant at the $p<.001$ level with correlation coefficients ranging from -.52 to .98 (i.e., moderate/strong association). Similar results were found in Model Two, with all standardized weights at the $p<.001$ level with correlation coefficients ranging from -.53 to .96 (moderate/strong associations).

Direct Effects of Latent Concepts on Endogenous Variables.

Model one: Perinatally HIV-infected (PHIV+) youth: youth assessed behavioral functioning. Four significant direct path coefficients were found from the latent, exogenous predictors to the endogenous variables, suggesting that these factors significantly predicted CF

and child-assessed behavioral functioning. *Caregiver Stress* was found to be significantly predictive of child-assessed BF*(standardized coefficient*=.51, *p*<.001; see Table 13), indicating that the higher a caregiver's reported stress, the more likely their child is to report at-risk and clinical responses on the youth self-report version of the BASC.

Two significant results were found pertaining to the direct effects of Disease Severity on CF. *Better Past Disease Severity* was found to be positively associated with CF *(standardized coefficient*=.40, *p*<.001), suggesting that the more severe one's disease, the more likely the child is to face significant cognitive impairment as an adolescent. In addition, *Late Presenter*s demonstrated a negative association with CF (*standardized coefficient* =-.19, *p*<.05). , suggesting that the younger the child begins treatment, the higher their CF. An additional Psychosocial variable, *Caregiver Educational Opportunity* demonstrated a significant positive association with CF (standardized coefficient =.33, *p* <.001), suggesting that the higher a caregiver's perceived competence, the higher a youth's CF.

Model two: Perinatally HIV-infected (PHIV+) youth: Caregiver assessed behavioral functioning. Five significant direct path coefficients were found from the latent, exogenous predictors to the endogenous variables, suggesting that these factors significantly predicted CF and child-assessed BF (see Table 13). Similar to Model One, *Caregiver Stress* was found to be positively associated with child-assessed BF*(standardized coefficient*=.50, *p*<.001), indicating that the higher a caregiver's reported stress, the more likely their child is to report at-risk and clinical responses on the youth self-report version of the BASC. Unlike Model One, in addition to *Caregiver Stress*, CF was also strongly associated with BF *(standardized coefficient*=-.29, *p*<.01), suggesting that a decrease in CF predicts an increase in caregiver reported BF.

As evidenced in Model One, *Better Past Disease Severity* was found to be positively associated with CF *(standardized coefficient*=.39, *p*<.001), suggesting that the more severe one's disease, the more likely the child is to face significant cognitive impairment as an adolescent. In addition, *Late Presenter*s were also found to be negatively associated CF *(standardized coefficient*=-.19, *p*<.05), suggesting that the later the child begins treatment, the lower their CF. An additional Psychosocial variable, *Caregiver Educational Opportunity* was found to be significantly predictive of CF (*standardized coefficient*=.34, *p*<.001), suggesting that the higher a caregiver's perceived competence, the higher a youth's CF.

PHIV+ model one and two adjustments. When adjusted for race, sex, and ethnicity, sensitivity analysis results varied significantly only for African-American youth which suggested that only *Better Past Disease Severity* (*standardized coefficient* =.32, *p*<.01), and *Caregiver Educational Opportunity* (*standardized coefficient* =.41, *p*<.001) predicted CF. *Caregiver Stress* continued to remain highly significant (*standardized coefficient* =.50, *p*<.01). Interestingly, sensitivity analyses suggested that African American race only significantly impacted youth in the PHIV+ child-assessed model (*standardized coefficient*=-.18, *p*<03) and no other model in the analyses.

Direct, Indirect and Total Effects for Perinatally HIV-infected (PHIV+) youth In structural equation mediation analysis, it is hypothesized that the independent variables (the exogenous side) of the model are significantly related to the dependent (endogenous) variable and the endogenous mediator is significantly related to the dependent (exogenous) variable (Baron & Kenny, 1986). For results from both Model One and Two, see Table 14.

Model one: Perinatally HIV-infected (PHIV+) youth: Youth assessed behavioral functioning. In the child-assessed PHIV+ Model, no indirect effects of the latent predictors on

BF were found. Only *Caregiver Stress* (direct effect=.51, $p<.001$) had a direct effect behavioral functioning, which contributed to the significant total effect on the model (total effect =.47, $p<.001$).

Model two: Perinatally HIV-infected (PHIV+) youth: Caregiver assessed behavioral functioning. In addition to a direct effect of *Caregiver Stress* (direct effect=.50, $p<.01$) which contributed to the significant total effect on the model (total effect =.44, $p<.01$), two additional indirect effects were found in Model Two, *Better Past Disease Severity* (indirect effect= -.12, $p<.05$) and *Caregiver Educational Opportunity* (indirect effect= -.10, $p<.05$). However, these results did not significantly influence the total effect on behavioral functioning.

Results: Perinatally HIV-Exposed Models (PHEU: Models Three and Four)

Model Fit

As was selected for both PHIV+ models, absolute (SRMR), parsimonious (RMSEA) and incremental (Bentler CFI) fit indices were selected *a priori* to examine how the hypothesized model fit the resulting data. The results of PHEU Models Three and Four can be found below.

Model Three: Perinatally HIV-Exposed (PHEU) Youth: Youth assessed behavioral functioning. The SRMR for the child-assessed PHEU model (Model Three) is .080, indicative of a fit approaching significance. The RMSEA for Model One is .063, indicative of adequate fit. The Bentler CFI for Model Three is .82, suggesting a good fit to the data.

Model Four: Perinatally HIV-Exposed (PHEU) Youth: Caregiver Assessed behavioral functioning. The SRMR for the caregiver-assessed PHEU model (Model Four) is .0831, indicative of weak fit. The RMSEA for Model Two is .0751, indicative of a fit approaching significance. The Bentler CFI for Model Four is .790, suggesting a good fit to the data.

Taken together, the results of the fit statistics suggest that the PHEU models have an overall better fit to the data when compared to the PHIV+ sample. Alternatively, these results should be interpreted with caution as fit statistics are often influenced by the number of variables within the model. As both PHEU models have fewer variables and factor loadings, it is expected that these fit statistics may be marginally stronger that the PHIV+ models.

Covariances Between Exogenous Predictors: Model Three and Four

Interestingly, no significant covariances were found between the exogenous predictors (*Family Emotional Stress*, *Caregiver Relationship* and *Caregiver Educational Opportunity*) in both Model Three (Perinatally HIV-Exposed Youth: Youth assessed Behavioral Functioning) and Model Four (Perinatally HIV-Exposed (PHEU) Youth: Caregiver Assessed Behavioral Functioning), suggesting that all psychosocial factors in the exposed sample did *not* correlate with each other and only independently influenced both CF and BF(see Appendix Da-k).

Factor Loadings: Endogenous Variables

In both Models Three and Four, all cognitive indices significantly loaded onto the CF concept at $p < .001$, with correlation coefficients between .48 and .80 (i.e., moderate-large associations; see Table 15). It is important to note that the indicator variables were expected to predict the latent variables, because the indicator variables were all subscales of FSIQ that comprise the CF latent concept.

Model Three: Perinatally HIV-exposed (PHEU) Youth: Youth assessed behavioral functioning. In the Perinatally HIV-exposed (PHEU) Youth: Youth assessed Behavioral Health Model (Model Three), all observed behavioral indices significantly loaded onto the observed BF variable at the $p<.001$ level, suggesting associations between the observed variables and the latent concept (see Table 15). Correlation coefficients were between -.62 and .81 (i.e., moderate

to large associations). The negative *Personal Adjustment* loading is not surprising as *Personal Adjustment* is reverse-scored on the BASC, meaning that *lower* scores indicate *poorer* behavioral function and an *increased* risk for clinical impairment. Again, it was expected that indicator variables would significantly predict the latent variables, as the subscales of the BASC comprise the "Mental Health" latent concept.

No significant path was evidenced between CF and Child-Assessed BF indicating that an increase cognitive function does not directly predict better behavioral functioning, although the non-significant correlation demonstrates this inverse relationship.

Model Four: Perinatally HIV-exposed (PHEU) Youth: Caregiver assessed behavioral functioning. In the Perinatally HIV-exposed (PHEU) Youth: Caregiver Assessed Behavioral Functioning Model (Model Four), all observed behavioral indices significantly loaded onto the observed BF variable at the $p<.001$ level, again suggesting strong associations between the observed variables and the latent concept (see Table 15). Correlation coefficients were between -.68 and .83 (moderate to large association). The negative *Adaptability* loading is not surprising as, like the *Personal Adjustment* score in the child-assessed BASC, it is reverse-scored, meaning that *lower* scores indicate *poorer* adaptability and an *increased* risk for clinical impairment. Again, it was expected that indicator variables would significantly predict the latent variables, as the subscales of the BASC comprise the BF latent concept.

Unlike Model Three, a significant path was evidenced between CF and Caregiver-Assessed BF *(standardized coefficient*= -54 (.116), $p<.001$) suggesting that the higher a child's CF, the lower clinical levels of caregiver-reported behavior. This pattern of results was demonstrated in the prior Model Two in which only a significant path was found between CF and Caregiver-Assessed BF.

Factor Loadings: Exogenous Variables: Models Three and Four

As both perinatally exposed models (PHEU) are from the same population and only differ regarding the assessment of BF (caregiver vs. child), findings will be presented simultaneously (see Table 15).

Psychosocial variables. ***Caregiver relationship.*** With the exception of one factor (*Caregiver is a biological parent*), all standardized weights within the measurement model in Model Three were significant at the $p<.001$ level, with standardized weights ranging from -.54 to .58, demonstrating moderate associations. These findings were nearly identical in Model Four, with three of the four standardized weights significant at the $p<.001$ level and moderate associations (-.54 to .58) with the exception of *Caregiver is Biological Parent*. These findings suggest that the biological status of the caregiver does *not* influence the total *Caregiver Relationship*.

Caregiver Educational Opportunity. All standardized weights within the measurement model of Model Three were significant at the $p<.01$ level with -.52 to .90 (moderate to large). These results were similar for Model Four, in which all standardized weights were significant at the $p<.01$ level, with correlation coefficients ranging from -.51 to .90 (moderate to large associations).

Family emotional stress. All standardized weights within the measurement model of Model Three were significant at the $p<.01$ level with correlation coefficients ranging from -.27 to .52 (small to moderate associations). These findings were quite different in Model Four in which all but one factor (*Number Supported by Household Income*) were found to be significant at the $p<.001$ level with all positive correlation coefficients ranging from .38 to .57 (moderate associations).

Direct Effects of Latent Concepts on Endogenous Variables.

Model Three: Perinatally HIV-exposed (PHEU) Youth: Youth assessed behavioral functioning. Three significant direct path coefficients were found from the latent, exogenous predictors to the endogenous variables, suggesting that these factors significantly predicted CF and child-assessed BF (see Table 16). *Family Emotional Stress* was found to be significantly predictive of child-assessed BF *(standardized coefficient*=.40, *p*=.001), indicating that the higher a family's reported stress, the more likely their child is to report at-risk and clinical responses on the youth self-report version of the BASC.

Two significant results were found pertaining to the direct effects of *Caregiver Relationship* and *Caregiver Educational Opportunity* on CF. *Caregiver Relationship* was found to be significantly predictive of CF *(standardized coefficient*=.32, *p*<.01), suggesting that the more positive a caregiver's well-being, the higher the child's CF. In addition, *Caregiver Educational Opportunity* was also found to be significantly predictive of better CF *(standardized coefficient*=.37, *p*<.001), suggesting that the more competent the caregiver the higher their child's CF .

Model Four: Perinatally HIV-exposed (PHEU) Youth: Caregiver assessed behavioral functioning. Five significant direct path coefficients were found from the latent, exogenous predictors to the endogenous variables, suggesting that these factors significantly predicted CF and caregiver-assessed behavioral functioning. Similar to Model Three, *Family Emotional Stress* was found to be significantly predictive of caregiver-assessed BF *(standardized coefficient*=.58, *p*<.001; see Table 16), indicating that the higher a family's reported stress, the more likely their caregiver is to report at-risk and clinical responses on the parent report version of the BASC. In addition, *Caregiver Educational Opportunity* was also found to be significant

(standardized coefficient=.25, *p*<.05). Unlike Model Three, in addition to *Family Emotional Stress,* CF was also highly significant, *(standardized coefficient*=-.54, p<.001), suggesting that a decrease in CF predicts an increase in caregiver reported clinical behaviors.

As evidenced in Model Three, both *Caregiver Relationship* and *Caregiver Educational Opportunity* were found to be significantly predictive of CF *(standardized coefficient*=.32, *p*<.01; coefficient=.38, *p*<.001, respectively). As can be seen by these results, *Caregiver Educational Opportunity* double-loaded onto *both* endogenous factors (CF and BF), suggesting that this latent concept is a particularly powerful predictor.

Direct, Indirect and Total Effects for Perinatally HIV-exposed (PHEU) Youth Model Three: Perinatally HIV-exposed (PHEU) Youth: Youth assessed behavioral functioning. In the child-assessed PHEU Model, no indirect effects of the latent predictors no BF were found (see Table 17). Only *Family Emotional Stress* (direct effect=.40, *p*<.01) had a direct effect *behavioral functioning*, which contributed to the significant total effect on the model (total effect =.38, *p*<.01).

Model Four: Perinatally HIV-exposed (PHEU) Youth: Caregiver assessed behavioral functioning. Interestingly, results significantly differed for Model Four, while *Family Emotional Stress* continued to direct effect (direct effect=.58, *p*<.001) on BF that contributed to the total effect (total effect=.53, *p*<.001), two other significant direct and indirect effects were found (see Table 17). Again, *Caregiver Educational Opportunity* was evidenced to be a significant predictor, having both a direct effect (direct effect=.25, *p*=.05) and indirect effect (indirect effect= -.20, *p*<.01) on behavioral functioning, although not influencing the total effect in the model. *Family Emotional Stress* had a direct effect on BF (direct effect=.58, *p*<.001) which contributed to the total effects found in the model (total effect=.52, *p*<.001).

CHAPTER 5

Discussion

Although a preponderance of extant literature suggests that BF and CF are related to both disease severity and psychosocial factors, very little is known regarding which of the environmental and disease-related variables have the greatest impact on the outcomes observed in PHEU and PHIV+ children, which may be due to the inherent complexity of the disease. Studies that only examine the direct or indirect effects of HIV may not comprehensively address the complex and enmeshed relationship psychosocial stressors and disease related information. In addition, it represents a unique contribution to existing HIV knowledge as it will directly compare behavioral and cognitive profiles among perinatally HIV-infected (PHIV+) youth and perinatally HIV-exposed but uninfected youth (PHEU).

By simultaneously examining disease severity and psychosocial factors and the potential mediating role of CF on BF within SEM, the current study addressed many of the unanswered questions regarding the cognitive and psychiatric sequelae of HIV in order to develop a model of research and clinical impact. Although several recent studies have examined the impact of environmental and biological variables associated HIV and its impact on CF and BF, many have used different combinations of concomitant factors, making the synthesis of these findings unascertainable. Historically, many studies have examined the impact of only *one* assemblage of variables on *one* aspect of functioning (e.g., solely investigating the impact disease severity on CF) which may not comprehensively encapsulate the actual biological and environmental impact of disease-related factors on cognitive and behavioral functioning.

The current study is the first of its kind to examine the potential mediating role of CF between disease severity, psychosocial stressors and BF. In both the general and HIV literature, a

strong association between lower CF and BF is well demonstrated (see Laughton et al., 2013; Malee et al., 2011; Salama et al., 2013) and suggests that specific neurological patterns of CF (e.g. executive functioning, inhibitory control, memory) may impact specific BF concerns including conduct disorder, negative coping skills and increased risk-taking (Laughton et al. 2013). The inclusion of CF as a mediator allowed close examination of both the direct and indirect effects of both disease severity and psychosocial stressors on specific areas of CF and the interplay between these specific areas of functioning on BF.

The present study was the first of its kind to statistically explore the differential impact of psychosocial stressors, disease severity and cognition on BF within a complex structural equation model, thus allowing identification of the best combination of concomitant variables that account for cognitive and behavioral sequalae associated with HIV exposure. *Caregiver Stress* and *Family Emotional Stress* predicted higher (worse) BF scores in PHIV and PHEU youth, aligning closely with Sameroff and Rosenblum (2006) and Smith et al.'s (2006) findings regarding the deleterious impact of compounding stressors on both cognitive and behavioral resilience in both general and HIV-exposed samples. Although it should not be overstated that these stress variables may *cause* these profiles, it does suggest that those families who are facing multiple environmental stressors may be at higher risk for BF and CF problems, similar to the conclusions made by Mellins and Malee (2013) in their comprehensive review of mental health functioning in PHIV youth. An addition psychosocial variable, *Caregiver Educational Opportunity* was also positively associated with caregiver-reported BF in PHEU youth. *Caregiver Educational Opportunity* and two disease severity variables, *Late Presenter* and *Better Past Disease Severity* were significant predictors of youth CF suggesting that previous disease status- despite current status – is a very important indicator of risk for later poor CF, a

particularly important finding for timing of treatment. These findings also align with current research regarding the function of age and its association with both clinical presentation of the disease and later CF (Becker et al, 2004). Interestingly, in the caregiver-reported BF in both the PHIV and PHEU models, higher child CF was associated with significantly lower (better) caregiver-reported BF, suggesting that caregivers may be more sensitive to BF than the youth informants. The current findings and their implications for future study are organized within the research questions posed in the introduction. Limitations and implications of the present findings for current research and practice are also described within this chapter.

Support for Research Questions and Associated Hypotheses

Research Question One: Do Disease Severity factors correlate with Psychosocial factors? As suggested by EFA results, necessary modifications to the model proposed during hypothesis development make it difficult to definitively provide full or partial support of this research question and its associated hypotheses. Nevertheless, several significant covariances were found between exogenous predictors in both PHIV+ models. In Model One (youth-assessed BF), significant covariance was found between *Disease Severity at Entry, Late Presenter* and *Better Past Disease Severity. Disease Severity at Entry* was also uniquely correlated to two psychosocial factors including *Home Environment* and *Caregiver Stress. Caregiver Stress* was also highly correlated with *Better Past Disease Severity* and *Home Environment*.

In Model Two (caregiver-assessed BF), *Disease Severity at Entry* continued to be a powerful covariate, significantly correlating with *Late Presenter, Better Past Disease Severity* and *Caregiver Stress*. In addition to correlating with *Disease Severity at Entry, Caregiver Stress* also correlated with both *Better Past Disease Severity* and *Home Environment*. Taken together, the significant covariances found in both models indicate that overall, Disease Severity factors

(*Late Presenter, Better Past Disease Severity, Disease Severity at Entry*) and Psychosocial Factors (*Home Environment, Caregiver Stress, Caregiver Educational Opportunity*) are significantly correlated suggesting that an unpredictable home environment, stress and caregiver aptitude may be associated with disease progression. These findings are consistent with Hochhauser, Gaur, Marone and Lewis' (2008) research indicating that HIV envelope protein-gp120 may only be toxic to the fronto-parietal region under conditions of high stress but not low stress, thus moderating the relationship between HIV and IQ. Future researchers should examine if this relationship is possibly predictive in nature whereby pre-existing psychosocial stressors may actually exacerbate disease severity.

Research Question Two: What is the association between psychosocial factors and both cognitive functioning and behavior? As hypothesized, psychosocial variables were found to be significant predictors of later cognitive and BF deficits, demonstrating that daily life stressors including poverty, trauma, and family disruption serve as risk factors for poor outcomes for PHIV+ youth. These findings contribute to the limited literature regarding the role of psychosocial variables and its influence on later cognitive and BF (Bauman, Camacho, Silver, Hudis, & Draiman, 2002, Elkington, Bauermeister & Zimmerman, 2010; Havens & Mellins, 2008; Lester et al., 2006; Smith et al., 2006). Across all models, three factors, *Caregiver Stress*, *Family Emotional Stress* and *Caregiver Educational Opportunity* demonstrated a predictive relationship with both later BF and CF. In both the caregiver and youth-assessed PHIV+ models, *Caregiver Stress* significantly predicted later behavior problems, supporting the findings of Mellins et al. (2008) and Nozyce et al. (2006).

Findings from the PHEU Models are indicative of more heterogeneous findings, potentially suggesting a more diverse psychosocial background for those youth that have been

exposed but not infected. In the PHEU youth-assessed model, *Family Emotional Stress* was found to be the only significant predictor of later behavioral functioning. In the PHEU caregiver-assessed model, the youth's CF, *Family Emotional Stress* and *Caregiver Educational Opportunity* were found to be significant predictors of later BF problems. In both PHEU models, *Caregiver Relationship* and *Caregiver Educational Opportunity* were predictive of child's CF.

These findings represent a unique contribution to the literature that has often relied on age-matched healthy controls, if any, in their analysis. Of additional interest are those factors that were found *not* to be statistically significant such as the *Home Environment* latent variable in the PHIV+ models (which included information related to marital status of the caregiver, illicit drug use and income level) and the *Parent-Child Relationship* latent variable (which included information related to marital status of the caregiver and PCRI score and income level) in the PHEU models. Similar factors included within these latent concepts may indicate that both marital status of the caregiver and income level may *not* be adequate predictors of CF and BF. It is speculated that while the caregiver's marital status and income may potentially influence the family system, if these experiences are not identified as stressful by either the youth or caregiver, they do not significantly predict problems associated with BF and CF.

Research Question Three: What is the association between disease severity markers and both cognitive functioning and behavioral functioning? As hypothesized, across both PHIV+ models, two disease severity factors, *Late Presenter* and *Better Past Disease Severity* were significant predictors of the youth's *CF*. *Disease Severity at Entry*, which included the most recent CD4% and pharmacological intervention (i.e. current medication) information was *not* found to be a significant predictor of later BF a unique finding and contribution to the literature.

Interestingly, both *Better Past Disease Severity* and the *Late Presenter* status only predicted CF, and demonstrated no significantly predictive relationship to behavioral functioning. The findings in the present study are dissimilar to those of Brouwers and colleagues (1995) and Misdrahi and colleagues (2004) who suggested a direct relationship between disease severity measures and behavioral dysfunction. These findings partially support the author's hypothesis, in that two of the three disease severity variables only significantly predict CF but were *not* found to be associated with later BF problems. Taken together, these findings align with the author's primary hypothesis that psychosocial variables were found to be more powerful predictors of *both* later cognitive and behavioral functioning, aligning with both Mellins et al.'s (2002; 2008) and Nozyce et al.'s (2006) findings that environmental stressors associated with behavior problems may be even more potent mediators in HIV-infected children than HIV infection itself.

Research Question Four: How does cognitive functioning mediate the relationship between disease and home psychosocial factors and behavior? CF was found to be a significant mediator in some, but not all, of the regressional pathways. In the caregiver-assessed PHEU sample, the effect of *Caregiver Relationship* on BF was mediated by CF, suggesting that the caregiver's relationship status (married, separated, divorced or widowed) and family income influence CF that, in turn, influences later BF problems. Perhaps most interestingly, in the caregiver-assessed PHEU sample, *Caregiver Educational Opportunity* was such a powerful predictor that it had both a direct *and* indirect (mediational) effect on later BF problems.

Findings from the PHIV+ models indicated significantly different mediational relationships. In the child-assessed PHIV+ group, *no* significant indirect relationships were found, indicating that the significant predictors only directly influenced cognitive and/or BF and that CF did *not* indirectly influence the relationship between predictors and later behavioral

functioning. In the caregiver-assessed PHIV+ sample, a mediational effect was demonstrated for both *Better Past Disease Severity* and *Caregiver Educational Opportunity*, suggesting that the effect of both *Better Past Disease Severity* and *Caregiver Educational Opportunity* factors on BF is fully mediated through CF. Although these findings only partially support the author's hypothesis, it is important to note that the present models demonstrated only marginal fit (see limitations), which is often considered an important pre-requisite to interpreting mediation results. The obtained results are an important inclusion to the current literature regarding the incorporation of mediational strategies in order to test theory (Bryan, Schmiege and Broaddus, 2006).

Research Question Five: Overall, how do behavioral and cognitive profiles differ between perinatally HIV-infected youth and perinatally HIV-exposed but uninfected youth? When comparing behavioral profiles of PHEU and PHIV+ samples, a powerful and potentially the most clinically significant finding arose. Across all *four* models (PHIV+ caregiver/youth assessed, PHEU caregiver/youth assessed), *Caregiver Stress* and *Family Emotional Stress* were the strongest predictors for later BF problems. Although the inclusion of specific variables slightly differed across the latent "stress" variables in the PHEU and PHIV samples, both "stress" variables included the number of negative life events, stressful life events and caregiver mental health problems. In fact, in the PHIV+ models, only *Caregiver Stress* predicted later BF problems. In the PHEU model, the inclusion of one additional variable, *Caregiver Educational Opportunity*, was also significantly predictive of behavioral functioning, suggesting that for those youth that were exposed but not infected, their caregiver's CF, household income and attainment of a high school degree was associated later BF. These

findings aligned with much of Mellins' work (2003, 2008) that has highlighted the important role of maternal mental health and CF as a predictor for youth mental health and behavior.

Similar to the behavioral profiles of both the PHIV+ and PHEU samples, the cognitive profiles of both PHIV+ and PHEU youth suggest analogous results, thus supporting the hypothesis that these profiles would not significantly differ. *Caregiver Educational Opportunity*, comprised of information related to the caregiver's IQ, their high school graduation rate and household income (PHEU models only: see EFA), was associated with CF in all *four* models. In fact, *Caregiver Educational Opportunity* was such a powerful predictor that it simultaneously double-loaded onto *both* cognitive and behavioral functioning in the PHEU caregiver assessed BF model, a unique statistical phenomena in SEM and an important finding. In addition, *Caregiver Relationship* (included in the PHEU models only), which contained observed factors such as caregiver marital status, income and scores on the PCRI was also associated with CF. As described initially, only disease severity was assessed in the PHIV+ models, which yielded two additional predictors, *Better Past Disease Severity* and *Late Presenter* that were significant in both parent and youth assessed models. Because the grouping dictated by the results of the EFA was slightly different from the proposed model, the ability to definitely respond to this research question and ascertain meaning across all models is difficult. Nevertheless, across all models, *Caregiver Stress* and *Family Emotional Stress* was associated with BF, suggesting that models *do not* differ substantially from each other. Alternatively, both *"Stress"* latent concepts contained slightly different variables, which indicate that models differed slightly across variable groupings and factor loadings. In addition, *Caregiver Educational Opportunity* demonstrated an associated relationship all models concerning CF, suggesting that these profiles may be even

more similar when examining the cognitive sequalae of the disease across PHIV+ and PHEU samples.

Limitations

Although the present study extends the current understanding of the role both psychosocial and disease severity factors on cognitive and BF among HIV-affected youth, this investigation is not without its limitations. SEM was initially termed "causal modeling" (Wright, 1921); however, the ability to infer an explicitly causal relationship between the exogenous and endogenous variables is cautioned and highly controversial (Bullock, Harlow & Mulaik, 1994). Though inferring causes from the findings is strongly discouraged, as described previously, the purpose of the current study was to test predictive relationships in order to develop a theoretical model. For example, although it cannot be concluded that *Family Emotional Stress causes* increased BF problems, these results suggest that *Family Emotional Stress* and BF have a positive correlation, meaning that an increase in *Family Emotional Stress* is associated with an increase in clinical presentation of overall scores on the BASC. In fact, future studies should explore the potential *reverse* the model to investigate whether preexisting BF and CF predicts psychosocial and disease related factors (i.e. BF *predicts* later family emotional stress)

In addition, model fit statistics (e.g. SRMR, RMSEA, and Bentler Comparative Fit Index) for the final model were not ideal. In an attempt to improve model fit, all paths from latent exogenous factors to BF with $p > 0.15$ and all paths from latent exogenous factors to CF with $p > 0.15$ were removed. Model fit statistics remained essentially the same after this update; fit statistics for each of the four SEM models before and after removal of paths with $p > 0.15$. Nevertheless, the goal of this concept was to examine the effects of specific HIV-related and psychosocial characteristics on BF and to evaluate whether CF mediated these relationships, not

to develop the best predictive model for behavioral functioning. The less than-ideal model fit indicates that, despite some significant associations between HIV-related and psychosocial characteristics and behavioral functioning, the factors of interest are not highly predictive of BF in and of themselves. Given the variability in BF and the difficulty in predicting this outcome (Bachanas et al., 2001), these results are not entirely surprising. Future iterations and post-hoc modifications of the model may remove the latent concepts that were found to be non-significant entirely which may improve overall model fit.

In addition, although the present study utilized a variety of multi-method and multi-informant measures to capture the latent exogenous variables, only one intelligence measure (the Wechsler testing series) and one behavioral assessment measure (the Parent Report and Self Report versions of the BASC) were used to capture cognitive and behavioral functioning, which in turn may be problematic as the Wechsler and BASC may not accurately represent the cognitive and behavioral abilities of the sample, and may be inherently culturally and ethnically biased (Malgady, 1996). It is important to note that these measures are widely used in both the research and clinical field of neuropsychological assessment, were also used as a primary assessment approach in much of the reviewed literature (Brackis-Cott et al., 2009; Smith et al., 2012; Stout et al. 1995) and are employed in the pediatric immunology clinics participating in PHACs.

Because the primary goal of the present study was to evaluate SEM as an approach to understand the complex interrelationships between home environment, caregiver characteristics, psychosocial characteristics, and CF on behavioral outcomes, other cognitive and behavioral measures may replace the BASC and Wechsler series in future research, perhaps explicitly

focusing on areas of cognitive (e.g., executive functioning) and behavioral (e.g., impulsivity) functioning that may be deleteriously affected in this population.

Missing data may also limit implications based on the obtained findings. As part of the inclusion criteria, there were no data missing on the cognitive and BF outcome variables, due to eligibility requirements (i.e., eligible participants were those with WISC or WAIS at year 3 visit and both parent BASC and child BASC within 2 years of WISC/WAIS.) Alternatively, there were missing data for some of the predictor variables (see Table 10). In order to avoid excluding children with missing values for one or more predictors (the maximum number of missing values for one child is 5, out of 26 predictors), missing values were replaced by assigning the largest category to the missing values. Although mean substitution is a widely used statistical technique to address missing data (Schumacher & Lomax, 2010), this may bias results particularly if a large amount of missing data is present. Because missing data was minimal, it is *not* expected that the mean substituted data would influence the overall strength of both the model and the findings, but should still be considered a potential limitation to the overall study.

Implication of Findings for Research

Despite these limitations, the present study represents a significant contribution to the existing pediatric HIV literature particularly regarding the utilization of SEM as an approach to understand the complex interrelationships between home environment, caregiver characteristics, psychosocial characteristics, and CF on behavioral outcomes. The inclusion of each factor, the grouping of the factors into latent constructs, and the relationships of these latent constructs are all strongly grounded in pre-existing literature and research. The current study was the first of its kind to simultaneously examine both disease severity and psychosocial factors within both HIV-infected and HIV-exposed samples all within a complex SEM in order to explicate a conceptual

model. In addition, the use of EFA strategies in order to "fine-tune" the model prior to SEM as a theoretical approach was also a unique contribution to the existing statistical literature. Results pertaining to the mediation analysis also are important findings for future research, as it suggests that both disease severity and psychosocial variables have both *direct* and *indirect* effects on BF as mediated through CF, but that these relationships are influenced by both HIV infection and informant.

Important implications for future research can also be found by examining the results of the factor analysis, including the use of both the Wechsler series and the BASC (PRS and YSR) as important tools to assess cognitive and BF with PHIV+ and PHEU youth. Across all four models, estimated CF index scores exhibited extremely high correlation with FSIQ suggesting that the Wechsler series continues to be an important tool to assess CF for HIV-impacted youth. Interestingly, for the PHIV group, the BASC-P domains load highly on Factor 1 and the BASC-C domains load highly on Factor 2. In contrast, for the PHEU group, it is the opposite -- the BASC-C domains load highly on Factor 1 and the BASC-P domains load highly on Factor 2. These discrepant findings suggest that, among the PHIV+ children, the factor representing the parent viewpoint (BASC-P domains) accounts for more of the common variance in the observed variables than the factor representing the child viewpoint (BASC-C domains); and that the opposite is true for the PHEU children. This finding may be due to the potential diligence and vigilance of PHIV+ caregivers to provide comprehensive behavioral information related to their child's diagnosis. The differences in these reports also support the necessity for multi-informant assessment when evaluating BF problems and thus justified fitting separate models for the two outcomes.

Across all models, three factors, *Caregiver Stress*, *Family Emotional Stress* and *Caregiver Educational Opportunity* demonstrated associated with both BF and CF, aligning closely with Sameroff and Rosenblum (2006) and Smith et al. (2006) findings regarding the deleterious impact of compounding stressors on both cognitive and behavioral resilience in both general and HIV-exposed samples. These findings also indirectly contribute to both Rhodes et al. (2005) and Lane et al.'s (2004) discussion of "structural violence" and "risk environment" in which one's personal stressors, toxic environment and received stigmatization within the existing macrosystem serve as possible barriers to adequate treatment thus negatively impacting both cognitive and behavioral resilience. The present findings indicate that psychosocial factors may play such a powerful role in both CF and BF that future iterations of this study could potentially examine the role of psychosocial factors in mediating the relationship between disease severity and CF and BF outcomes. In addition, utilizing more advanced statistical methodologies such as hierarchical linear modeling (HLM), future studies should examine these specific stress-related variables and their longitudinal impact on cognitive and BF in order to contribute to what is known regarding the developmental trajectories of both PHIV+ and PHEU children.

Implication of Findings for Clinical Practice

The findings in the current study also have important implications for clinical practice, particularly concerning the factors that were found to be predictive of later cognitive and BF dysfunction. As described previously, an increase in both *Caregiver Stress* and *Family Stress* was associated with later cognitive and BF problems regardless of immunologic severity or disease status (PHEU and PHIV+). The results of these analyses confirm that it is necessary to

examine the developmental outcomes of children by looking at all factors that influence them, not just health, and their interactions.

Although it should not be overstated that these stress variables may *cause* these profiles, it does suggest that those families who are facing the most environmental stressors are at higher risk for later problems. Clinicians should continue to develop more elegant and advanced methods to assess family and personal stress in order to establish risk profiles for HIV exposed youth and their families. The results from the EFA regarding what factors could be included within these latent *"Stress"* concepts could serve as potential indices within the *Caregiver* and *Family Stress* measure. This same measure development strategy could also be used for PHIV+ youth in order to examine the specific areas within the *Late Presenter* and *Better Past Disease Severity* factors may place the child at a higher risk for later cognitive problems. In both PHEU models, *Caregiver Educational Opportunity* was found to be an important predictor of both cognitive and behavioral functioning, suggesting that comprehensive maternal care including educational and financial support may enhance resilience for HIV-exposed children even before they are born. This finding is an important clinical implication for psychologists working with sexually active HIV+ youth and parents of newborns. The role of Caregiver Educational Opportunity and maternal health has also been well established as an important contributor to cognitive and BF in the current literature (Abrams et al., 2003; Coscia et al., 2001; Mellins et al., 2003).

In the PHIV+ models, it was found that both *Better Past Disease Severity* and the *Late Presenter* status predicted only CF, suggesting that the more clinically significant one's disease severity and the later timing of this significance (i.e., - 3 months vs. 5 years) may negatively impact a child's CF, an important finding for clinicians monitoring the health trajectories of their

HIV+ patients. These findings also align with current research regarding the function of age and its association with both clinical presentation of the disease and CF (Becker et al., 2004)

Implications for National and International HIV Policy Development

In addition to impacting the way in which clinicians and researchers assess and intervene on the behavioral and cognitive sequalae of HIV, the obtained results may have significant implications for both domestic and international policy regarding HIV treatment, particularly with regards to the role of structural violence as it connects to the communities most affected by the disease around the world (Qureshi, 2013). Future iterations of this study may investigate culturally variant definitions of stress and the way these influence daily functioning, particularly in low resource countries in the developing world, where significant stressors such as famine, displacement and war may further exacerbate or even supersede concerns associated with HIV disease severity (Maes & Shifferaw, 2011).

The findings in this study that related to the role of caregiver stress and well-being align with current national initiatives to fund HIV/AIDs and maternal child health (MCH) through the 6-year, $63 billion Global Health Initiative authorization of the President's Emergency Plan for AIDS Relief (PEPFAR) and the Mother and Child Campaign (Leeper and Reddi, 2010) which has particularly focused on countries within sub-Saharan Africa that remain most devastated by HIV/AIDs transmission and mortality. Alternatively, current national and international policy has focused almost exclusively on solely ameliorating disease transmission and severity, thereby omitting the role of family, environmental and caregiver stress and its impact on CF, BF and the disease itself. These sobering findings provide support for Farmer et al.'s (2006) theory regarding the desocialization of scientific inquiry even at the international policy level. This is discussed by Leeper and Reddi (2010) in their opinion piece to the Journal of AIDS, who argue

that both national and international HIV/AIDs care must be family-centered within an integrated service delivery model in order to support both caregiver and pediatric health outcomes.

In addition, persistent social stigma associated with those living with HIV continues to plague international HIV policy development, particularly in countries in which the political and religious paradigm may negatively affect access to scientifically-based educational materials and contraception. Future international iterations of this study may examine the role of cultural variants of stress, social stigma and access to contraception as a potential mediator of both disease severity and psychosocial factors.

Conclusion

In conclusion, the current study represents an important contribution to the study of perinatally acquired HIV, the utilization of SEM for theory testing and the general understanding of the impact of caregiver and family stress on later cognitive and socio-emotional resilience (see Appendix E). Despite limitations regarding restricted causal assumptions, the obtained findings add to our understanding of the cognitive and behavioral profiles of children infected with HIV and the way in which these profiles relate to those youth that have been exposed yet remain uninfected. The key factors that served as potential predictors may be utilized to establish informed assessment and treatment methodologies that take into account the powerful impact of individual and family stress, caregiver educational opportunity and timing of disease presentation in order to establish risk profiles for those in our community who continue to remain most vulnerable to HIV exposure and infection.

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Table 1. Reason not included in SEM analysis

Frequency	Cohort		
	Infected	Uninfected	Total
No Year 3 WISC/WAIS	137	45	182
	62.27	59.21	
No later Parent BASC	36	11	47
	16.36	14.47	
No later Child BASC	40	13	53
	18.18	17.11	
BASC not within 2 yrs of WISC/WAIS	6	4	10
	2.73	5.26	
Invalid WISC/WAIS or BASC-C/BASC-P	1	3	4
	.45	3.95	
TOTAL	220	76	296

Table 2: Demographic data of AMP protocol		
Characteristic	PHEU (*n*=200)	PHIV+ (*n*=358)
Male	104 (52.0%)	164 (45.8%)
Age at Entry in Years Mean (*SD*)	10.53 (2.45)	12.1 (2.53)
Race		
Black ,multiracial other	129 (64.5%)	256 (71.5%)
White Only	66 (33%)	84 (23.5%)
Hispanic	73 (36.9%)	96 (26.8%)
Child: English Primary Language	152 (76.0%)	306 (85.5%)

Table 3. Home environment factors by cohort

Characteristic		HIV Infection Status	
		Infected (N=231)	Uninfected (N=151)
Caregiver WASI FSIQ	N	172	108
	Mean (s.d.)	90.77 (15.71)	85.05 (13.11)
Caregiver WASI Category	Not Done	59 (26%)	43 (28%)
	< 70	8 (3%)	8 (5%)
	70-<85	64 (28%)	47 (31%)
	85+	100 (43%)	53 (35%)
Caregiver relationship	Single Biological Mother	61 (26%)	86 (57%)
	Single Biological Father	9 (4%)	2 (1%)
	Both Biological Parents	31 (13%)	33 (22%)
	Other relative	56 (24%)	13 (9%)
	Other non-relative	74 (32%)	17 (11%)
Marital status of caregiver	Married	97 (42%)	47 (31%)
	Separated/divorced	36 (16%)	26 (17%)
	Widowed	27 (12%)	8 (5%)
	Single, never married	71(31%)	70 (46%)
Caregiver high school graduate	No	56 (24%)	47 (31%)
	Yes	175 (76%)	104 (69%)
Annual household income <$20K	No	127 (57%)	49 (33%)
	Yes	95 (43%)	99 (67%)
	Unknown	9	3
Total # in household	1-2	67 (29 %)	45 (30%)
	3-4	100 (43%)	74(49%)
	5 or more	64 (42%)	32(21%)
# supported by household income	1-2	35 (15%)	21 (14%)
	3-4	100 (43%)	69 (46%)
	5 or more	96 (42%)	61 (40%)

Caregiver mental health problem (CDQ)	No	155 (73%)	90 (63%)
	Yes	58 (27%)	54 (38%)
	Unknown	18	7
Caregiver drug abuse (CDQ)	No	208 (98%)	138 (96%)
	Yes	5 (2%)	6 (4%)
	Unknown	18	7
# of reported drugs used last 6 months	0	132 (62%)	74 (51%)
	1	44 (21%)	36 (25%)
	2 or more	37 (17%)	34 (24%
	Not reported	18	7
# Stressful life events	0	103 (45%)	56 (37%)
	1	55 (24%)	39 (26%)
	2-3	51 (22%)	39 (26%)
	4+	22 (10%)	17 (11%)
Life events checklist category	Invalid age	5 (2%)	1 (1%)
	0 or less	98 (44%)	52 (35%)
	1-2	70 (31%)	53 (35%)
	3-4	36 (16%)	25 (17%)
	5+	15 (7%)	19 (13%)
	Unknown	7	1
# negative life events	Invalid age	5 (2%)	1 (1%)
	0 or less	70 (31%)	32 (21%)
	1-2	78 (35%)	53 (35%)
	3-4	40 (18%)	27 (18%)
	5+	31 (14%)	37 (25%)
		7	1
PCRI: Support problem	No	209 (93%)	119 (85%)
	Yes	15 (7%)	21 (15%)
	Unknown	7	11
PCRI: Involvement problem	No	164 (73%)	111 (79%)
	Yes	60 (27%)	29 (21%)
	Unknown	7	11

PCRI: Communication problem	No	175 (78%)	112 (80%)
	Yes	49 (22%)	28 (20%)
	Unknown	7	11

Table 4. HIV and ARV-related characteristics for PHIV+ youth

Characteristic		Total (N=231)
Nadir CD4%	Median (Q1, Q3)	19 (12, 25)
Nadir CD4% Category	0-<15%	75 (32%)
	15-<25%	93(40%)
	25%+	63 (27%)
Age at nadir CD4%	Median (Q1, Q3)	3.40 (1.50, 8.10)
Nadir CD4 count (cell/uL)	Median (Q1, Q3)	388 (224, 603)
Age at nadir CD4 count	Median (Q1, Q3)	7.40 (3.70, 10.00)
Peak HIV RNA viral load (copies/mL)	Median (Q1, Q3)	464,480 (125,862, 750,000)
Peak VL Category	0-<50,000	31 (13%)
	50,000- <500,000	89 (39%)
	500,000- <750,000	34 (15%)
	750,000+	77 (33%)
Age at peak VL	Median (Q1, Q3)	1.80 (0.40, 4.70)
CDC Class C	No	175 (76%)
	Yes	56 (24%)
HIV related encephalopathy prior to entry	No	212 (92%)
	Yes	19 (8%)
CD4% at entry	Median (Q1, Q3)	34 (28,29)
Entry CD4% Category	0-<15%	6(3%)
	15-25%	32 (14%)
	25%+	193 (84%)
CD4 count at entry (cells/uL)	Median (Q1, Q3)	776 (572,999)
Log Entry RNA VL	Median (Q1, Q3)	2.34 (1.70, 2.63)
HIV RNA Category at Entry	0-400	171 (75%)
	401-10,000	40 (17%)
	10,000-100,000	17 (7%)
	1000,000+	1 (0%)
	Unknown	2
Age at ARV initiation (yrs)	Median (Q1, Q3)	0.40 (0.00, 1.50)

Age at HAART initiation (yrs)	Median (Q1, Q3)	2.20 (0.60, 4.90)
ARV Regimen at entry	HAART with PI	162 (70%)
	HAART without PI	38(16%)
	Non-HAART ARV	19(8%)
	Not on ARV	12 (5%)

Table 5. Cognitive outcomes by cohort

Characteristic		HIV Infection Status		
		Infected (N=231)	Uninfected (N=151)	Total (N=382)
Age at WISC	Mean (s.d)	13.71 (1.97)	13.01 (1.83)	13.41 (1.94)
WISC/WAIS FSIQ	Mean (s.d.)	85.95 (15.74)	88.17(13.96)	86.82 (15.08)
WISC/WAIS FSIQ	<70	32(14%)	14(9%)	46 (12%)
Category	70-<85	67 (29%)	43(28%)	110 (29%)
	85-<100	91 (39%)	62(41%)	153 (40%)
	100+	41(18%)	32 (21%)	73 (19%)
WISC/WAIS Verbal IQ	Mean (s.d.)	88.37 (15.39)	87.90 (14.02)	88.18 (14.85)
WISC/WAIS Processing Speed	Mean (s.d.)	88.55 (15.10)	91. 17 (13.73)	89.58 (14.61)
WISC/WAIS Perceptual Reasoning	Mean (s.d.)	90.09 (15.06)	92.80 (14.87)	91.16 (15.02)
WISC/WAIS Working Memory	Mean (s.d.)	88.06 (14.93)	90.68 (13.13)	89.09 (14.29)

Table 6. Behavioral outcomes by cohort

Characteristic		HIV Infection Status		
		Infected (N=231)	Uninfected (N=151)	Total (N=382)
Age at Parent BASC	Mean (s.d)	15.33 (2.36)	14.34 (2.15)	14.94 (2.33)
BASC-P BSI T-score	Mean (s.d.)	49.21 (10.49)	51.82 (11.02)	50.24 (10.77)
BASC-P BSI Behavior Summary (Caregiver)	Not at risk	196(85%)	121(80%)	317(83%)
	At risk	25(11%)	19(13%)	44(12%)
	Clinically Significant	10(4%)	11(7%)	21(5%)
BASC-P Adaptability T-score	Mean (s.d)	51.25(10.71)	47.78 (10.43)	49.88 (10.72)
BASC-P Adaptability Behavior	Not at risk	192(83%)	118(78%)	310(81%)
	At risk	36(16%)	25(17%)	61(16%)
	Clinically Significant	3(1%)	8(5%)	11(3%)
BASC-P Internalizing T-score	Mean (s.d.)	47.56 (10.17)	49.85 (12.15)	48.47 (11.03)
BASC-P Internalizing Behavior	Not at risk	206(89%)	124(82%)	330(86%)
	At risk	20(9%)	16(11%)	36(9%)
	Clinically Significant	5(2%)	11(7%)	16(4%)
BASC-P Externalizing T-score	Mean (s.d.)	49.05(10.70)	51.89(10.85)	50.17(10.83)
BASC-P Externalizing Behavior	Not at risk	200(87%)	126(83%)	326(89%)
	At risk	20(9%)	12(8%)	32(8%)
	Clinically Significant	11(5%)	13(9%)	24(6%)
Age at Child BASC	Mean (s.d)	15.33(2.36)	14.33(2.16)	14.94(2.34)
BASC-C ESI T-score	Mean (s.d)	46.14(9.09)	45.58(7.63)	45.92(8.54)
BASC-C ESI Behavior Summary (Child)	Not at risk	214(93%)	146(97%)	355(93%)
	At risk	14(6%)	4(3%)	21(5%)
	Clinically Significant	3(1%)	1(1%)	6(2%)
BASC-C Personal Adjustment T-score	Mean (s.d.)	51.82(8.65)	52.30(7.96)	52.01(8.38)

BASC-C Personal Adjustment Behavior	Not at risk	214(93%)	141(93%)	355(93%)
	At risk	12(5%)	9(6%)	21(5%)
	Clinically Significant	5(2%)	1(1%)	6(2%)
BASC-C Internalizing T-Score	Mean (s.d.)	46.06(8.87)	45.70(8.83)	45.92(8.85)
BASC-C Internalizing Behavior	Not at risk	213(92%)	144(95%)	357(93%)
	At risk	13(6%)	5(3%)	18(5%)
	Clinically Significant	5(2%)	2(1%)	7(2%)
BASC-C School Problems T-score	Mean (s.d.)	48.19(9.61)	47.49(9.62)	47.91(9.61)
BASC-C School Problems Behavior	Not at risk	206(89%)	137(91%)	343 (90%)
	At risk	20(9%)	7(5%)	27(7%)
	Clinically Significant	5(2%)	7(5%)	12(3%)
BASC-C Inattention/Hyperactivity T-score	Mean (s.d.)	50.87(11.63)	50.61(10.99)	50.76(11.37)
BASC-C Inattention/Hyperactivity Behavior	Not at risk	181(78%)	122(81%)	303(79%)
	At risk	38(16%)	23(15%)	61(16%)
	Clinically Significant	12(5%)	6(4%)	18(5%)

Table 7. Pearson correlations between the WISC/WAIS domains.

	WISC/WAIS Domain	Verbal IQ	Perceptual Reasoning	Working Memory	Processing Speed
Overall	Verbal IQ	0.49*	0.64	0.59	0.47
	Perceptual Reasoning	--	0.49*	0.57	0.49
	Working Memory	--	--	0.45*	0.50
	Processing Speed	--	--	--	0.33*
PHIV	Verbal IQ	0.52*	0.66	0.59	0.53
	Perceptual Reasoning	--	0.51*	0.56	0.56
	Working Memory	--	--	0.44*	0.53
	Processing Speed	--	--	--	0.40*
PHEU	Verbal IQ	0.48*	0.62	0.61	0.36
	Perceptual Reasoning	--	0.46*	0.59	0.37
	Working Memory	--	--	0.47*	0.42
	Processing Speed	--	--	--	0.21*

Table 8. Factor pattern loadings and final communality estimates from a factor analysis on cognitive functioning variables

WISC/WAIS Domain	Overall (n=384)		PHIV (n=233)		PHEU (n=151)	
	Factor 1	Comm.	Factor 1	Comm.	Factor 1	Comm.
Verbal IQ	0.76	0.58	0.78	0.60	0.76	0.57
Perceptual Reasoning	0.76	0.58	0.78	0.60	0.74	0.55
Working Memory	0.73	0.53	0.72	0.52	0.75	0.56
Processing Speed	0.62	0.39	0.69	0.47	0.50	0.25

*Principal factor method used for extraction; SMC used for prior communality estimates**;** no rotation when only 1 factor extracted

Table 9a. Pearson correlations between BASC-C and BASC-P domains. *Squared multiple correlations are on the diagonals.*

		BASC-C				BASC-P		
		Schl Prob	**Inatt/Hyp**	**Pers Adj**	**Intern**	**Ext**	**Int**	**Adapt**
Overall	***BASC-C Domain***							
	School problems	0.25*	0.41	0.30	0.42	0.10	-0.03	0.09
	Inattention/Hyperactivity	--	0.36*	0.40	0.53	0.26	0.19	0.24
	Personal Adjustment	--	--	0.34*	0.56	0.18	0.16	0.21
	Internalizing	--	--	--	0.47*	0.15	0.21	0.19
	BASC-P Domain							
	Externalizing	--	--	--	--	0.49*	0.54	0.63
	Internalizing	--	--	--	--	--	0.36*	0.48
	Adaptability	--	--	--	--	--	--	0.44*
PHIV	***BASC-C Domain***							
	School problems	0.22*	0.36	0.23	0.36	0.17	-0.03	0.08
	Inattention/Hyperactivity	--	0.33*	0.37	0.52	0.25	0.22	0.26
	Personal Adjustment	--	--	0.38*	0.60	0.20	0.26	0.20
	Internalizing	--	--	--	0.49*	0.14	0.23	0.20
	BASC-P Domain							
	Externalizing	--	--	--	--	0.49*	0.50	0.65
	Internalizing	--	--	--	--	--	0.37*	0.52
	Adaptability	--	--	--	--	--	--	0.48*
PHEU	***BASC-C Domain***							
	School problems	0.38*	0.48	0.41	0.53	0.02	-0.02	0.13
	Inattention/Hyperactivity	--	0.42*	0.45	0.55	0.29	0.16	0.23
	Personal Adjustment	--	--	0.33*	0.50	0.17	0.04	0.24
	Internalizing	--	--	--	0.46*	0.19	0.18	0.17
	BASC-P Domain							
	Externalizing	--	--	--	--	0.52*	0.58	0.59
	Internalizing	--	--	--	--	--	0.37*	0.42

Adaptability	--	--	--	--	--	--	0.39*	*Principal factor method used for extraction; SMC used for prior communality estimates**;** oblique varimax rotation applied

Table 9b. Rotated factor pattern matrix and final communality estimates from a factor analysis on Behavioral Functioning variables. *High factor loadings (>0.40) are noted by *.*

	Overall (n=384)			PHIV (n=233)			PHEU (n=151)		
	Factor 1	**Factor 2**	**Comm.**	**Factor 1**	**Factor 2**	**Comm.**	**Factor 1**	**Factor 2**	**Comm.**
BASC-C Domain									
School problems	0.56*	-0.06	0.30	-0.03	0.48*	0.22	0.69*	-0.10	0.46
Inattention/Hyperactivity	0.61*	0.15	0.44	0.15	0.58*	0.40	0.65*	0.17	0.50
Personal Adjustment	0.59*	0.10	0.39	0.11	0.61*	0.42	0.61*	0.07	0.40
Internalizing	0.74*	0.06	0.57	0.04	0.76*	0.59	0.71*	0.09	0.55
BASC-P Domain									
Externalizing	0.01	0.76*	0.59	0.75*	0.004	0.57	0.01	0.79*	0.63
Internalizing	-0.004	0.65*	0.43	0.64*	0.04	0.43	-0.06	0.67*	0.43
Adaptability	0.04	0.71*	0.52	0.75*	0.01	0.58	0.10	0.64*	0.44

* Values under "Factor 1" and "Factor 2" are from the Rotated Factor *Pattern* Matrix (standardized regression coefficients)

Table 10. Rotated factor pattern matrix (standardized regression coefficients) and final communality estimates from factor analyses on HIV disease severity variables. High factor loadings (>0.40) are highlighted denoted*.

	3 Factor Model				4 Factor Model				
	Factor 1	**Factor 2**	**Factor 3**	**Comm.**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Comm.**
Better Past Disease Severity									
Nadir CD4%	-0.026	0.816*	0.075	0.68	-0.035	-0.708*	0.276	-0.208	0.69
Age at Nadir CD4%	0.460*	0.009	-0.267	0.36	0.429*	-0.121	-0.381	0.023	0.40
Log Peak VL	-0.563*	-0.172	-0.058	0.34	-0.546*	0.127	-0.101	0.112	0.34
Age at Peak VL	0.759*	-0.215	0.034	0.60	0.742*	0.145	-0.125	0.099	0.60
Age at HAART initiation	0.534*	-0.0003	-0.133	0.35	0.508*	0.071	-0.012	-0.252	0.38
Disease Severity at Entry									
Encephalopathy	-0.016	-0.655*	0.049	0.43	-0.002	0.745*	0.125	-0.102	0.53
Log RNA at Entry	-0.022	-0.042	-0.585*	0.34	-0.060	0.000	-0.491*	-0.245	0.34
CD4% at Entry	-0.051	0.236	0.648*	0.51	-0.011	-0.086	0.716*	0.071	0.57
On HAART at entry	-0.051	-0.186	0.553*	0.35	-0.008	-0.002	0.110	0.680*	0.51

*Principal factor method used for extraction; SMC used for prior communality estimates**;** oblique varimax rotation used;

** Values under "Factor 1", "Factor 2", etc. are from the Rotated Factor *Pattern* Matrix (standardized regression coefficients)

Table 11a. Rotated factor pattern matrix (standardized regression coefficients) and final communality estimates from factor analyses on psychosocial variables among PHIV youth (n=233). *High factor loadings (>0.40) are denoted*.*

	2 Factor Model				**3 Factor Model**				**4 Factor Model**				
	Factor 1	**Factor 2**	**Comm.**		**Factor 1**	**Factor 2**	**Factor 3**	**Comm.**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Comm.**
Home Environment													
Biological caregiver	0.338	-0.236	0.21		0.546*	-0.007	-0.052	0.30	-0.106	0.088	0.032	0.715*	0.51
Married/widowed	-0.527*	-0.084	0.26		-0.367	-0.224	-0.248	0.28	0.111	-0.106	0.595*	0.039	0.39
# supp. by household income	-0.381	0.073	0.16		-0.515*	0.018	-0.101	0.27	0.005	0.150	0.617*	-0.083	0.38
Low income	0.250	-0.398	0.27		0.530*	-0.002	-0.222	0.34	0.207	-0.074	-0.291	0.382	0.34
# of negative life events	0.282	-0.209	0.15		-0.004	0.483*	-0.137	0.26	0.153	0.476*	0.076	0.122	0.28
# of stressful life events	0.512*	0.102	0.25		0.021	0.556*	0.200	0.34	-0.168	0.587*	-0.023	0.097	0.37
Caregiver													
Caregiver WASI (< 85)	-0.164	-0.594*	0.33		-0.155	0.316	-0.607*	0.48	0.686*	0.177	0.062	-0.141	0.51
HS graduate	0.350	0.757*	0.57		-0.204	0.194	0.730*	0.59	-0.687*	0.297	-0.050	-0.222	0.59
Any psych problem	0.625*	-0.144	0.45		0.344	0.509*	0.053	0.47	0.034	0.428*	-0.371	0.164	0.47
# of drugs used in last 6 months	0.333	-0.360	0.30		0.368	0.248	-0.200	0.30	0.165	0.231	-0.087	0.404*	0.33
Any PCRI problem	0.220	-0.098	0.07		-0.009	0.344	-0.048	0.12	0.154	0.254	-0.189	-0.144	0.16

*Principal factor method used for extraction; SMC used for prior communality estimates**;** oblique varimax rotation used;

** Values under "Factor 1", "Factor 2", etc. are from the Rotated Factor *Pattern* Matrix (standardized regression coefficients)

Table 11b. Rotated factor pattern matrix (standardized regression coefficients) and final communality estimates from factor analyses on psychosocial variables among PHEU youth (n=151). High factor loadings (>0.40) are denoted *.

	2 Factor Model			**3 Factor Model**				**4 Factor Model**				
	Factor 1	Factor 2	Comm.	Factor 1	Factor 2	Factor 3	Comm.	Factor 1	Factor 2	Factor 3	Factor 4	Comm.
Home Environment												
Biological caregiver	-0.191	0.045	0.04	-0.002	-0.070	0.256	0.07	-0.090	-0.281	0.008	-0.110	0.10
Married/widowed	0.732*	0.234	0.53	0.145	0.691	-0.218	0.54	0.088	0.149	0.703*	0.205	0.58
# supp. by household income	0.323	-0.304	0.23	-0.370	0.303	-0.059	0.26	-0.122	0.663*	0.077	-0.286	0.49
Low income	-0.645*	0.121	0.46	0.104	-0.441	0.477*	0.48	-0.028	-0.572*	-0.309	-0.220	0.52
# of negative life events	-0.116	0.314	0.12	0.370	-0.135	-0.049	0.16	0.469*	0.113	-0.217	-0.075	0.28
# of stressful life events	0.039	0.576*	0.33	0.614*	0.032	-0.077	0.37	0.604*	-0.081	0.032	0.072	0.38
Caregiver												
Caregiver WASI (< 85)	0.032	0.256*	0.06	0.102	0.269	0.418*	0.25	0.073	-0.127	0.272	-0.363	0.25
HS graduate	0.282	-0.062	0.09	0.080	0.001	-0.571*	0.32	-0.050	-0.082	0.119	0.676*	0.46
Any psych problem	0.049	0.590*	0.34	0.587*	0.099	0.027	0.35	0.624*	0.001	0.054	-0.085	0.40

# of drugs used in last 6 months	-0.080	0.578*	0.36	0.519*	0.082	0.261	0.37	0.386	-0.407*	0.183	-0.076	0.40
Any PCRI problem	-0.413*	-0.091	0.17	0.054	-0.521*	-0.130	0.28	0.104	-0.027	-0.535*	0.098	0.31

*Principal factor method used for extraction; SMC used for prior communality estimates**;** oblique varimax rotation used;
** Values under “Factor 1”, “Factor 2”, etc. are from the Rotated Factor *Pattern* Matrix (standardized regression coefficients)

Table 11c. Rotated factor pattern matrix (standardized regression coefficients) and final communality estimates from factor analyses on psychosocial variables among all youth (n=384). *High factor loadings (>0.40) are denoted *.*

	2 Factor Model			3 Factor Model				4 Factor Model				
	Factor 1	**Factor 2**	**Comm.**	**Factor 1**	**Factor 2**	**Factor 3**	**Comm.**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Comm.**
Home Environment												
Biological caregiver	0.265	0.334	0.23	0.112	-0.344	0.233	0.24	0.056	-0.065	0.003	0.598*	0.39
Married/widowed	-0.400*	-0.073	0.18	-0.067	0.500*	0.064	0.27	-0.037	0.544*	0.021	-0.008	0.31
# supp. by household income	-0.384	-0.055	0.16	-0.006	0.544*	0.091	0.29	0.031	0.514*	0.103	-0.127	0.30
Low income	0.249	0.473	0.34	-0.018	-0.523*	0.329	0.42	-0.062	-0.448*	0.276	0.253	0.43
# of negative life events	0.354	0.135	0.17	0.488*	0.049	0.122	0.26	0.472*	-0.002	0.127	0.032	0.26
# of stressful life events	0.530*	-0.084	0.27	0.613*	0.027	-0.107	0.36	0.589*	0.009	-0.134	0.092	0.36
Caregiver												
Caregiver WASI (< 85)	-0.144	0.487*	0.22	0.119	0.184	0.524*	0.30	0.126	0.108	0.565*	-0.061	0.34
HS graduate	0.226	-0.618*	0.36	0.156	0.076	-0.599*	0.36	0.164	0.045	-0.577*	-0.112	0.37
Any psych problem	0.516*	0.155	0.33	0.514*	-0.152	0.087	0.36	0.480*	-0.161	0.061	0.138	0.36
# of drugs used in last 6 months	0.343	0.361	0.31	0.340*	-0.187	0.290	0.32	0.293	-0.019	0.130	0.440*	0.37
Any PCRI problem	0.276	-0.011	0.07	0.119	0.184	0.524*	0.08	0.210	-0.269	0.052	-0.190	0.15

*Principal factor method used for extraction; SMC used for prior communality estimates**;** oblique varimax rotation used; ** Values under "Factor 1", "Factor 2", etc. are from the Rotated Factor *Pattern* Matrix (standardized regression coefficients)

Table 12: Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-infected (PHIV) youth in PHACS AMP Study (n=231)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
Behavioral Functioning	BASC-C Inattention/Hyperactivity T-score	0.59 (0.052) <.0001	--
	BASC-C Internalizing T-score	0.89 (0.042) <.0001	--
	BASC-C Personal Adjustment T-score	-0.66 (0.049) <.0001	--
	BASC-C School Problems T-score	0.43 (0.061) <.0001	
	BASC-P Externalizing T-score	--	0.78 (0.042) <.0001
	BASC-P Internalizing T-score	--	0.65 (0.048) <.0001
	BASC-P Adaptability T-score	--	-0.83 (0.040) <.0001
Cognitive Functioning	WISC/WAIS Perceptual Reasoning	0.79 (0.033) <.0001	0.79 (0.033) <.0001
	WISC/WAIS Processing Speed	0.69 (0.041) <.0001	0.69 (0.041) <.0001
	WISC/WAIS verbal IQ	0.83 (0.030) <.0001	0.83 (0.030) <.0001
	WISC/WAIS working memory	0.72 (0.039) <.0001	0.71 (0.039) <.0001
Late Presenter	Age at HAART initiation (yrs)	0.51 (0.060) <.0001	0.52 (0.060) <.0001

Table 12: Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-infected (PHIV) youth in PHACS AMP Study (n=231)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
Better Past Disease Severity	Age at nadir CD4%	0.56 (0.057) <.0001	0.57 (0.057) <.0001
	Age at peak VL	0.85 (0.050) <.0001	0.84 (0.050) <.0001
	log peak VL	-0.50 (0.060) <.0001	-0.50 (0.060) <.0001
	CDC Class C	-0.81 (0.053) <.0001	-0.81 (0.052) <.0001
	HIV-related encephalopathy prior to entry	-0.64 (0.056) <.0001	-0.64 (0.055) <.0001
	Nadir CD4%	0.56 (0.059) <.0001	0.55 (0.059) <.0001
Disease Severity at Entry	On HAART with PI at study entry	0.09 (0.078) 0.26	0.09 (0.078) 0.24
	On HAART without PI at study entry	0.10 (0.078) 0.21	0.09 (0.078) 0.22
	On other ARV at study entry	-0.11 (0.078) 0.16	-0.11 (0.078) 0.15
	CD4% at entry	0.79 (0.089) <.0001	0.80 (0.090) <.0001
	Log Entry RNA VL	-0.56 (0.076) <.0001	-0.55 (0.076) <.0001
Home Environment	Caregiver is biological parent(s)	--	0.14 (0.080) 0.09

Table 12: Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-infected (PHIV) youth in PHACS AMP Study (n=231)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
	Caregiver is a single biological parent	0.26 (0.075) 0.0007	--
	Caregiver is both biological parents	-0.23 (0.076) 0.002	--
	Caregiver is a relative	0.18 (0.077) 0.02	--
	Annual household income < $20K	0.23 (0.076) 0.003	0.23 (0.078) 0.003
	Married or widowed	-0.75 (0.066) <.0001	-0.72 (0.073) <.0001
	Separated or divorced	0.56 (0.066) <.0001	0.57 (0.071) <.0001
	# of reported drugs used last 6 months	0.15 (0.078) 0.06	0.17 (0.079) 0.03
	# supported by household income	-0.41 (0.070) <.0001	-0.42 (0.072) <.0001
Caregiver Stress	PCRI: Any problem	0.25 (0.082) 0.002	0.28 (0.082) 0.0007
	Caregiver mental health problem (CDQ)	0.50 (0.077) <.0001	0.49 (0.078) <.0001
	# negative life events	0.47 (0.077) <.0001	0.46 (0.078) <.0001
	# Stressful life events	0.46 (0.077) <.0001	0.47 (0.078) <.0001
Caregiver Educational Opportunity	Caregiver WASI ≥ 85	0.98 (0.095) <.0001	0.96 (0.087) <.0001

Table 12: Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-infected (PHIV) youth in PHACS AMP Study (n=231)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
	Caregiver WASI not done	-0.52 (0.069) <.0001	-0.53 (0.068) <.0001
	Caregiver high school graduate	0.36 (0.067) <.0001	0.36 (0.067) <.0001

Table 13. Direct path coefficents from full SEM to PHIV+ youth in PHACs AMP study

Model	Latent Predictor	Cognitive Functioning Coefficient (SE) p-value	Behavioral Functioning Coefficient (SE) p-value
SEM Models in PHIV+ Youth, N=231			
Child-assessed Behavioral Functioning SRMR=0.0814 RMSEA=0.0800 BCF Index=0.6127 R^2=0.22	Cognitive Functioning	--	-0.20 (0.107) 0.06
	Late Presenter	-0.19 (0.084) 0.02*	0.11 (0.099) 0.28
	Better Past Disease Severity	0.40 (0.089) <.0001***	0.16 (0.122) 0.18
	Disease Severity at Entry	0.05 (0.098) 0.59	0.04 (0.112) 0.70
	Home Environment	0.05 (0.100) 0.64	-0.12 (0.116) 0.31
	Caregiver Stress	0.20 (0.127) 0.12	0.51 (0.147) 0.0006***
	Caregiver Educational Opportunity	0.33 (0.072) <.0001***	0.02 (0.084) 0.80
Caregiver-assessed Behavioral Functioning SRMR=0.818 RMSEA=0.0826 BCF Index=0.6412 R^2=0.22	Cognitive Functioning	--	-0.29 (0.109) 0.007**
	Late Presenter	-0.19 (0.084) 0.02*	0.03 (0.103) 0.78
	Better Past Disease Severity	0.39 (0.089) <.0001***	0.24 (0.125) 0.06
	Disease Severity at Entry	0.05 (0.098) 0.61	0.04 (0.114) 0.70
	Home Environment	0.06 (0.102) 0.59	-0.20 (0.123) 0.10
	Caregiver Stress	0.18 (0.128) 0.16	0.50 (0.153) 0.001**
	Caregiver Educational Opportunity	0.34 (0.072) <.0001***	0.15 (0.090) 0.09

Table 14. Direct, indirect and total effects on Behavioral Functioning from full structural equation models (SEMs) for perinatally HIV-infected (PHIV) youth in PHACS AMP Study

		Behavioral Functioning (F1) Coefficient (SE) p-value		
Model	**Latent Predictor**	**Direct**	**Indirect**	**Total**
SEM Models in PHIV+ Youth, N=231				
Youth-assessed Behavioral Functioning	*Late Presenter*	0.11 (0.099) 0.28	0.04 (0.027) 0.15	0.15 (0.095) 0.13
	Better Past Disease Severity	0.16 (0.122) 0.18	-0.08 (0.050) 0.11	0.08 (0.105) 0.43
	Disease Severity at Entry	0.04 (0.112) 0.70	-0.01 (0.021) 0.61	0.03 (0.111) 0.77
	Home Environment	-0.12 (0.116) 0.31	-0.01 (0.020) 0.63	-0.13 (0.115) 0.27
	Caregiver Stress	0.51 (0.147) 0.0006***	-0.04 (0.039) 0.31	0.47 (0.139) 0.0008***
	Caregiver Educational Opportunity	0.02 (0.084) 0.80	-0.07 (0.038) 0.08	-0.05 (0.076) 0.55
Caregiver-assessed Behavioral Functioning	*Late Presenter*	0.03 (0.103) 0.78	0.06 (0.033) 0.09	0.08 (0.098) 0.39
	Better Past Disease Severity	0.24 (0.125) 0.06	-0.12 (0.056) 0.04*	0.12 (0.107) 0.25
	Disease Severity at Entry	0.04 (0.114) 0.70	-0.01 (0.029) 0.62	0.03 (0.113) 0.79
	Home Environment	-0.20 (0.123) 0.10	-0.02 (0.029) 0.58	-0.22 (0.122) 0.08
	Caregiver Stress	0.50 (0.153) 0.001**	-0.05 (0.049) 0.28	0.44 (0.146) 0.002**
	Caregiver Educational Opportunity	0.15 (0.090) 0.09	-0.10 (0.043) 0.02*	0.05 (0.080) 0.50

Table 15. Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-exposed uninfected (PHEU) youth in PHACS AMP Study (n=151)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
Behavioral Functioning	BASC-C Inattention/Hyperactivity T-score	0.70 (0.055) <.0001	--
	BASC-C Internalizing T-score	0.81 (0.048) <.0001	--
	BASC-C Personal Adjustment T-score	-0.62 (0.062) <.0001	--
	BASC-C School Problems T-score	0.66 (0.058) <.0001	--
	BASC-P Externalizing T-score	--	0.83 (0.048) <.0001
	BASC-P Internalizing T-score	--	0.70 (0.056) <.0001
	BASC-P Adaptability T-score	--	-0.68 (0.057) <.0001
Cognitive Functioning	WISC/WAIS Perceptual Reasoning	0.79 (0.044) <.0001	0.80 (0.042) <.0001
	WISC/WAIS Processing Speed	0.48 (0.071) <.0001	0.48 (0.071) <.0001
	WISC/WAIS verbal IQ	0.80 (0.043) <.0001	0.79 (0.043) <.0001
	WISC/WAIS working memory	0.75 (0.047) <.0001	0.75 (0.046) <.0001

Table 15. Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-exposed uninfected (PHEU) youth in PHACS AMP Study (n=151)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
Caregiver Relationship	PCRI: Any problem	-0.58 (0.088) <.0001	-0.57 (0.088) <.0001
	Caregiver is biological parent	0.07 (0.103) 0.50	0.07 (0.102) 0.52
	Annual household income < $20K	-0.38 (0.094) <.0001	-0.38 (0.093) <.0001
	Married or widowed	0.58 (0.088) <.0001	0.58 (0.088) <.0001
	Separated or divorced	-0.54 (0.089) <.0001	-0.54 (0.089) <.0001
Caregiver Educational Opportunity	Caregiver WASI ≥ 85	0.90 (0.112) <.0001	0.90 (0.104) <.0001
	Caregiver WASI not done	-0.52 (0.089) <.0001	-0.51 (0.085) <.0001
	Caregiver high school graduate	0.24 (0.088) 0.006	0.24 (0.087) 0.006
	Annual household income < $20K	-0.26 (0.088) 0.003	-0.26 (0.087) 0.002
Family Emotional Stress	Caregiver mental health problem (CDQ)	0.48 (0.096) <.0001	0.47 (0.090) <.0001
	# of reported drugs used last 6 months	0.40 (0.098) <.0001	0.38 (0.094) <.0001
	# negative life events	0.48 (0.096) <.0001	0.51 (0.088) <.0001
	# Stressful life events	0.52 (0.095) <.0001	0.57 (0.087) <.0001

Table 15. Loadings of observed variables on latent variables from full structural equation models (SEMs) for Perinatally HIV-exposed uninfected (PHEU) youth in PHACS AMP Study (n=151)

		Loading (SE) p-value	
Latent Variable	**Observed Variable**	**Child-assessed Behavioral Functioning**	**Caregiver-assessed Behavioral Functioning**
	# supported by household income	-0.27 (0.102) 0.008	-0.19 (0.100) 0.06

Table 16. Direct path coefficents from full SEM to PHEU youth in PHACs AMP study

Model	Latent Predictor	Cognitive Functioning Coefficient (SE) p-value	Behavioral Functioning Coefficient (SE) p-value
SEM Models in PHEU Youth, N=151			
Youth-assessed Behavioral Functioning SRMR=0.0809 RMSEA=0.0634 BCF Index=0.8282 R^2=0.14	Cognitive Functioning	--	-0.13 (0.124) 0.29
	Family Emotional Stress	0.15 (0.120) 0.21	0.40 (0.124) 0.001
	Caregiver Relationship	0.32 (0.107) 0.003	0.11 (0.133) 0.42
	Caregiver Educational Opportunity	0.37 (0.100) 0.0002	-0.01 (0.116) 0.96
Caregiver-assessed Behavioral Functioning SRMR=0.0831 RMSEA=0.0751 BCF Index=0.7890 R^2=0.49	Cognitive Functioning	--	-0.54 (0.116) <.0001
	Family Emotional Stress	0.12 (0.118) 0.30	0.58 (0.111) <.0001
	Caregiver Relationship	0.32 (0.107) 0.003	0.21 (0.127) 0.10
	Caregiver Educational Opportunity	0.38 (0.098) <.0001	0.25 (0.114) 0.03

Table 17. Direct, indirect and total effects on Behavioral Functioning from full structural equation models (SEMs) for perinatally HIV-exposed but uninfected (PHEU) youth in PHACS AMP Study

		Behavioral Functioning (F1) Coefficient (SE) p-value		
Model	**Latent Predictor**	**Direct**	**Indirect**	**Total**
SEM Models in PHEU Youth, N=151				
Youth-assessed Behavioral Functioning	Caregiver Relationship	0.11 (0.133) 0.42	-0.04 (0.044) 0.34	0.06 (0.120) 0.59
	Caregiver Educational Opportunity	-0.01 (0.116) 0.96	-0.05 (0.048) 0.30	-0.05 (0.103) 0.60
	Family Emotional Stress	0.40 (0.124) 0.001**	-0.02 (0.027) 0.47	0.38 (0.121) 0.002**
Caregiver-assessed Behavioral Functioning	Caregiver Relationship	0.21 (0.127) 0.10	-0.17 (0.075) 0.02*	0.04 (0.118) 0.72
	Caregiver Educational Opportunity	0.25 (0.114) 0.03*	-0.20 (0.073) 0.005**	0.05 (0.101) 0.62
	Family Emotional Stress	0.58 (0.111) <.0001***	-0.07 (0.070) 0.35	0.52 (0.111) <.0001***

FIGURE 1: Exclusion of Participants

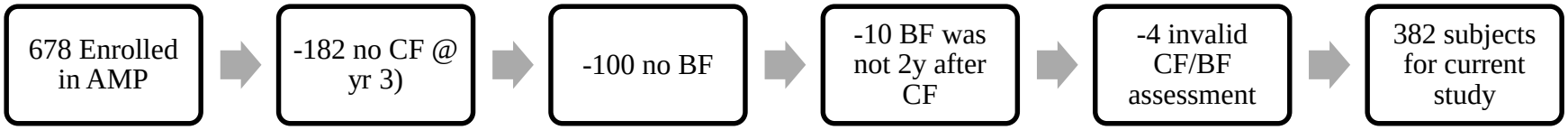


FIGURE 2: Proposed Conceptual Model: PHIV+

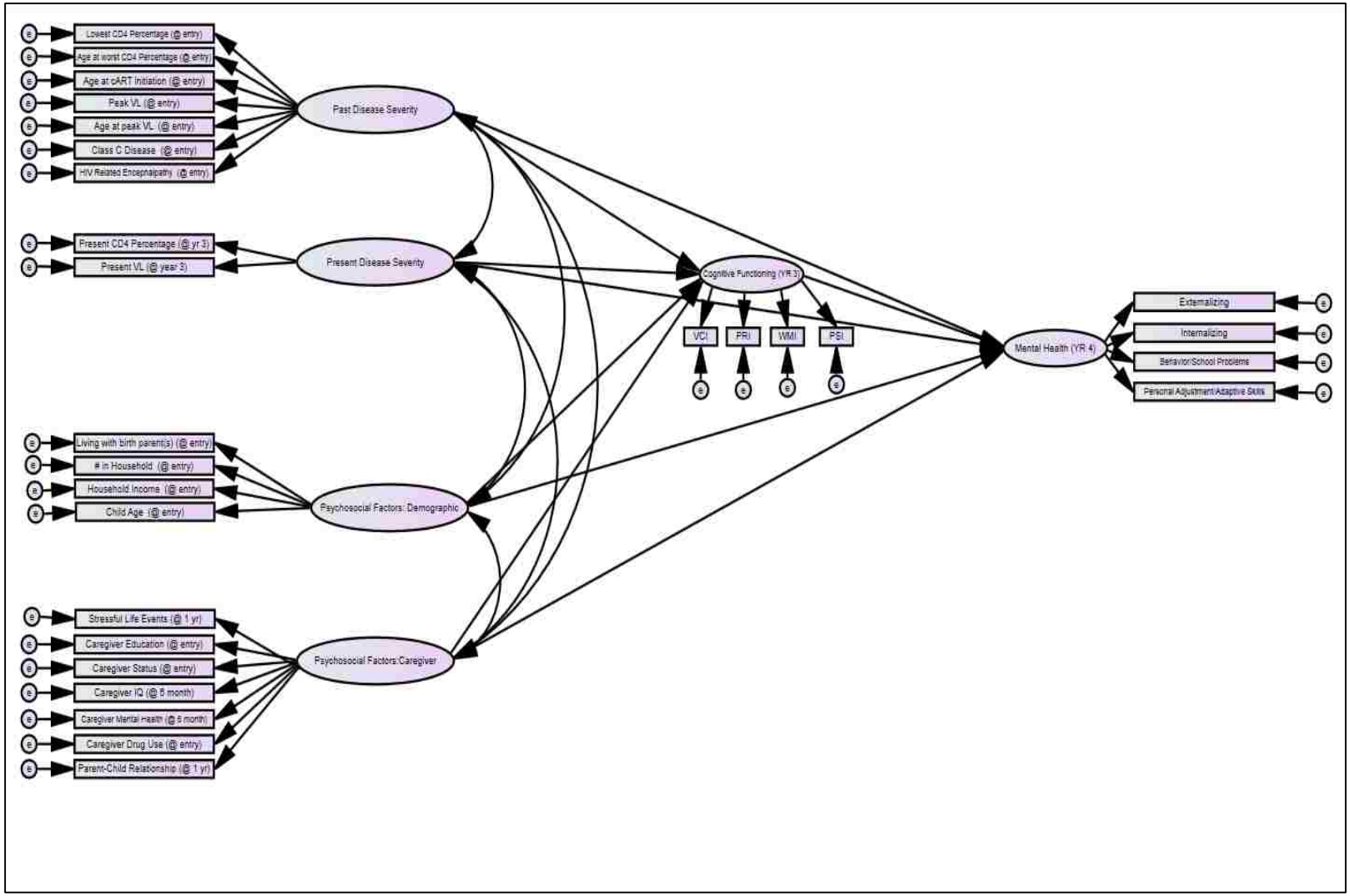


FIGURE 3: Proposed Conceptual Model: PHEU

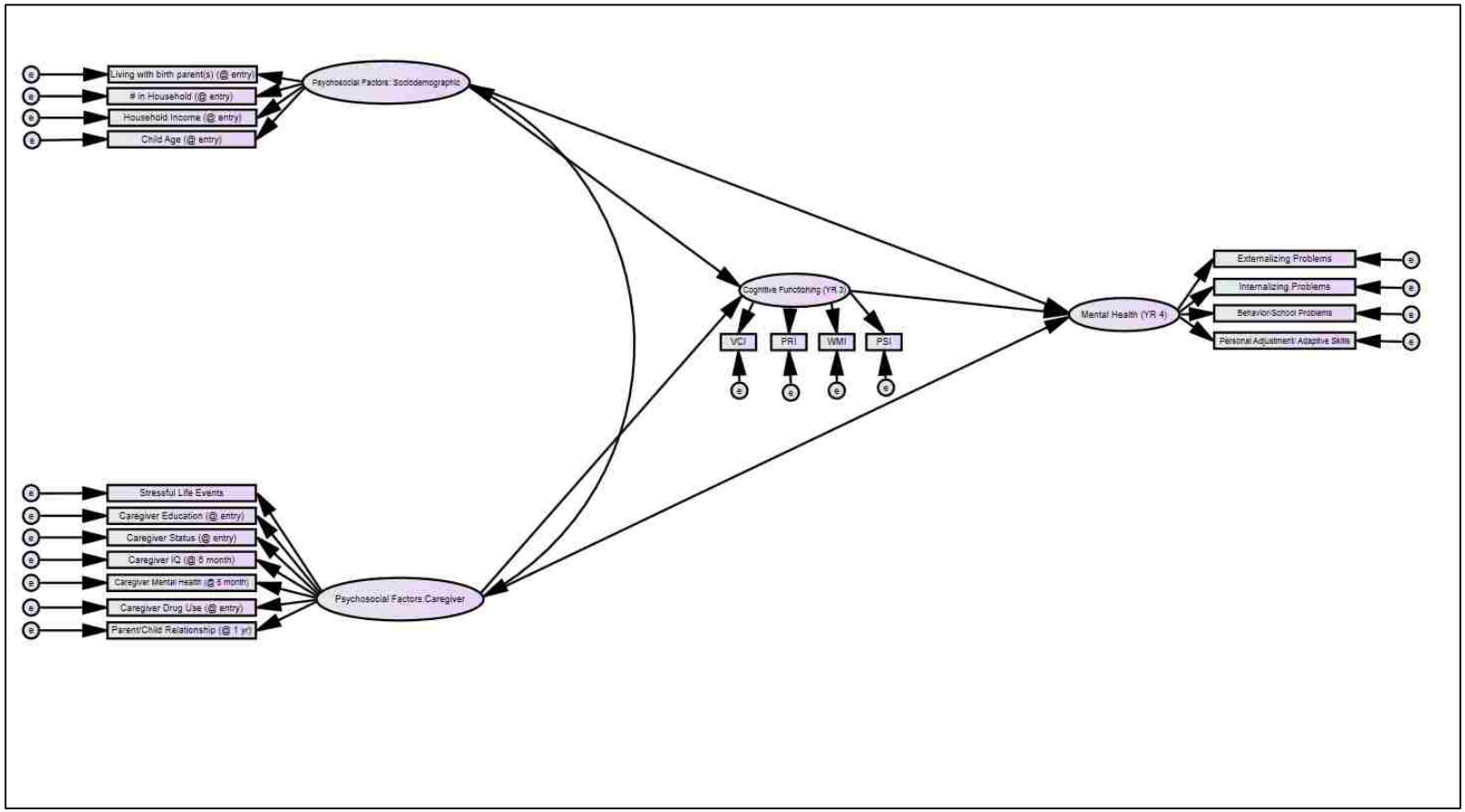


FIGURE 4: Finalized Conceptual Model: PHIV+ Youth Assessed BF Model

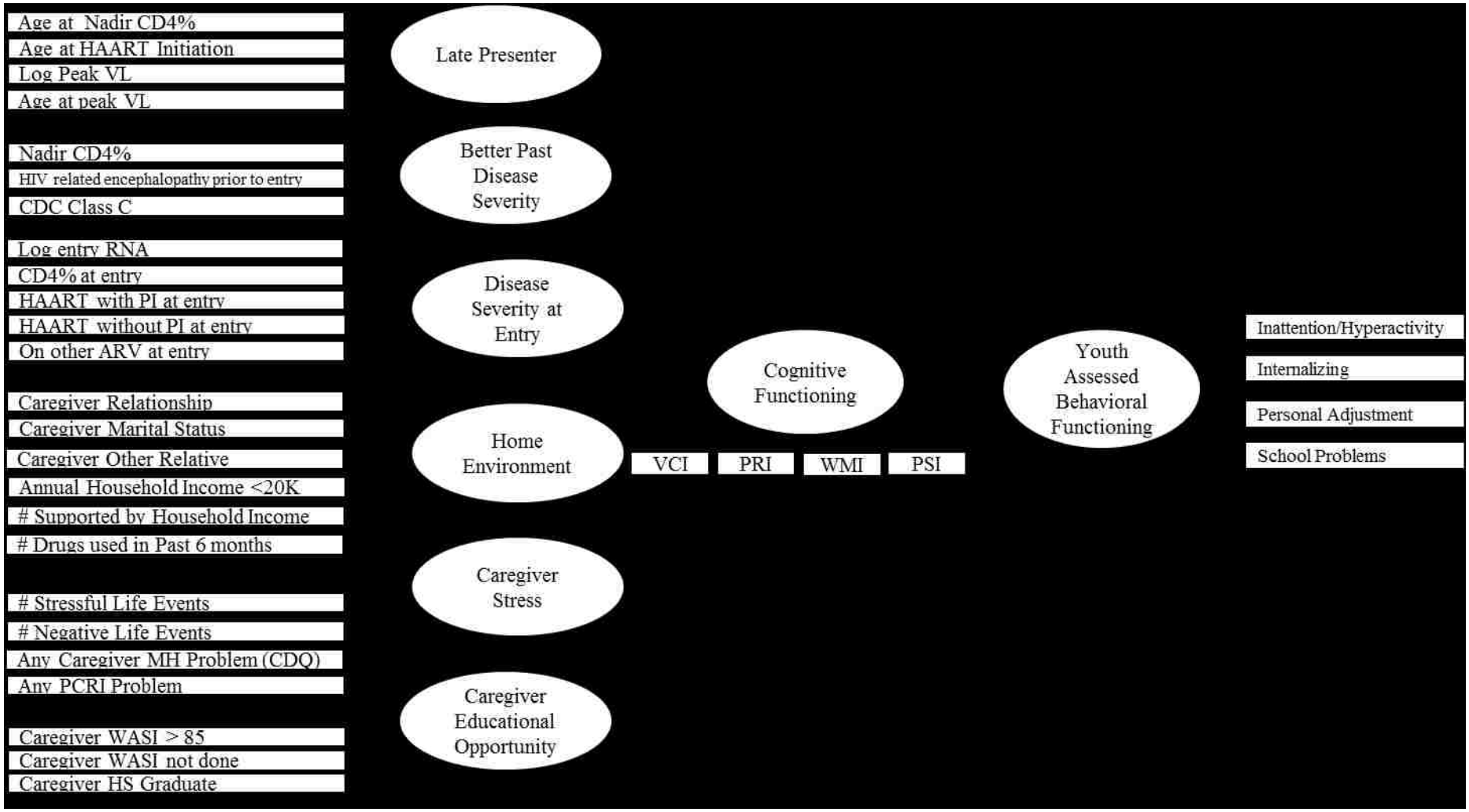


FIGURE 5: Finalized Conceptual Model: PHIV+ Caregiver Assessed BF Model

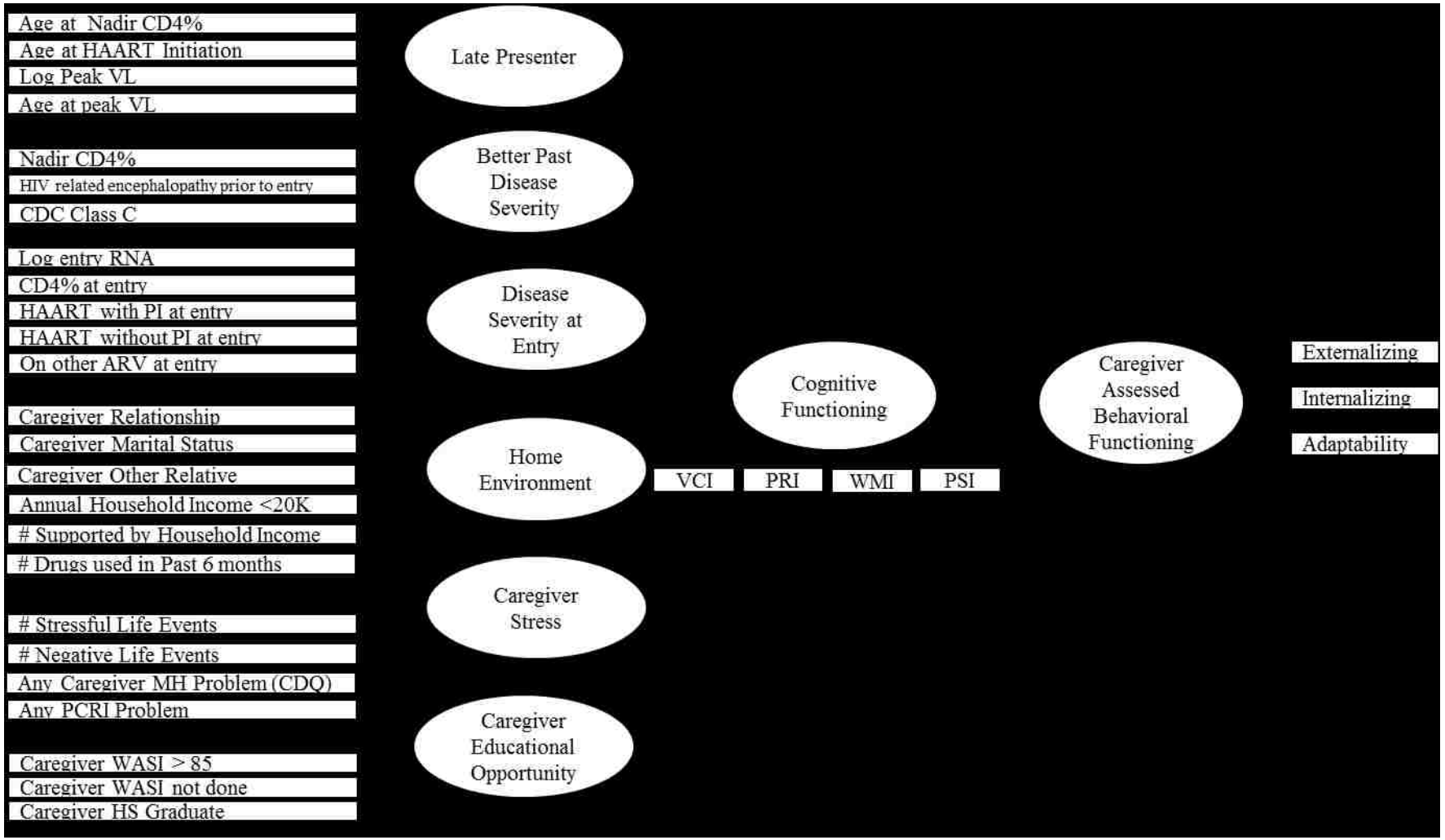


FIGURE 6: Finalized Conceptual Model PHEU Youth Assessed BF

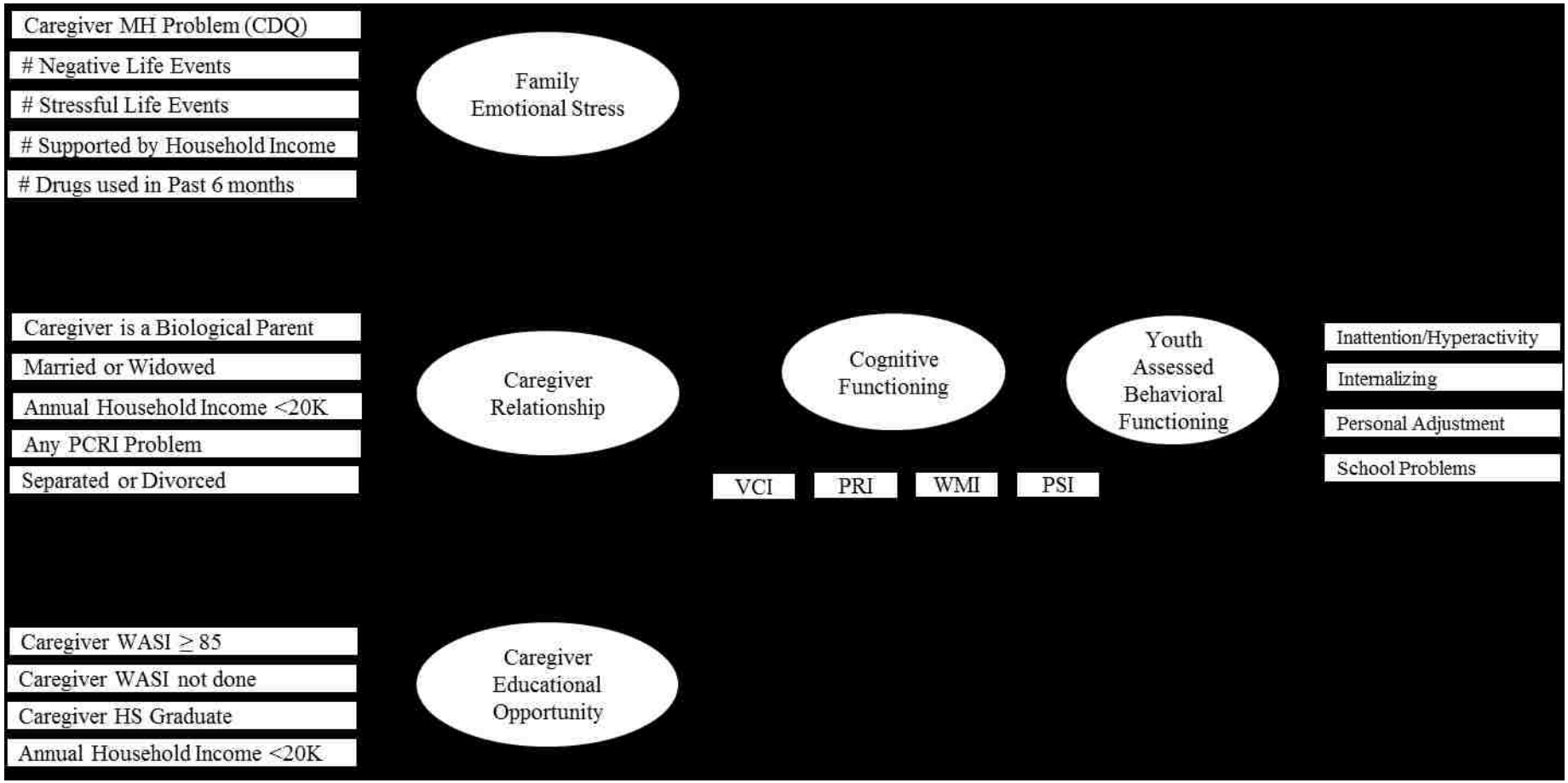
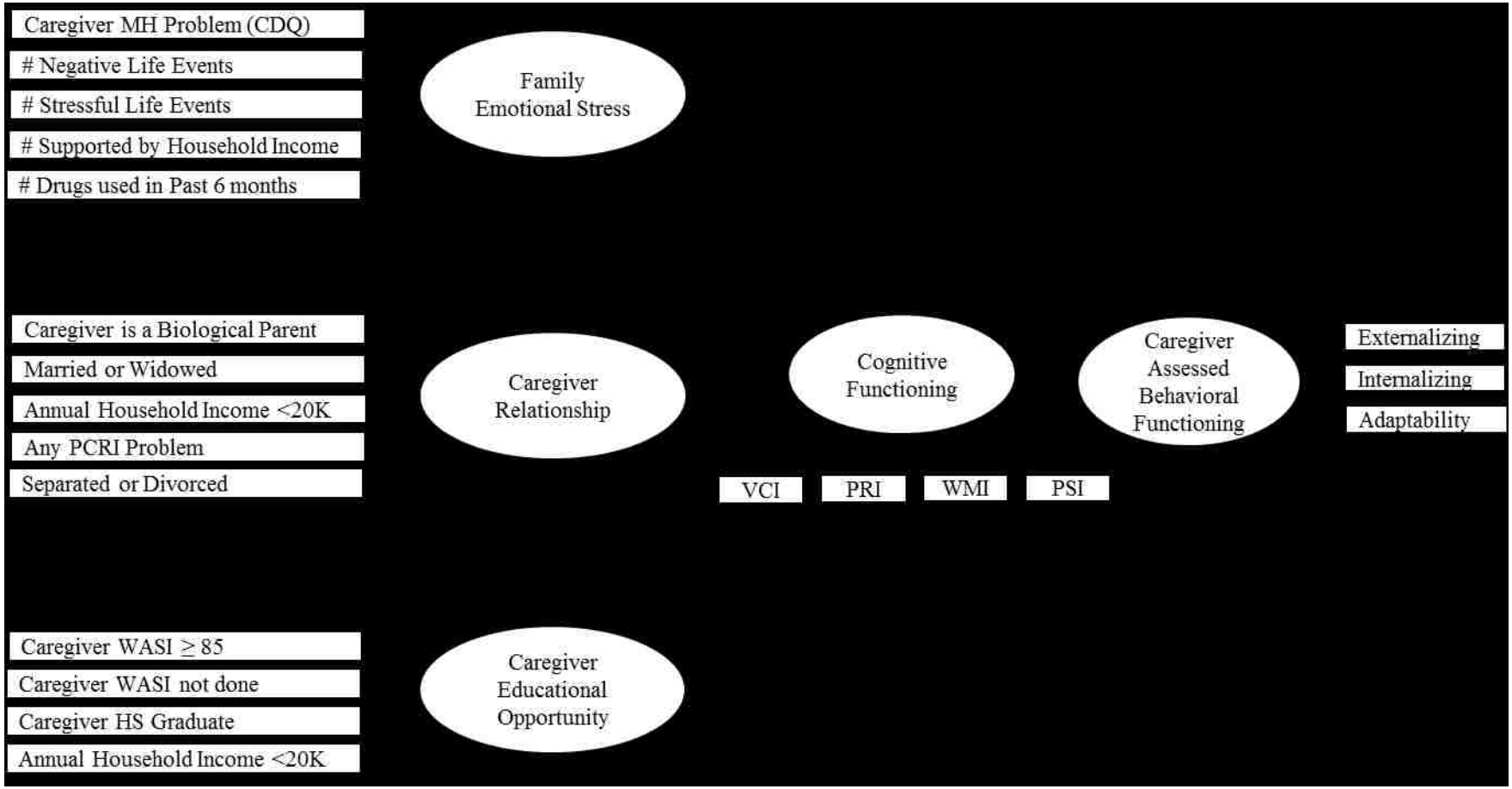


FIGURE 7: Finalized Model PHEU Caregiver Assessed BF



APPENDIX A: Review of Literature
A1: HIV and its Direct Effect on Cognitive Functioning

Author (s)	Publication Year	Population/(Country of Origin)	Measures	Major Findings
Chang, L., Speck, O., Miller, E. N., Braun, J., Jovicich, J., Koch, C., ... & Ernst, T.	2001	11 adult male patients and age-matched seronegative controls (USA)	*f*MRI technology and brain regions activated during sequential letter-number tasks were mapped on the brain surface	Task-dependent activation patterns may be due front-parietal brain injury observed in patients with HIV, resulting in decreased ability to modulate attention.
Stout, J. C., Salmon, D. P., Butters, N., Taylor, M., Peavy, G., Heindel, W. C., ... & HNRC Group.	1995	147 HIV+ males and age matched seronegative controls (USA)	Reading Span Test and the Digit Span subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987)	Deficits in working memory are apparent in HIV-infected individuals with more significant impairments than in individuals with less symptomatic HIV
Castelo, J. M. B., Sherman, S. J., Courtney, M. G., Melrose, R. J., & Stern, C. E	2006	14 HIV+ adult patients and age-matched seronegative controls (USA)	Changes in blood oxygenation level-dependent signal in HIV+ participants during an episodic encoding task and National Adult Reading Test (NART: Nelson & Willison, 1991)	HIV+ demonstrated significantly lower verbal IQ. HIV+ group differed in response accuracy on both repeated and novel picture tasks (p<.001). *f*MRI scans revealed that the HIV group demonstrated significantly reduced signal intensity changes in the right posterior hippocampus, right inferior frontal gyrus, and left lingual gyrus and more activity within lateral frontal and posterior parietal regions.
Sahakian, B. J., Elliott, R., Low, N., Mehta, M., Clark, R. T., & Pozniak, A. L.	1995	18 HIV+ males and 22 seronegative controls (UK)	Assessed the patients' visuospatial memory, attention and executive function using the CANTAB batter y and the National Adult Reading Test (NART: Nelson & Willison, 1991)	Parietal dysfunction in executive functioning and demonstrated that the cognitive deficits associated with HIV are present even before the onset of clinical symptoms

Olesen, P. J., Schendan, H. E., Amick, M. M., & Cronin-Golomb, A.	2007	14 HIV+ men and 12 seronegative age-matched controls (USA)	Examined differences on a mental rotation task, hierarchal pattern perception task and additional neuropsychological measures including Standardized Road-Map Test of Direction Sense (Money, 1976), The Hooper Visual Organization Test (Hooper, 1983), the Benton's Judgment of Line Orientation test (JLO; Benton, Varney, & Hamsher, 1978) and The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983).	HIV+ participants demonstrated significantly longer reaction time (p<.001) and more errors (p<.001). Significant differences were found on both the Roadmap Assessment (p<.01) and the JLO(p<.01).
Brackis-Cott, E., Kang, E., Dolezal, C., Abrams, E. J., & Mellins, C. A.	2009	43 PHIV+ children and adolescents perinatally HIV infected and perinatally exposed controls (USA)	Peabody Picture Vocabulary Test, Third Edition (PPVT-III; Dunn& Dunn, 1959) and the Reading Subtest of the Wide Range Achievement Test, Third Edition (WRAT-3; Wilkenson & Robertson, 2006). Caregivers were interviewed regarding demographic characteristics and current academic placement	HIV-positive participants scored lower than exposed controls on both the PPVT-III (M=83.8 vs. 87.6, $t=2.21$, p<.05) and on the WRAT-3 (M=88. 2 vs. 93.8, t=2.69. p<.01). HIV immunologic status remained significantly associated with PPVT-III and WRAT-3 standard scores

A2: HIV and its Indirect Effect on Cognitive Functioning

Author (s)	Publication Year	Population/(Country of Origin)	Measures	Major Findings
Hochhauser, C. J., Gaur, S., Marone, R., & Lewis, M.	2008	141 children treated at a large pediatric AIDS clinic from 1993 to 2000 (USA)	Indicators of environmental risk including caregiver demographics, stability of child's schedule, number of children in home and changes in home occupants and combined into one global risk score.	Significant positive correlation between CD4 and IQ (r=.25, p<.05) , with higher levels of immunocompetence predicting higher IQ scores. CD4 and IQ was significant in the high environmental risk group (r=.48, p<.01). The protein-gp120 may only be toxic to the fronto-parietal region under conditions of high stress but not low stress, thus moderating the relationship between HIV and IQ
Coscia, J. M., Christensen, B. K., Henry, R. R., Wallston, K., Radcliffe, J., & Rutstein, R.	2001	43 caregivers and their HIV+ children (USA)	Self-reports of home environment including play materials, parental involvement, variety of stimulation, and parental attitudes toward the provision of a cognitively stimulating environment were completed by caregivers. McCarthy Scales of Children's Abilities (MSCA; McCarthy, 1972), the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler, 1989) and the Wechsler Intelligence Scale for Children–3rd Edition (WISC-III; Wechsler, 1990). Participants ' medical charts were reviewed for information pertaining to disease severity factors.	SES was significantly correlated with home environment,r^2=.32, F (1, 41) = 18.9, p< .001, and with child IQ, ($r^{2=}$ .18, F (1, 41) =8.9,p< .05). Home environment was significantly associated with IQ after controlling for SES, (R^2=.13, F change= 7.3, p< .001). Health status and home environment accounted for 63% of the variance in IQ scores.

Dobrova-Krol, N. A., Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Juffer, F.	2010	64 Ukrainian uninfected and HIV-infected children reared in families and institutions (Ukraine/Netherlands)	Early Childhood HOME Inventory (Bradley et al.1993). Measures of disease severity and development included CD4 counts, diurnal salivary cortisol sampling, and measures of physical growth including height, weight and head circumference. Cognitive ability was measured using the Dutch SON-R (Tellegen& Laros, 1993), a test of nonverbal intelligence including visual-spatial abilities and abstract reasoning.	Both groups of HIV-infected children had lower supine length at birth than their uninfected counterparts, with a significant difference between uninfected family-reared children and HIV-infected institution-reared children (p< .01). Cognitive performance on the SON–R of the uninfected family-reared children was in the average range (M = 98.94, SD = 19.59). Performance of HIV-infected family-reared children was in the borderline deficiency range (M = 79.07, SD = 16.90). Performance of the uninfected institution-reared children (M = 69.73, SD = 21.28) and HIV-infected children (M = 64.00, SD = 8.59) fell in the range of mental deficiency. Significant overall effects were found for rearing environment, F(3, 44) = 10.23, p< .01, and for HIV status, F(3, 44) = 3.01, p <.05. Main effects for rearing environment and HIV status for both height and cognitive performance and a higher than the environment of HIV-infected family-reared children on the Physical Environment subscale, (F(1, 27) = 24.11, p< .01 (d =1.94), and the Variety subscale, F(1, 27) = 8.23, p< .01 (d =1.11), and significantly lower on the Acceptance subscale, F(1, 27) = 13.31, p < .01 (d = 2.84).

Green, J. E., Radu, V. Saveanu, R. V., &Bornstein, R. A.	2004	30 HIV-negative and 50 HIV+ men with and without a past history of alcohol abuse. (USA)	The test battery included the WAIS-R, Wisconsin Card Sorting Test Verbal Fluency Test, Verbal Concept Attainment Test Trail Making Test, visual span forward and backward from the Wechsler Memory Scale—Revised, Grooved Pegboard Test, Paced Auditory Serial Addition Test, and Selective Reminding Test. Depression and anxiety were measured using the Hamilton Rating Scale for Anxiety and the Hamilton Rating Scale for Depression	Significant main effect for history of alcohol abuse on the summary impairment rating ($F(1,76)=4.9$. $p<.04$). Significant effects for alcohol use history on measures of verbal reasoning ($F(1,76)=4.8$, $p<.05$), auditory information processing ($F(1,76)=5.92$, $p<.05$), reaction time for both the dominant ($F(1,76)=5.35$, $p<.05$) and non-dominant hand ($F(1,76)=8.82$, $p<.01$), and verbal IQ ($F(1,76)=8.21$, $p<.01$). Significant effects for HIV status were observed on measures of delayed recall ($F(1,76)= 4.6$, $p<.05$), total learning ($F(1,76)=5.64$, $p<.05$, and dexterity for both the dominant ($F(1,76)=5.70$, $p<.05$) and non-dominant hand ($F(1,76)=5.72$, $p<.05$).

A3: HIV and its Direct Effect on Behavior

Author (s)	Publication Year	Population/(Country of Origin)	Measures	Major Findings
Brouwers, P., Vlugt, H. V. D., Moss, H., Wolters, P., & Pizzo, P.	1995	58 symptomatic HIV+ children and 30 age matched controls (USA/Netherlands)	A computed tomography scan and a Q-sort measure of behavior	Significant correlations were found between overall behavioral severity rating and overall and component CT scan (r from .22 to .55, p<.05), suggesting that across both groups increases in behavioral severity was correlated with increased white matter abnormalities. Significant positive correlations were found for depressed/autistic-like behavior (r=.47and .45, p<.01). A positive correlation was found between increased nonsocial behavior and CT scan (r=.37, p<.05). The degree of ventricular enlargement was associated with ratings on the apathetic/withdrawn and self-stimulating behavior scales (r=.38 and .41, p<.05).
Misdrahi, D., Vila, G., Funk-Brentano, I., Tardieu, M., Blanche, S., & Mouren-Simeoni, M. C.	2004	17 PHIV+ children (France)	Psychiatric diagnosis using DSM-III criteria, CDC classes of encephalopathy	The most frequent diagnoses were major depression (47%) and ADHD (29%). However, only major depression was significantly associated with the results of the clinical neurological abnormalities found on the neuroimaging profiles (p<.01). The percentages of CD4 lymphocytes were close to 0 for more than 80% of children

presenting with psychiatric complications. Mis*d*rahi and colleagues concluded that psychiatric complications should be regarded as a factor of disease severity due to the finding of concomitant low percentage of CD4 lymphocytes.

A4: HIV and its Indirect Effect on Behavior

Author (s)	Publication Year	Population/(Country of Origin)	Measures	Major Findings
Mellins, C. A., Kang, E., Leu, C. S., Havens, J. F., & Chesney, M. A.	2003	307 PHIV infected and exposed children and mothers (USA)	Mothers completed measures of behaviors annually Data were also collected on prenatal drug exposure; child age, gender, and ethnicity; caregiver relationship to child; and birth complications.	Multivariate analyses comparing the HIV-infected children with perinatally-exposed but uninfected children from similar backgrounds failed to find an association between either HIV status or prenatal drug exposure and poor behavioral outcomes. The strongest correlates of increased behavioral symptoms were demographic characteristics including caregiver relationships and income level, suggesting that unlike previous studies which found the imperative role of HIV infection and prenatal drug exposure, other biological and environmental factors are were the only significant contributors toward later behavior problems (p<.05).
Mellins, C. A., Brackis-Cott, E., Dolezal, C., Leu, C. S., Valentin, C., & Meyer-Bahlburg, H. F.	2008	Participants included 220 HIV +/- early adolescents (10–14 years) and their mothers (USA) .	Individual interviews were conducted regarding youth depression, anxiety, externalizing and internalizing behavior problems using the Child Depression Inventory (CDI; Kovacs, 1992) and the trait scale of the State Trait Anxiety Inventory-Child version (STAI-C;	HIV status of mothers alone did not predict youth mental health. Older youth age was significantly related to depression (r= .17, p<.05). Youth victimization was related to depression (r= .30, p<.001), anxiety (r=.19, p<.01), internalizing disorders (r=.25, p<.001) and externalizing

Spielberger,1994).Contextual predictors included the mother's age, ethnicity, income, employment, and whether they lived with a partner. Mother's HIV Status and Youth Knowledge of Mother's HIV Status, Mother's Health. Maternal mental health was assessed using the Beck Depression Inventory (BDI: Beck, 1987) and the trait scale from the adult STAI (Spielberger, 1987). Maternal and child support was assessed through the use of parent and child interviews.

disorders (r= .28, p<.001). Household income was associated with depression (r=-.14, p<.05) anxiety r=-.18,p<.01 and internalizing disorders (r=.27, p<.05).Maternal physical health was associated with depression (r= .19, p<.01), anxiety (r=.20, p<.0), internalizing problems (r=.17, p<.05) and externalizing problems (r= .19, p<.01). Maternal depression was associated with depression, (r=.15, p<.05), anxiety (r=.24, p<.001) internalizing problems r=.36, p<.001), and externalizing problems (r=.27, p<.001). Similarly, maternal anxiety was associated with pediatric anxiety (r= .20, p<.01), internalizing problems (r= .29, p<.001) and externalizing problems (r=.23, p<.001). These results suggest a unique combination of individual, maternal demographic factors account for the primary behavioral manifestations of HIV.

A5: Simultaneously Examining Direct and Indirect Effects

Author (s)	Publication Year	Population/(Country of Origin)	Measures	Major Findings
Howland, L. C., Gortmaker, S. L., Mofenson, L. M., Spino, C., Gardner, J. D., Gorski, H., ... & Oleske, J	2000	618 HIV-1-infected children (USA)	Severity of immune suppression was indicated by the CDC HIV classification syndrome and negative life events were categorized as none, one, or greater than one.	More than one negative life event was associated with an increased risk of immune suppression (odds ratio [OR]: 2.76; 95% confidence interval [CI]: 1.44,5.31), controlling for baseline CD4 count, total life events, and other covariates.
Howland, L. C., Storm, D. S., Crawford, S. L., Ma, Y., Gortmaker, S. L., & Oleske, J. M.	2007	1,018 HIV+ children and youth 5 to 21 years of age enrolled in a longitudinal follow-up study (USA)	General health measures including measures of symptoms and perceived distress were included with the assessment of behavior problems using the Behavior Problems Index (Peterson & Zill, 1986).	Multivariate logistic regressions suggested that children with higher behavior problems scores were more likely to report a change in housing (p<.01) or a family member being sick (p<.01). Children with higher depressive symptom scores were more likely to report a family member being hospitalized (p<.01) or sick (p<.01). For each additional reported negative life event, there was an increase in the odds of behavior problems (p<.01; [OR] 1.26, 95% CI 1.13-1.41).
Nozyce, M. L., Lee, S. S., Wiznia, A., Nachman, S., Mofenson, L. M., Smith, M. E., ... & Pelton, S.	2006	274 HIV+ children (ages 2-17). (USA)	Behavioral Functioning was examined using the Connors' Parent Rating Scale (Connors, Sitarenios, Parker & Epstein, 1998). Cognitive functioning was assessed with the WISC-III. Children's neurological functioning was assessed through computer tomography and magnetic resonance imaging.	All children included in the sample had a mean FSIQ below the mean score of 100 in the general population (p<.001) Children with HIV demonstrated higher ratings of somatization, learning problems, hyperactivity, conduct and anxiety problems and scored less than established population means on verbal

				(M=85), performing *(M*=90) and FSIQ *(M*= 86). Children with a higher WISC-III IQ were significantly less likely to exhibit behaviors associated with ADHD. Hyperactivity was more frequent in children with a WISC-III score below the general population mean (*p*<.01).
Smith, R., Chernoff, M., Williams, P.L., Malee, K.M., Sirois, P.A., Kammerer, B…& Rutstein, R.	2012	PHIV+/C (n = 88), PHIV+/NoC (n = 270) and PHEU (n = 200) youth aged 7–16 years (USA)	Wechsler Intelligence Scale for Children, Fourth Edition and the Adaptive Behavior Assessment System, Second Edition	Overall mean scores on measures of cognitive and adaptive functioning were in the low average range for all 3 groups. Mean full-scale intelligence quotient scores were significantly lower for the PHIV+/C group than the PHIV+/NoC and PHEU groups (mean = 77.8 versus 83.4 and 83.3, respectively), whereas no significant differences were observed between the PHEU and PHIV+/NoC groups in any domain. Lower cognitive performance for the PHIV+/C group was primarily attributable to a prior diagnosis of encephalopathy.

APPENDIX B

Variable/Factor Index: Exogenous Variables

Latent Variable	Factor	Data Collected	Description	Variable Type
Disease Severity				
Better Past Disease Severity				
	1.Nadir CD4 Percentage	At Entry	Lowest CD4 cell percentage measures after the diagnosis of HIV infection	Analysis as both continuous and categorical variable Grouped: 0-14%, 15-24%,>=25%
	2. Age at Nadir CD4 Percentage	At Entry	Age when lowest CD4 count occurred	Age in Years
	3. Age at HAART initiation	At Entry	Age at initiation of first highly active antiretroviral therapy	Age in Years
	4. Peak VL (log 10)	At Entry	Highest recorded viral load	RNA Viral Load $Log_{10,}$<400
	5. Age at peak VL	At Entry	Chronological age at viral load	Age in years
	6. Class C Disease	At Entry	As defined by the Centers for Disease Control, Class C disease is described as AIDs-defining illness.	Yes/No
	7. Encephalopathy	At Entry	Diagnosis of encephalopathy abstracted from medical chart data and physician diagnosis.	Yes/No
Present Disease Severity (at time of BASC)				
	1. CD4% at Entry	At BASC	Present CD4 percentage	Analysis as both continuous variable and categorical (i.e.<15, 15-24, and >24)

	2. VL at Entry ($\log_{10}$)	At BASC	Present(RNA) VL	RNA VL analyzed as <=40, 40-1000, <1000
	3. ARV Regimen at Entry	At BASC	Antiretroviral therapy (HAART) and pharmacological intervention (PI) present at entry	Categorical variable: HAART with PI, HAART without PI, Non-HAART ARV, not on ARV.

Latent Variable	Factor	Data Collected	Description	Variable Type	Form ID
Psychosocial Factors					
Sociodemographic					
	1. Marital Status of Caregiver	At entry	Caregiver Marital status included current family structure including single parent, both parents and/or other relative/caregiver.	Categorical Variable	DMW0076 Q8
	2. Caregiver Relationship	At Entry	This variable includes information regarding current living situation including recorded adoption, foster care placement, living with birthparents or other family member (such as grandparents)	Categorical Variable	CHG0035
	3. Total Number Living in Household	At Entry	Current number of people living in household	Categorical Variable	DMW0076
	4. Total Number Supported by Household Income	At Entry	Number of family members living on accrued income	Categorical (1-2, 3-4, 5or more, none)	Calculated
	5. Low Income	At Entry	Categorical variable created if family is considered below the federal poverty line	Categorical variable < $20,000	DMW0076 Q11
	6. Negative Life Events	At 1 year visit	Number of negative life events experienced by the child including home trauma, abuse, frequent moves, family addiction and sudden death of a family member.	Continuous numeric assignment to number of negative life events	QLW0106

	7. Stressful Life Events	At 1 year visit	Number of stressful life events reported from the caregiver-reported QOL form	Continuous numeric assignment to number of stressful life events	QOL Form
Caregiver					
	1. Caregiver High School Graduate	At Entry	Caregiver completed high school education	Categorical (yes, no, unknown)	DMW0076 Q7
	3. Caregiver IQ	At 6 month visit	Information regarding parent's IQ as measured by a standardized assessment such as the WASI	FSIQ Score	
	4. Caregiver Mental Health Problem	At 6 month visit	Potential diagnosis of *any* mental health disorder as indicated on the Client Diagnostic Questionnaire (screener)	yes/no	QLW0105
	5. Number of Drugs used in Last 6 months	At entry	Information regarding parent's current and previous use of illicit substances as indicated on the CDQ	Categorical variable (# of yes responses, items 1-10)	QLW0105 (# of yes responses, items 1-10)
	6. Any PCRI problem	At 1 year visit	Relationship Quality Measured on PCRI	Continuous variable	NE4169(PH200)

* Table represents a-priori/pre-EFA variable organization

APPENDIX C:

Description of Behavioral Assessment Scale for Children-II

Clinical Categories: no concern, at-risk, clinical

Dx= potentially associated clinic diagnosis*

Index	Subtests	Description/Associated Diagnosis
Externalizing Problems		
	Hyperactivity	(Dx*: ADHD-H) Standing still, noisy, talking while others are talking
	Aggression	(Dx*: Conduct Disorder) Physical or emotional harm to others/property
	Conduct Problems	(Dx*: Conduct Disorder) Socially deviant/disruptive behavior
Internalizing Problems		
	Anxiety	(Dx* anxiety diagnosis) General fears, nervousness and worry
	Depression	(Dx* Depression) Loneliness, sadness, inability to enjoy life
	Somatization	(Dx*: Anxiety) Complains about minor physical problems
School Problems		

	Attention Problems	(Dx* ADHD) Presence/Absence of ADHD symptoms
	Learning Problems	(Dx*: : Learning Disabilities) Academic challenges
Behavior Problems		
	Atypicality	(Dx*: psychopathology) Unusual thoughts/perceptions
	Withdrawal	(Dx*: Autism/Mental Retardation) Avoids social contact
Adaptive Behavior		
	Adaptability	Temperament variables associated with achievement
	Social Skills	Interpersonal skills
	Leadership	Leadership Potential: Good community and school behavior
	Study Skills	(highly correlated with School Problems) School Adaptation
	Functional Communication	Express Ideas/Communicate, Activities of Daily Living

Appendix D (a-k).Covariance Matrices

Table Da-b. Mixed Correlation Matrix for HIV Disease Severity variables (PHIV group only, n=233). Correlations are either a Pearson correlation, polyserial correlation, or polychoric correlation, depending on variable type. Correlations with absolute value > 0.20 are highlighted in yellow.

Table Da	***Better Past Disease Severity***				
	nadircd4p	**agenadircd4p**	**logpeakVL**	**agepeakVL**	**agehaart**
nadircd4p	1.000	-0.019	-0.149	-0.204	-0.058
agenadircd4p	--	1.000	-0.237	0.460	0.326
logpeakVL	--	--	1.000	-0.443	-0.268
agepeakVL	--	--	--	1.000	0.456
agehaart	--	--	--	--	1.000
cdc_c	--	--	--	--	--
enceph	--	--	--	--	--
logrna_entry	--	--	--	--	--
cd4p_entry	--	--	--	--	--
HAART_noPI	--	--	--	--	--
HAART_PI	--	--	--	--	--
Other_ARV	--	--	--	--	--
No_ARV	--	--	--	--	--
HAART	--	--	--	--	--

Table Db	***Disease Severity at Entry***								
	cdc_c	**enceph**	**logrna_entry**	**cd4p_entry**	**HAART_noPI**	**HAART_PI**	**Other_ARV**	**No_ARV**	**HAART**
nadircd4p	-0.568	-0.576	-0.099	0.387	0.161	-0.207	0.191	0.040	-0.150
agenadircd4p	0.001	-0.090	0.256	-0.364	0.002	-0.101	0.009	0.267	-0.149
logpeakVL	0.258	0.125	0.010	0.050	-0.080	0.188	-0.122	-0.229	0.205

agepeakVL	0.128	0.113	0.161	-0.227	0.079	-0.076	-0.139	0.177	-0.029
agehaart	-0.043	-0.009	0.114	-0.147	0.096	-0.312	0.128	0.407	-0.331
cdc_c	1.000	0.996	0.178	-0.246	-0.078	0.114	-0.156	0.015	0.097
enceph	--	1.000	0.018	-0.014	-0.316	0.148	-0.117	0.218	-0.060
logrna_entry	--	--	1.000	-0.438	-0.172	-0.135	0.062	0.548	-0.340
cd4p_entry	--	--	--	1.000	0.105	0.100	-0.182	-0.327	0.285
HAART_noPI	--	--	--	--	1.000	-0.999	-0.969	-0.999	0.965
HAART_PI	--	--	--	--	--	1.000	-0.994	-0.989	0.999
Other_ARV	--	--	--	--	--	--	1.000	-0.917	-0.999
No_ARV	--	--	--	--	--	--	--	1.000	-0.999
HAART	--	--	--	--	--	--	--	--	1.000

Table Dc-e. Mixed Correlation Matrix for Psychosocial variables (PHIV+ group only, n=233). Correlations are either a Pearson correlation, polyserial correlation, or polychoric correlation, depending on variable type. Correlations with absolute value > 0.20 are highlighted in yellow.

Table Dc	**Psychosocial Factors: *Home Environment***					
	cgvrel_singleparent	**cgvrel_both**	**cgvrel_relative**	**cgvrel_nonrelative**	**cgvrel_biological**	**maritst_marriedwid**
cgvrel_singleparent	1.000	-0.976	-0.986	-0.992	0.999	-0.291
cgvrel_both	--	1.000	-0.971	-0.978	0.999	0.396
cgvrel_relative	--	--	1.000	-0.988	-0.997	-0.224
cgvrel_nonrelative	--	--	--	1.000	-0.997	0.251
cgvrel_biological	--	--	--	--	1.000	-0.047
maritst_marriedwid	--	--	--	--	--	1.000

Table Dd	**Psychosocial Factors: *Home Environment***							**Psychosocial Factors: Caregiver**
	maritst_sepdiv	**maritst_single**	**tothousecat**	**tothouseinccat**	**lowincome**	**neglecat**	**slecat**	**cgwasicat_notdone**
cgvrel_singleparent	0.110	0.248	-0.093	-0.152	0.405	0.079	0.138	0.037
cgvrel_both	-0.290	-0.297	-0.017	0.108	-0.070	0.167	0.024	0.045
cgvrel_relative	0.223	0.091	-0.203	-0.274	0.114	0.116	0.091	-0.029
cgvrel_nonrelative	-0.182	-0.169	0.282	0.338	-0.461	-0.288	-0.230	-0.040
cgvrel_biological	-0.035	0.076	-0.091	-0.078	0.324	0.163	0.135	0.058
maritst_marriedwid	-0.997	-0.999	0.293	0.419	-0.172	-0.101	-0.137	-0.106
maritst_sepdiv	1.000	-0.979	-0.383	-0.347	0.126	0.091	0.076	-0.015
maritst_single	--	1.000	-0.073	-0.234	0.109	0.051	0.103	0.128

Table Dd	Psychosocial Factors: *Home Environment*							Psychosocial Factors: Caregiver
	maritst_sepdiv	maritst_single	tothousecat	tothouseinccat	lowincome	neglecccat	slecat	cgwasicat_notdone
tothousecat	--	--	1.000	0.830	-0.169	-0.083	0.067	-0.063
tothouseinccat	--	--	--	1.000	-0.293	0.028	-0.022	-0.005
lowincome	--	--	--	--	1.000	0.103	0.143	0.263
neglecccat	--	--	--	--	--	1.000	0.359	-0.097
slecat	--	--	--	--	--	--	1.000	-0.181
cgwasicat_notdone	--	--	--	--	--	--	--	1.000

Table De	Psychosocial Factors: Caregiver					
	cgwasicat_lt85	cgwasicat_85p	hsgrad	anypsych	ndrugcat	anypcriprob
cgvrel_singleparent	-0.103	0.061	-0.073	0.301	0.362	0.053
cgvrel_both	-0.115	0.063	-0.129	-0.006	0.159	-0.238
cgvrel_relative	0.396	-0.369	-0.088	0.066	-0.174	0.300
cgvrel_nonrelative	-0.215	0.219	0.243	-0.388	-0.347	-0.187
cgvrel_biological	-0.153	0.089	-0.139	0.272	0.420	-0.081
maritst_marriedwid	0.026	0.065	-0.152	-0.383	-0.122	-0.107
maritst_sepdiv	-0.014	0.025	0.239	0.253	0.043	0.090
maritst_single	-0.019	-0.090	0.024	0.246	0.107	0.059
tothousecat	0.070	-0.011	-0.095	-0.181	-0.215	-0.047
tothouseinccat	0.072	-0.061	0.066	-0.239	-0.191	-0.111
lowincome	0.095	-0.302	-0.347	0.247	0.158	0.056
neglecccat	0.220	-0.125	-0.079	0.241	0.195	0.146
slecat	0.012	0.135	0.270	0.329	0.147	0.149
cgwasicat_notdone	-0.988	-0.997	-0.176	-0.273	-0.532	-0.120
cgwasicat_lt85	1.000	-0.999	-0.460	0.166	0.219	0.140
cgwasicat_85p	--	1.000	0.619	0.057	0.187	-0.030

Table De	Psychosocial Factors: Caregiver					
	cgwasicat_lt85	cgwasicat_85p	hsgrad	anypsych	ndrugcat	anypcriprob
hsgrad	--	--	1.000	0.062	-0.155	-0.026
anypsych	--	--	--	1.000	0.334	0.269
ndrugcat	--	--	--	--	1.000	0.113
anypcriprob	--	--	--	--	--	1.000

Table Df-h. Mixed Correlation Matrix for Psychosocial variables (PHEU group only, n=151). Correlations are either a Pearson correlation, polyserial correlation, or polychoric correlation, depending on variable type. Correlations with absolute value > 0.20 are highlighted in yellow.

Table Df	**Psychosocial Factors: *Home Environment***					
	cgvrel_singleparent	**cgvrel_both**	**cgvrel_relative**	**cgvrel_nonrelative**	**cgvrel_biological**	**maritst_marriedwid**
cgvrel_singleparent	1.000	-0.998	-0.997	-0.999	0.999	-0.473
cgvrel_both	--	1.000	-0.967	-0.967	0.975	0.492
cgvrel_relative	--	--	1.000	-0.986	-0.999	0.030
cgvrel_nonrelative	--	--	--	1.000	-0.999	0.161
cgvrel_biological	--	--	--	--	1.000	-0.129
maritst_marriedwid	--	--	--	--	--	1.000

Table Dg	**Psychosocial Factors: *Home Environment***							**Psychosocial Factors: Caregiver**
	maritst_sepdiv	**maritst_single**	**tothousecat**	**tothouseinccat**	**lowincome**	**neglecccat**	**slecat**	**cgwasicat_notdone**
cgvrel_singleparent	-0.076	0.502	-0.039	-0.175	0.120	-0.007	0.025	0.047
cgvrel_both	-0.380	-0.301	0.031	0.159	-0.018	-0.052	-0.039	-0.094
cgvrel_relative	0.367	-0.334	-0.264	-0.173	0.150	0.092	-0.011	0.458
cgvrel_nonrelative	0.246	-0.349	0.240	0.272	-0.310	0.021	0.019	-0.489
cgvrel_biological	-0.386	0.417	-0.021	-0.079	0.145	-0.066	-0.007	-0.032

Table Dg	**Psychosocial Factors: *Home Environment***							**Psychosocial Factors: Caregiver**
	maritst_sepdiv	**maritst_single**	**tothousecat**	**tothouseinccat**	**lowincome**	**neglecccat**	**slecat**	**cgwasicat_notdone**
maritst_marrieddwid	-0.985	-0.999	0.079	0.158	-0.380	-0.158	0.084	-0.140
maritst_sepdiv	1.000	-0.992	-0.072	-0.125	0.347	0.254	0.134	0.045
maritst_single	--	1.000	-0.026	-0.069	0.172	-0.016	-0.168	0.101
tothousecat	--	--	1.000	0.841	-0.418	-0.079	-0.136	-0.101
tothouseinccat	--	--	--	1.000	-0.434	-0.014	-0.184	-0.070
lowincome	--	--	--	--	1.000	0.065	0.098	0.107
neglecccat	--	--	--	--	--	1.000	0.392	-0.195
slecat	--	--	--	--	--	--	1.000	0.015
cgwasicat_notdone	--	--	--	--	--	--	--	1.000

Table Dh	**Psychosocial Factors: Caregiver**					
	cgwasicat_lt85	**cgwasicat_85p**	**hsgrad**	**anypsych**	**ndrugcat**	**anypcriprob**
cgvrel_singleparent	-0.310	0.280	0.019	-0.021	0.036	0.099
cgvrel_both	0.391	-0.356	-0.108	-0.049	0.191	-0.161
cgvrel_relative	-0.084	-0.488	0.006	0.148	-0.135	0.062
cgvrel_nonrelative	0.073	0.268	0.132	-0.007	-0.288	-0.008
cgvrel_biological	-0.005	0.034	-0.092	-0.080	0.268	-0.029

Table Dh	Psychosocial Factors: Caregiver					
	cgwasicat_lt85	cgwasicat_85p	hsgrad	anypsych	ndrugcat	anypcriprob
maritst_marriedwid	0.183	-0.062	0.311	0.063	0.050	-0.401
maritst_sepdiv	-0.033	-0.009	0.326	0.048	-0.030	0.512
maritst_single	-0.155	0.064	-0.463	-0.091	-0.028	0.034
tothousecat	0.077	0.015	-0.000	-0.177	-0.333	-0.201
tothouseinccat	0.066	0.000	-0.171	-0.127	-0.311	0.005
lowincome	0.241	-0.324	-0.226	-0.023	0.163	0.211
negleccat	-0.006	0.187	-0.109	0.237	0.092	0.120
slecat	0.018	-0.032	0.017	0.382	0.269	-0.006
cgwasicat_notdone	-0.994	-0.993	-0.194	-0.288	-0.607	-0.047
cgwasicat_lt85	1.000	-0.999	-0.190	0.109	0.223	-0.088
cgwasicat_85p	--	1.000	0.388	0.144	0.295	0.131
hsgrad	--	--	1.000	-0.158	-0.074	0.126
anypsych	--	--	--	1.000	0.374	0.112
ndrugcat	--	--	--	--	1.000	0.017
anypcriprob	--	--	--	--	--	1.000

Table Di-k. Mixed Correlation Matrix for Psychosocial variables (Overall, n=384). Correlations are either a Pearson correlation, polyserial correlation, or polychoric correlation, depending on variable type. Correlations with absolute value > 0.20 are highlighted in yellow.

Table Di	**Psychosocial Factors: *Home Environment***					
	cgvrel_singlepar ent	**cgvrel_bo th**	**cgvrel_relat ive**	**cgvrel_nonrela tive**	**cgvrel_biologi cal**	**maritst_married wid**
cgvrel_singlepare nt	1.000	-0.988	-0.989	-0.994	0.999	-0.412
cgvrel_both	--	1.000	-0.969	-0.974	0.989	0.396
cgvrel_relative	--	--	1.000	-0.975	-0.996	-0.095
cgvrel_nonrelativ e	--	--	--	1.000	-0.999	0.279
cgvrel_biological	--	--	--	--	1.000	-0.159
maritst_married wid	--	--	--	--	--	1.000

TableDj	**Psychosocial Factors: *Home Environment***							**Psychosocial Factors: Caregiver**
	maritst_sep div	**maritst_sin gle**	**tothousec at**	**tothouseinc cat**	**lowinco me**	**neglecc at**	**sleca t**	**cgwasicat_notd one**
cgvrel_singlepar ent	0.041	0.401	-0.085	-0.151	0.362	0.096	0.109	0.053
cgvrel_both	-0.326	-0.258	-0.004	0.130	-0.001	0.084	0.004	-0.014
cgvrel_relative	0.242	-0.076	-0.192	-0.238	0.031	0.056	0.041	0.094
cgvrel_nonrelati ve	-0.060	-0.268	0.276	0.305	-0.472	-0.241	-0.176	-0.143
cgvrel_biologica l	-0.134	0.257	-0.087	-0.069	0.357	0.150	0.111	0.044
maritst_marrie dwid	-0.992	-0.999	0.222	0.318	-0.293	-0.154	-0.066	-0.125
maritst_sepdiv	1.000	-0.984	-0.261	-0.259	0.205	0.161	0.101	0.012

TableDj	**Psychosocial Factors: *Home Environment***							**Psychosocial Factors: Caregiver**
	maritst_sepdiv	**maritst_single**	**tothousecat**	**tothouseinccat**	**lowincome**	**neglecccat**	**slecat**	**cgwasicat_notdone**
maritst_single	--	1.000	-0.063	-0.163	0.181	0.055	0.002	0.122
tothousecat	--	--	1.000	0.834	-0.259	-0.089	-0.013	-0.080
tothouseinccat	--	--	--	1.000	-0.327	0.009	-0.086	-0.031
lowincome	--	--	--	--	1.000	0.128	0.139	0.209
negleccat	--	--	--	--	--	1.000	0.376	-0.130
slecat	--	--	--	--	--	--	1.000	-0.097
cgwasicat_notdone	--	--	--	--	--	--	--	1.000

Table Dk	Psychosocial Factors: Caregiver					
	cgwasicat_lt85	cgwasicat_85p	hsgrad	anypsych	ndrugcat	anypcriprob
cgvrel_singleparent	-0.160	0.104	-0.065	0.201	0.257	0.080
cgvrel_both	0.147	-0.133	-0.132	-0.004	0.193	-0.193
cgvrel_relative	0.249	-0.342	-0.031	0.040	-0.198	0.221
cgvrel_nonrelative	-0.150	0.249	0.232	-0.306	-0.356	-0.143
cgvrel_biological	-0.061	0.020	-0.154	0.202	0.395	-0.042
maritst_marriedwid	0.072	0.039	0.054	-0.227	-0.081	-0.222
maritst_sepdiv	-0.020	0.008	0.274	0.170	0.015	0.270
maritst_single	-0.064	-0.046	-0.214	0.123	0.075	0.054
tothousecat	0.069	0.004	-0.050	-0.185	-0.266	-0.107
tothouseinccat	0.069	-0.038	-0.030	-0.191	-0.240	-0.066
lowincome	0.162	-0.324	-0.316	0.173	0.189	0.118
negleccat	0.136	-0.019	-0.108	0.257	0.169	0.138
slecat	0.018	0.065	0.153	0.355	0.203	0.088
cgwasicat_notdone	-0.990	-0.995	-0.186	-0.271	-0.556	-0.089
cgwasicat_lt85	1.000	-0.999	-0.353	0.149	0.228	0.049
cgwasicat_85p	--	1.000	0.530	0.077	0.215	0.029
hsgrad	--	--	1.000	-0.054	-0.134	0.035
anypsych	--	--	--	1.000	0.366	0.205
ndrugcat	--	--	--	--	1.000	0.078
anypcriprob	--	--	--	--	--	1.000

APPENDIX E: Sample Press Release

Since the AIDs crisis of the 1980s, scientists have believed that IQ and mental health problems historically associated with an HIV diagnosis were connected to the disease itself. Today, HIV infection has shifted from a terminal disease to a chronic illness due to advances in medical treatment. However, for minority populations who face additional economic, social, and financial barriers, HIV continues to be a crisis, with youth13–29 accounting for 39% of all new infections[1]. Youth infected with or exposed to HIV through maternal transmission continue to remain at an increased risk for both mental health problems, including depression, anxiety, and attention deficit hyperactivity disorder (ADHD); and IQ challenges including attention and concentration problems and language development, all which may negatively affect school success and long-term life outcomes.

Using a large multi-center database from the National Institute of Health, Dr. Hermetet-Lindsay compared youth patients' HIV disease information to general family information including stressful life events, family makeup, household income, parent's drug use, parent's mental health, education level, parent IQ and negative life events in order to investigate the interaction of these variables across time on IQ and mental health. Dr. Hermetet-Lindsay found that household income, drug use and higher levels of stress experienced by both the family and the parent were associated with an increase in mental health problems. The parent's IQ and high school graduation status in combination the timing of the youth's worst HIV symptoms were associated with deficits in IQ, suggesting that youth who experienced their worst HIV symptoms *later* in their childhood had more IQ problems.

These findings suggest that mental health and IQ problems historically associated HIV may not be due to the disease itself, but due to the multiple challenges experienced by communities in our country most vulnerable to infection, often low-income minority

neighborhoods within large urban centers that experience poverty, poor educational opportunity, multiple life stressors and exposure to drugs on their streets and in their families. This suggests that many of the risk factors identified in this study can be addressed within the walls of the youth's school and supported through government policy and initiatives in order to stop the HIV crisis in urban communities. School-level interventions such as adequate, comprehensive and individualized drug and sexual education programming may prevent continued risk for HIV infection in low-income urban communities.

An increased emphasis on high school graduation and retention may be particularly important for teen parents, as this study found that graduating is not only associated with household income, but also connected to their unborn child's IQ. For the medical field, the results of this study highlight the need for an increased focus on HIV disease monitoring throughout childhood long after maternal transmission in order to curtail the long-term cognitive effects of the disease. In addition, these findings support the important role of pediatric psychologists who may ameliorate sources of stress for families impacted by HIV by connecting them to social programming and providing mental health counseling for parents and children.

Hermetet-Lindsay's findings suggest that community, medical and national policy efforts have the opportunity to both *prevent* continued HIV transmission and *intervene* on the cognitive and mental health aspects of the disease as they are not solely related to HIV itself, but also due to the continued exposure of stress, family discordance, drug abuse and school drop-out that plague low income communities in our country. Together, local and national efforts can work collaboratively so that HIV is no longer crisis for *any* community in this nation.