PERINATAL HIV EXPOSURE AND INFECTION AND ITS ASSOCIATION WITH CAREGIVER DEPRESSION SYMPTOMS AND CHILD EXECUTIVE FUNCTION

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ABSTRACT

Survival is possible for children perinatally exposed to or infected by Human Immunodeficiency Virus (HIV) in the post-combined antiretroviral therapy era, but the long-term effects of HIV exposure on children and their caregivers are still being explored. Identifying factors affecting children's ability to thrive within an HIV context has great public health significance, particularly within a sub-Saharan context where the burden of HIV is felt disproportionately by women and children. Additionally, caregiver mental health is an important focus given its bidirectional relationship with child behavior. Previous studies on these topics have not included a full complement of HIV exposure or infection groups, considered how caregivers' mental health may depend on child serostatus, and or are investigated in HIV endemic areas.

The three aims presented in this dissertation will explore how perinatal HIV infection and exposure can affect caregivers and school-aged children. In Aim one, we compare depressive symptoms among caregivers of 3 groups of 6-10-year-old children in Uganda with known HIV exposure status: children HIV-infected perinatally (CPHIV, n=102), children born to HIV-infected mothers, but HIV-negative (CPHEU, n=101), and HIV-unexposed, uninfected community controls (CHUU, n=103). Caregiver depression symptoms were assessed using the Hopkins Symptom Checklist. In Aims two and three, child executive functioning (EF) assessed by caregiver report was compared across the three HIV exposure groups; effect modification of these associations by social support and wealth was also explored. We used random effects general linear models to estimate mean differences among the three HIV exposure groups. Adjusted models included caregiver age, education, social support, lifetime trauma, and wealth as covariates.

In aim one, we observed that perinatal HIV exposure status was associated with mean caregiver depression symptoms. Specifically, in unadjusted analyses, depression symptoms were higher among CPHEU compared to CPHIV caregivers (unstandardized beta coefficient [*B*]=-3.5, 95% confidence interval [CI] -5.3, -1.8). We also observed that caregiver social support modified the findings above ($p < 0.10$) with CPHEU caregivers with lower social support and lower wealth reporting higher caregiver depressive symptoms compared to CPHIV caregivers. We repeated all analyses within the subsample of biological mothers to examine whether their own diagnostic status drove any findings we observed; our pattern of results remained unchanged.

For Aim two, in our unadjusted analyses, perinatal HIV exposure was not associated with the Global Executive Composite (GEC) and Metacognition Index (MCI) scores of EF. However, for the Behavioral Regulation Index (BRI), the CPHIV group had lower levels of problems relative to the CHUU and CPHEU groups (*B*= -0.40, 95% CI -0.77, -0.03, *B*=-0.40, 95%CI -0.76, -0.02 respectively). For Aim three, we observed that the child's sex and caregiver depression symptoms modified the association between HIV status and specific subscales of EF.

Future directions for this work should include investigation into what drives the difference in caregiver depression symptoms between exposure groups. Additionally, collecting longitudinal measures of child EF and caregiver depression would help further interrogate time order between caregiver and child functioning among families affected by HIV. Lastly, continued investigation on how our findings relate to outcomes linked to EF such as academic achievement and behavioral problems would help to establish the importance of EF as a potential intervention target to improve school readiness.

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LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
GALT	Gut-Associated Lymphoid Tissue
BBB	Blood Brain Barrier
CDC	The Centers for Disease Control and Prevention
MTCT	Mother-to-child transmission
NRTI	Nucleotide Reverse Transcriptase Inhibitors
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
AZT	Azidothymidine
CART	Combined Antiretroviral Therapy
LMIC	Lower-Middle Income Countries
WHO	World Health Organization
PROMISE	Promoting Maternal-Infant Survival Everywhere
3TC	Lamivudine
LPVR	Ritonavir-boosted lopinavir
TDF	Tenofovir
FTC	Emtricitabine
ART	Antiretroviral Treatment
BMD	Bone Mineral Density
CPHIV	Children Perinatally HIV Infected

CPHEU	Children Perinatally HIV Exposed, Uninfected
CHUU	Children HIV unexposed, uninfected
CNS	Central Nervous System
PHE	Progressive HIV-1 Encephalopathy
HAND	HIV-Associated Neurocognitive Disorder
HPV	Human Papilloma Virus
SES	Socio-Economic Status
EF	Executive Functioning
CIPHER	Collaborative Initiative for Paediatric HIV Education and Research
KHC	Kawaala Health Center

CHAPTER 1: BACKGROUND LITERATURE AND AIMS

1.1 Introduction

Since the beginning of the Human Immunodeficiency Virus (HIV) epidemic in the 1980s, an estimated 75.7 million people have been infected and 32.7 million people have died from Acquired Immunodeficiency Syndrome (AIDS) [1]. Thankfully, the HIV/AIDS disease burden today is not what it once was. Availability of treatment and updated protocols have reduced incident HIV infections by 40% since its peak in 1997 and HIV-related mortality by 60% since its peak in 2004 [1, 2]. However, new infections are alarmingly high, and the burden of disease is still significant. For example, nearly 38 million people are living with HIV worldwide, with 1.7 million newly infected in 2019 – nearly 4500 new infections every day [1]. In addition, nearly 700,000 people died from AIDS-related illnesses in 2019 [2].

The progress made in fighting HIV has not been felt equally throughout the world. While Eastern and Southern Africa experienced a 49% reduction in AIDS-related deaths since 2010, an estimated 300,000 of the ~700,000 HIV-related deaths in 2019 took place there [2]. In addition, 20.7 million of the 38 million people living with HIV in 2019 were in Eastern and Southern Africa [2], and in 2019, sub-Saharan Africa accounted for 59% of new infections worldwide [3]. It is clear that while new infections have been decreasing from their historical peaks, sub-Saharan Africa shoulders a disproportionate burden of new infections along with illness and mortality.

Women and children are particularly vulnerable to the HIV pandemic, and in sub-Saharan Africa, they bear the majority of HIV disease-related burdens. Women and girls represented 48% of incident HIV infections globally in 2019, [1] and in Sub-Saharan Africa, women and girls comprise 59% of all new HIV infections in the region [1]. In Eastern and

Southern Africa, five in six new infections among adolescents aged 15-19 years were girls [1]. Women are also living with HIV in greater proportions than men. For example, the prevalence of HIV in young women in Eastern and Southern Africa was 3.2 per 100,000 in 2019, compared to 1.4 in young men, and this disparity becomes even more stark among reproductive-aged women [2].

There are many reasons why women and girls living in this region are particularly vulnerable to HIV infection. To begin, the risk of HIV seroconversion for each heterosexual act is twice as high for the female compared to the male partner [4, 5]. This may be attributable to the physical characteristics of the female genital tract, history of past sexually transmitted infections, and/or the inflammatory and microbial profile of the cervicovaginal mucosa [4, 6-10]. Apart from these factors, regions that have significant gender-based power imbalances have been found to put women at an increased risk for HIV. This vulnerability is often driven by gender-based violence, and while there is limited research linking gender inequality and gender-based violence to HIV, partner violence and male controlling practices have been associated with HIV serostatus in women [11]. Globally, 35% of women have experienced physical and/or sexual violence at some point in their life [1]. In some regions, women who have experienced this type of violence from intimate partners are 1.5 times more likely to acquire HIV than women who do not experience such violence [1].

Age-based discrepancies in HIV prevalence also illustrate how young women and girls are at higher risk for infection compared to men and boys. For example, young women 15-19 years of age are twice as likely than young men to be living with HIV [12]. This is thought to be the result of age-disparate relationship between older men and younger women, leading to a more rapid rise in HIV prevalence among young females compared to males [13]. Additionally,

the type of partnerships that females report also put them at greater risk of exposure to HIV. For example, young women report fewer lifetime partners compared to men and their most recent partners are typically marital. However, in these relationships, sex is more frequent, partners are often older and have experienced more historical risk of exposure to HIV, and condom use is less common [13]. Furthermore, girls have higher rates of school incompletion and poverty leading to female sex work adding further risk [14, 15]. These disparities in education, economic advantage, and relationships, along with difficulty in condom negotiation due to power imbalances and lack of knowledge surrounding HIV transmission all contribute to increased risk of HIV for young women and girls [14, 15].

1.2 HIV Transmission & Pathophysiology

Sexual transmission of HIV is the most common mode of transmission globally, with injection drug use, exposure to infected blood products, and vertical transmission from infected mother to the infant being less common forms [16]. Infection is initiated when the virus crosses a mucosal barrier as a cell-free virus, infected cell, or viron attached to dendritic cells or Langerhans cells, and subsequently attaching to CD4+ cells [16, 17]. The activated CD4+ cells then spread the virus throughout the gut-associated lymphoid tissue (GALT) and later to the secondary lymphoid tissues to establish stable tissue viral reservoirs [16]. During the acute infection stage which lasts 2-4 weeks, there is a massive depletion of CD4+ T cells paired with high levels of plasma viremia [16]. For most people, acute HIV infection then results in persistent viral replication, and without antiretroviral treatment, plasma viremia levels remain detectible [16]. HIV also enters the brain early after systemic infection by crossing the blood-brain barrier (BBB) via infected monocytes/macrophages and CD4+ T lymphocytes [18, 19]. Following acute infection, ongoing viral replication and the destruction of the immune system

signifies the latent stage which can last from weeks to years [20]. Left untreated, HIV infection results in progressive immune destruction signaled by drops in CD4+ and CD8+ cell counts, resulting in a diagnosis of AIDS once clinical thresholds of CD4+ counts have been reached [20]. The Centers for Disease Control and Prevention (CDC) defines the transition from HIV to AIDS when CD4+ counts are less than 14% of total lymphocytes, when a CD4+ count is less than 200 cells/μL of blood, or when at least one specified opportunistic infection occurs (e.g., pulmonary tuberculosis, recurrent pneumonia, invasive cervical cancer) [21].

Mother-to-child transmission (MTCT) or vertical transmission represents the most common route for pediatric infection [22]. MTCT can occur during gestation, during delivery, or after delivery through breastfeeding [22]. These routes of vertical transmission are associated with different timelines for detecting infection in the infant. For example, infants infected via intrauterine transmission may have detectable virus within 48 hours of birth, whereas infants infected during the antepartum period may test negative until 7-90 days after birth, with even more variable timeframes associated with infection via breastfeeding [23]. In fact, only 50% of HIV-infected infants have negative virologic assays at birth [23]. That said, irrespective of the exact point of infection, MTCT represents the key route for infection in children and is an important timeframe for intervention.

1.3 HIV Treatment

We now live in an era of highly effective drug therapies for HIV. Three of the most common classes of antiretroviral drugs include Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and protease inhibitors. NRTIs represent the first pharmaceutical treatments made available for HIV. They work by blocking the functional assembly of reverse transcriptase, the enzyme responsible for converting

HIV ribonucleic acid (RNA) into deoxyribonucleic acid (DNA). NNRTIs also target reverse transcriptase, but in contrast to NRTIs, directly bind to the fully assembled enzyme to inhibit its function [24, 25]. Protease inhibitors work by preventing viral building blocks from assembling to form mature particles capable of infecting other cells [24]. Protease inhibitors are often used in combination with each other to treat HIV infection, a therapeutic approach described as combined Antiretroviral Therapy (cART).

Access to reliable testing and high-quality treatment are primary factors in the prevention of HIV, and standards of care have changed as new treatment modalities became available. In 1985, the first diagnostic antibody test was developed for HIV, and shortly after, clinical trials were designed to test new treatments for HIV, with the first being azidothymidine (AZT) in 1987 [26-28]. Other NRTIs were approved shortly afterward and used in patients with advanced HIV, but with limited success in survival benefits past 24 weeks [26]. At this time, additional monotherapies were discovered, but these often came with toxic side effects or were associated with rapid development of resistance [26]. A turning point for HIV treatment occurred in 1996 when NNRTIs and protease inhibitors were approved for use [26]. Although also prone to developing resistance when prescribed on their own, NNRTIs and protease inhibitors are highly successful at suppressing viral load when combined, subsequently preventing transmission and dramatically reducing mortality from HIV [26]. However, these advancements were not available universally. For example, zidovudine, the first NRTI to be proven effective at preventing MTCT in 1994, had significantly reduced the number of newly infected children in high-income countries. However, due to the high cost and need for frequent dosages, pregnant women in lower-middle-income countries (LMIC) were not able to benefit from this advancement until years later [29].

The risk of MTCT at the beginning of the epidemic was estimated to be between 15-35% globally, with lower rates reported in Europe and the highest rates in Africa [22, 30]. Even as recently as 2010, the World Health Organization (WHO) standard protocol in treatment for HIV focused on waiting until a person (including pregnant women) became "sick enough" (with CD4 counts 350 cells/μL or less) to begin antiretroviral treatment [31]. Additionally, prior to 2010, if a pregnant woman tested positive but had a CD4 count below 350 cells/μL, they were often only given a single dose of nevirapine (an NNRTI) during labor, along with two weeks of treatment postnatally for both the mother and baby [32]. This focus on treatment and prophylaxis on only the very sick led to high rates of vertical transmission, particularly for women with unreliable access to health care and screening.

As the need for better treatment protocols became apparent, a clinical trial called the Promoting Maternal-Infant Survival Everywhere (PROMISE) study was created to compare the safety and efficacy of new antiretroviral treatment regimens to reduce MTCT of HIV. The PROMISE study was the first African-based, randomized, multi-site trial to test the safety and efficacy of treatment protocols for pregnant women and their babies and was initiated in 2011. When comparing two different cART regimens (zidovudine (AZT), lamivudine (3TC), and ritonavir-boosted lopinavir (LPVr) vs. tenofovir (TDF), emtricitabine (FTC) and LPVr) to the current standard of care (zidovudine during pregnancy, single-dose nevirapine during labor, and two weeks of tenofovir and emtricitabine after delivery), [33] it was found that the two new perinatal triple treatment regimens reduced MTCT to 0.5-0.6% compared to 1.8% with the standard protocol [33]. In 2013, the World Health Organization (WHO) changed its recommendations based on the PROMISE findings, and the perinatal triple treatment became the WHO-recommended standard of care. This protocol, known as Option B+, also recommended

that treatment not be withheld until the patient became "sick enough' and instead be initiated as soon as HIV had been diagnosed. This recommendation pertained to both pregnant women and children living with HIV and decoupled treatment initiation from CD4 counts. By 2015, most sub-Saharan countries had implemented the Option B+ protocols as their national standard.

With this change, MTCTs significantly reduced child HIV incidence, with global antiretroviral treatment (ART) coverage for HIV+ mothers increasing from 50% to 77% between 2010 and 2015; by 2020, nearly 85% of pregnant women globally had access to antiretrovirals [12, 34]. Because NRTIs and NNRTIs are known to cross the placental barrier, they are an effective way to prevent transmission in utero [35, 36]. Today, it is possible for pregnant women who are HIV+ to deliver children who are HIV- if they have access to high-quality antiretrovirals throughout pregnancy that suppress their viral loads to prevent transmission during the pre-and post-natal periods. However, there is still an unmet global need for access to early testing and treatment. Globally, in 2020, 150,000 new infections in children were due to MTCT [37]; 43% of this total was attributable to women being unaware of their serostatus during pregnancy, 25% due to interruptions in treatment during pregnancy or while breastfeeding, 23% due to women becoming infected during pregnancy or while breastfeeding, and 9% due to lack of viral suppression even though the mother was taking antiretrovirals [37]. Prevalence of MTCT within the sub-Saharan region of Africa is still reported to range from 15-40%, depending on the country and availability of treatment [38-40]. However, in 2019, there were 15 million children worldwide who were born HIV exposed during pregnancy, but were not infected, with 10 million living in Eastern and Southern Africa [2]. As a result, today there continues to be a growing number of children who were exposed in this way to HIV, including in sub-Saharan Africa.

1.4 Systemic effects of HIV infection in children

Following initial infection, HIV affects the body in several ways, and as documented by numerous studies, this is also true for children infected through the MCTC route. Low bone mineral density (BMD) is common in HIV-infected adults, and children infected by HIV are also at higher risk for this outcome due to their long-term exposure to the virus and antiretrovirals [41, 42]. Children perinatally HIV infected (CPHIV) also have issues with growth and physical development, including shorter stature, lower body weights, and delayed puberty compared to uninfected children [43, 44]. HIV infection is also known to cause cardiac issues among children and young adults who do not otherwise have cardiovascular risk factors; these outcomes have been attributed to a higher risk for congenital cardiovascular malformations as well as accelerated atherosclerosis [45]. Although stillbirth, preterm birth, and low birthweight have declined significantly in the era of cART, children exposed to HIV perinatally are at increased risk of being born preterm, particularly when a protease inhibitor is used [43, 46]. Compounding these issues, meta-analyses in the United States and Europe have found CPHIV are also at a higher risk for treatment failure and are less likely to achieve viral suppression than HIV-infected adults, which can lead to increases in drug resistance over their lifespan [43]. Data from LMIC are sparse on this topic but suggest similar trends [43, 47].

Children perinatally HIV exposed, born uninfected (CPHEU) are also at risk for poor health outcomes, despite not developing HIV infection themselves. A large cohort study based in Zimbabwe during the pre-cART era found that CPHEU had worse health outcomes than HIV unexposed children (CHUU), including lower birth weights, impaired growth, and higher morbidity and mortality [48]. Although not well understood, there is evidence that CPHEU have higher inflammatory markers, fewer T-cells, and in general lower levels of maternal IgG from

their mother during pregnancy and while breastfeeding, which may lessen their ability to respond to infection early in life [49].

1.5 HIV neuropathogenesis in children

In addition to these health issues, HIV exposure has also been shown to affect the brain. HIV can cause central nervous system (CNS) disease either primarily through the immunological effects of the virus or secondarily through an opportunistic infection by way of the aforementioned immune deficiency [20]. The virus does not directly infect the neurons of the brain; instead, it infects macrophages and other cells in the CNS which in turn cause CNS damage [20]. As previously stated, HIV enters the brain early after infection and crosses the BBB via infected monocytes/ macrophages and CD4+ T lymphocytes [18, 19]. These cells preferentially infect the brain vs other organs, and autopsied brain tissue has been found to contain HIV within perivascular macrophages and microglia which are responsible for HIV replication [18]. Astrocytes can also be infected, and with fetal astrocytes thought to be more susceptible to HIV compared to astrocytes of adults, they play an important role in pediatric HIV encephalopathy [18]. If left untreated, the CNS of children appears to be more vulnerable to HIV-related neurological complications compared to adults [18, 19]. Additionally, because the CNS is relatively isolated from systemic circulation, it might be a protected space for HIV to slowly replicate or remain latent, serving as a reservoir for the virus [19].

The most severe manifestation of these brain-based impacts is progressive HIV-1 encephalopathy (PHE), which involves the clinical deterioration of higher cognitive functions and is associated with white matter disease and cerebral atrophy [50]. A large portion of the adult population living with HIV develops cognitive impairment, now classified as HIV-associated neurocognitive disorder (HAND), with one meta-analysis estimating the prevalence of HAND at

~43% within HIV-infected adults globally and 72% in sub-Saharan Africa [51, 52]. Different from the long latent period in adults from HIV infection to neurological conditions, in children, neurological disease is often the first AIDS-defining event [18]. During the pre-cART era, the highest incidence rate of HIV-related CNS manifestations occurs in the first 2 years of life [18]. Before the widespread use of cART, 13-15% of children infected with HIV and 35-50% of children with AIDS were documented to have PHE [18]. cART can prevent and reverse PHE, but some residual behavioral problems, neurologic, cognitive, and scholastic impairments, and risk for relapse of PHE-related problems may remain [18, 53, 54].

1.6 Chronic disease and survival in the cART era

Chronic viral infection, long-term exposure to cART, and other treatments as well as a higher risk for opportunistic infections contribute to the diversification of morbidity and mortality in the post-cART era [55]. Better treatments and protocols have decreased new infections in children and increased the survival of those living with HIV, including among mothers accessing treatment during pregnancy. However, as individuals with access to treatment live longer (approximately 7 fewer years overall in a US-based population compared to non-HIV infected adults and within 10 years of an average life expectancy in an LMIC study [56, 57]), they may experience more chronic disease idiopathically, directly from infection, or as side effects of long-term exposure to cART. In a US-based survey, approximately 10% of people living with HIV also were diagnosed with diabetes, higher than the 8% prevalence among the general population [58]. Global estimates of hypertension in people living with HIV is around 25% [59]. Even with cART, people living with HIV have a higher risk of developing cancer, with a more severe clinical course and lower survival rate than those non-infected, with 10-20% of all deaths in HIV+ patients attributed to cancer [60]. That said, opportunistic infections remain

the most common cause of death for people living with HIV in the cART era worldwide, with hepatitis and liver-related infections representing the highest mortality risk conditions [61]. The infection rate of human papillomavirus (HPV) in women with HIV can be as high as 91% in some sub-Saharan regions, leading to an increased risk for invasive cervical cancer within this population [62, 63]. Additionally, certain antiretrovirals such as protease inhibitors are also associated with an increased risk of myocardial infarction, particularly with long-term exposure [64, 65]. This constellation of additional morbidities has added to the burden of HIV disease itself and associated difficulties with employment, leading to poverty and an increase in stress burden among adults living with the disease [66]. Although there appears to be an increased risk of non-communicable disease with infection and exposure to HIV, data suggests this is due to social and demographic differences such as food security, caregiver employment and low birth weight that co-occur with HIV exposure [67].

1.7 Pediatric HIV: Transition in Focus to Functional Survival

Now that children exposed to or infected by HIV with access to treatment can survive past childhood and well into adulthood, there is interest in evaluating how this exposure early in life may affect how they develop and function in the post-cART era. In addition to their own enhanced survival, children with HIV are also less likely to be orphaned or cared for by a non-biological parent [68]. Furthermore, as MTCT has been disrupted in both LMIC and non-LMIC contexts, families now include more CPHEU. However, both CPHIV and CPHEU families struggle with the antecedents and sequelae of HIV infection, including poverty, lower education levels, lifetime stress or trauma, and the lasting effects of chronic illness [69-71]. These types of environmental stressors can have a significant impact on maternal stress and anxiety, which have been found to be negatively associated with child development [72, 73]. Additionally, caregiving

with a physical illness like HIV/AIDS has been shown to negatively affect positive parenting through decreased engagement, routine disruption, and increased parental absence [74, 75].

1.8 Pediatric HIV: Environmental systems & child development

The caregiving environment is highly complex and is influenced by a myriad of environmental factors, and Bronfenbrenner's ecological systems model provides a conceptual framework to understand how these complexities impact child development and vice versa. In brief, this model conceptualizes the environment as five systems with varying proximity to the child, including the microsystem (e.g., the child and individuals with direct influence such as a parent or caregiver; impacts of illness or treatment of the child), mesosystem (e.g., interactions between the child/parent and child/teacher or child/ clinician), exosystem (e.g. the places or psychological space where interactions take place like the home or school), macrosystem (e.g., the cultural and subcultural values norms and expectations relating to childcare and development) and chronosystem (e.g., secular change) [76-78].

Within a HIV context, there are many ways in which these levels interact to inform environment a child is developing within. Previous literature has focused more on microsystem variables, such as viral exposure or specific treatment regimens, and their effect on child functioning. However, mesosystem variables like home environment and parental stress are becoming increasingly important when researching the effects of HIV on child development. Research is now showing how HIV can impact the development of children through the child's environment, by way of poverty, food insecurity, and community stigma that also leads to poor caregiver mental health [72]. Caregiver depression, the most commonly researched variable addressing home environment, and caregiver stress have been associated with internalizing and externalizing problems in children as well as cognitive functioning [71, 78, 79]. Consistent with

ecological theory principles, there is also evidence that children's behavioral problems can influence caregiver mental health, exhibiting a bi-directional relationship [80, 81]. Most research has been focused on the direction from maternal depression to child functioning, but less is known about the reverse relationship, particularly in sub-Saharan Africa and within an HIV context.

1.9 Caregiver mental health and depression: a salient developmental context

Studies describing the mental health of caregivers have primarily focused on maternal depression [18, 79, 82, 83] relative to other psychological difficulties. Depression among women with HIV is worryingly common, with one global survey showing that 82% of women with HIV report symptoms of the disorder [84, 85]. Within HIV-endemic areas, caregivers can face additional stressors such as the loss of a partner, poverty, and lower education levels, all while managing their own HIV diagnosis [70, 86, 87]. Additionally, studies have shown that caregiving to ill children also impacts a caregiver's mental and physical health [88]. For example, multiple studies have indicated that caregivers to chronically ill or HIV-infected children have more anxiety, depression, and lower levels of health-related quality of life [70, 88, 89].

As caregivers, particularly those who are living with HIV themselves, are faced with compounded burdens, there are residual effects experienced by their children. In higher-income countries, chronic and severe depression in caregivers is associated with behavioral problems in children [82, 90, 91]. A meta-analytic review of 193 studies corroborates this finding, stating maternal depression (clinical diagnosis or self-report symptom rating) was significantly associated with higher levels of child internalizing, externalizing, and general psychopathology symptoms as well as lower levels of positive affect, though all associations were small in

magnitude [82]. This association is not evenly experienced by all families, with some studies finding socioeconomic status (SES) of the family acting as a moderator between caregiver depression and child psychopathology, with stronger associations observed among low-income families compared to middle, higher, or mixed-income families [82]. Besides income, social support appears to be protective against caregiver depression, [69] but it is unclear how this may differ across HIV exposure groups. With that said, the psychological challenges faced by HIV+ persons within their own lives are important in their own right and should be investigated in order to promote better health outcomes for this population.

1.10 Child Neurocognition as a key functional outcome

Characterizing the environmental context in which children are developing is important to understanding the links between an exposure (such as pediatric HIV) and any child development outcome, given that these outcomes are heterogeneous and multi-determined. Neurocognitive outcomes of children have been of particular interest due to their importance for functional survival later in life and the knowledge that HIV is able to cross the BBB. In addition to the effects of caregiver depression on child behavior and functioning, another outcome of perinatal HIV exposure that warrants further investigation is how HIV exposure and infection affect child cognition, as well as the reverse effect of child behavior on caregiver mental health. As evidence for neurocognitive effects of HIV exposure began to emerge, the literature shifted from documenting HIV encephalopathy and survival of infants to potential developmental challenges for children with perinatal HIV exposure and infection. However, the literature varied in methodology and study populations, making comparison and consensus difficult. Findings from these studies were also difficult to interpret due to the role of cART and timeline of its availability within the study population. With all these caveats, the literature has shown that

perinatal HIV exposure and/or infection was associated with a detrimental effect on neurocognition. One large systematic review showed 81% of their included 54 studies found perinatal HIV exposure to negatively affect neurocognitive development irrespective of how it was measured [92]. Complicating matters, however, the comparison groups in these studies were not consistent (some compared CPHIV to CPHEU while others compared only to CHUU), heavily focused on infants and young children, and were very geographically biased, mostly in North America or Europe [92]. Furthermore, these findings were often complicated by how ill the child was [92, 93]. Often, the findings were mixed, and adjusted analyses using demographic and child health information attenuated findings to small or null effects [94]. Less is known about cognitive development later in childhood. Specifically, individual constructs within these general cognition measures have not been thoroughly researched, particularly in sub-Saharan contexts.

One particular facet of child cognitive functioning receiving attention in the context of perinatal HIV exposure is executive functioning (EF), a set of overlapping cognitive processes that allow an individual to control and coordinate thoughts, actions, and behaviors driven by the prefrontal cortex of the brain [95]. EF is an important functional measure due to its association with real-world outcomes, including academic achievement, employment, and medication adherence [93, 96-98]. Despite varying definitions of the construct, common elements of EF include: working memory, behavioral inhibition, and task switching [99]. Thanks to improvements in neuroimaging that can track activity in the brain throughout development, the prefrontal cortex is shown to undergo a projected developmental trajectory that extends to early adulthood (~age 25) [100]. Due to this extended window of development, processes like EF that

are subserved by the prefrontal cortex may be particularly amenable to intervention and environmental influences.

To this end, one of the influences receiving much attention is the familial environment. Previous research has found that a child's early home environment, including caregiver involvement and stimulation and household income, is associated with neurocognitive development within an HIV-positive cohort [94, 101]. Additionally, previous research has found that maternal depression and anxiety are associated with poor child socio-emotional, cognitive, and physical development concurrently and across time – within both non-HIV and HIV-affected children [102-104]. In studies that evaluate the impacts of perinatal HIV on cognition or EF, caregiver mental health is not investigated as a potential modifier despite links to both the exposure and outcome as well as its relevance as a potential intervention target [94, 101, 105]. Additionally, child EF has been shown to vary significantly by sex but little research has investigated this as a potential effect modifier [106, 107]. Understanding how sex differences act as modifiers to the HIV-exposure/EF association would also be important in identifying key risk groups for interventions, given that males experience greater morbidities following exposure to perinatal health risks compared to females [108-110].

Previous work with HIV-exposed children and cognition has focused on infancy and early childhood (< age 6) and has shown perinatal HIV exposure to be associated with negative neurocognitive outcomes [92, 111-113]. However, today, neuropsychological functioning in middle childhood is becoming an increasingly important focus for HIV research, in part because processes like EF are important predictors of healthy adult functioning. In addition, EF is responsible for higher-order neural processes such as goal-setting, organization, and planning, something that is of particular importance when needing to adhere to their drug regimens

throughout their life in order to remain healthy and eliminate the risk of HIV transmission [113, 114]. EF and specific indices within the measure such as cognitive control are also considered key predictors of success in school [115], making it an ideal target for research and potential intervention in middle childhood, as children begin their formal education.

1.11 Dissertation Aims

There are many challenges faced when addressing how perinatal HIV infection might affect children as they reach school-age. The ecological systems model explains how the various features of the environment in which children develop before entering school and caregiver mental health significantly impact child development. Thus, there is a need to better characterize the contexts in which children who are perinatally exposed and/or infected develop, such as their caregiver's mental health. As part of this process, it is important to understand how the social and economic effects of HIV and a child's behavior are interrelated to caregiver stress and mental health, which are critical to understanding this relationship.

Importantly, there are few studies that include the full complement of HIV exposure groups (CPHIV, CPHEU, and CHUU) when investigating cognitive outcomes in middle childhood. CPHEU in particular represent the "new normal" as global populations become increasingly able to access cART. Therefore, it is important to investigate potential differences between this group and CPHIV. It is also crucial to identify key risk groups and modifiable variables that could be addressed with interventions while the brain systems responsible for EF are still plastic. There has not been significant focus on the identification of modifiable factors such as caregiver mental health and socioeconomic hardship associated with perinatal HIV exposure and child and caregiver outcomes. If we are to truly pivot research from child survival

to helping them thrive, understanding points of intervention or risk groups to target is a crucial next step.

The aims of this dissertation address these knowledge gaps and involve the secondary analysis of Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) study data. The sample includes Ugandan children and their primary caregivers enrolled from Kawaala Health Center (KHC) in the Kawempe Division of Kampala, Uganda. Approximately equal numbers of children with three HIV exposure statuses were enrolled in the study: children with perinatally acquired HIV infection (CPHIV), children with perinatal HIV exposure, but no infection at enrollment (CPHEU), and children with no perinatal HIV exposure and no infection at enrollment (CHUU). Cross-sectional data on the child was assessed in middle childhood (6-10 years), along with caregiver mental health and socio-economic factors.

The specific aims include:

Aim 1: To evaluate the association of perinatal HIV exposure status and caregiver depression symptoms

1a: To investigate effect modification of social support and wealth on the association of perinatal HIV exposure status on caregiver depression symptoms

1b: To perform a sensitivity analysis among biological caregivers to evaluate the impact of caregiver serostatus on any associations observed

Aim 2: To evaluate the association of perinatal HIV exposure status and child executive functioning

2a: (originally posed as Aim 3 at dissertation proposal defense): To investigate whether sex or caregiver depression symptoms modify the association between perinatal HIV exposure status and child executive functioning

CHAPTER 2 (Aim 1): PERINATAL HIV EXPOSURE AND INFECTION AND CAREGIVER DEPRESSIVE SYMPTOMS

2.1 Introduction

In 2020, an estimated 37.7 million people globally were living with human immunodeficiency virus (HIV) [12]. Availability of effective antiretrovirals, government testing programs, and treatment protocols have reduced acute immunodeficiency syndrome (AIDS)-related deaths by 64% since the epidemic's peak in 2004 and by 47% since 2010 [12]. Despite this progress, new infections are still problematic, and the burden of HIV is significant, particularly within sub-Saharan Africa. In this region, 12.4 million women over the age of 15 are living with HIV [116]. This group represents a core population responsible for caregiving, and how this group is able to function has a significant effect on the environment where HIV-exposed and infected children grow and develop.

Survival is now possible for children perinatally exposed to or infected by HIV if they have access to combined antiretroviral therapy (cART). However, it is important to identify factors that can affect children's ability to thrive following initial exposure or infection. The caregiving environment may be one such context to consider, given its impact on all aspects of development [117, 118]. In HIV-endemic areas, caregivers are faced with many significant stressors such as the loss of a spouse, lower employment, wealth, and education levels, and perhaps coping with their own HIV diagnosis [70, 86, 87]. Caregiving in this type of environment has been found to increase the risk of psychosocial problems for the caregiver and negatively affect their mental health [74, 86, 87]. To date, studies of caregiver mental health have focused mostly on maternal depression [18, 79, 82, 83] relative to other psychological difficulties.

In high-income countries, chronic and severe depression in caregivers is associated with behavioral problems in children [82, 90, 91]. In a meta-analytic review of 193 studies using either cross-sectional data or one follow-up timepoint, maternal depression (clinical diagnosis or symptom rating) was associated significantly with higher levels of child internalizing, externalizing, and general psychopathology symptoms as well as lower levels of positive affect, though all associations were small in magnitude [82]. However, a large longitudinal study found that clinical diagnoses of major depressive disorder in caregivers were associated with an increase in child internalizing and externalizing problems and that these associations strengthened over time [79]. Additionally, the socioeconomic status (SES) of the family may act as a moderator between caregiver depression and child psychopathology, with stronger associations observed among low-income families compared to middle, higher, or mixed-income families[82].

To date, these findings have not been placed in an HIV context, where caregiver mental health takes on even greater significance. Globally, depression among women who are HIV+ is alarmingly common. One global survey showed 82% of HIV+ women report symptoms of the disorder, with 24% reporting depression before HIV diagnosis and 74% reporting depression since or due to their diagnosis [84, 85]. Within lower-middle-income countries (LMIC), some of which are also HIV endemic, caregiver depression also has been associated with lower cognitive scores, more behavioral problems, and lower executive functioning (EF) in children [71, 72, 113, 119]. However, the contribution of child HIV serostatus to these associations is unclear. This is because these studies often do not include HIV-exposed, uninfected or unexposed, uninfected groups for comparisons [120-122]; in those that do, one reported lower levels of emotional well-being, a measure strongly associated with depression, among caregivers of HIV-exposed,

uninfected children compared to caregivers of HIV infected (CPHIV) and HIV unexposed children, [89] and another well-powered study (n=611) also observed higher levels of depression in caregivers of HIV infected children compared to caregivers of HIV exposed, uninfected or unexposed children, but the findings were not statistically significant [119]. Both findings represent unadjusted, descriptive analyses from studies designed to address the impacts of caregiver mental health on other outcomes, namely child behavior. However, the parent-child relationship is not unidirectional [80, 81]. Thus, investigations that focus squarely on the impact of child factors on caregiver mental health are warranted [81].

To this end, one factor receiving much attention in the pediatric literature is chronic illness. For example, a review of 26 individual studies found that parents of chronically ill children experienced more anxiety and depression than parents caring for unaffected children [88]. In the context of HIV specifically, particularly within LMIC, the literature is more limited. One study from Ghana evaluated caregivers of children who are HIV+ and found higher levels of depression symptoms among caregivers, but the contribution of their own HIV serostatus was unclear and the study did not include an exposed, uninfected comparison group [123]. In a longitudinal study including female caregivers who are HIV+ in Uganda, researchers found that child behavioral problems predicted caregiver depression symptoms over the 24 months of the study after controlling for depression at a previous timepoint, suggesting that child behavior might also be a factor associated with caregiver mental health [80]. However, the research did not include comparison groups of uninfected children. The caregiver's own serostatus and associated health burdens also contribute to their risk of depression and anxiety, furthering the importance of this research. These data are needed to more fully understand the relationship

between caregiver mental health and child health and behavior, and what might be done to address the significant health burden of caregiver depression in HIV endemic areas.

Our goal was to address these knowledge gaps by evaluating depression symptoms in a sample of caregivers in Uganda, a country that continues to suffer disproportionately from the effects of the HIV epidemic. To do this, we evaluated whether caregiver depression symptoms vary across child serostatus based on perinatal exposure to HIV. We also assessed whether factors that may co-occur with caregiver depression symptoms (family wealth, caregiver education, employment status, lifetime trauma, and social support) account for any associations observed. Additionally, we reviewed if observed findings were modified by factors that could be targeted for intervention, such as family wealth and social support.

2.2 Methods

Study Population & Design

We performed a cross-sectional analysis using data from the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) study. The sample included Ugandan children (6-10 years old) and their primary caregivers enrolled from Kawaala Health Center (KHC) in Kawempe Division of Kampala, Uganda from 3/15/17 and 9/15/18. Approximately equal numbers of children with three HIV exposure statuses were enrolled in the study: children with perinatally acquired HIV infection (CPHIV, n=102), children with perinatal HIV exposure, but no infection at enrollment (CPHEU, n=101), and children with no perinatal HIV exposure and no infection at enrollment (CHUU, n=103). We included children with available information on self-reported caregiver depression in our analysis (missing n=3 from both CPHIV and CPHEU groups, n=1 from CHUU). Caregivers were eligible for participation regardless of number of children already enrolled in the study; the data presented here were collected from

245 unique caregivers. The study protocol was approved by the research ethics review committees of Michigan State University (IRB Protocol#: 16-828), Makerere University College of Health Sciences, School of Medicine (Protocol REC REF# 2017-017), and the Uganda National Council for Science and Technology (Protocol #: SS 4378). All caregivers (n=245) gave written informed consent and all children provided assent for study participation.

Measures

Perinatal HIV exposure and infection: Perinatal HIV exposure was ascertained from and verified through KHC medical records. For the CPHEU and CPHIV groups, serostatus was monitored through 18 months of age using DNA-polymerase chain reaction tests. Serostatus at enrollment was assessed using HIV-rapid diagnostic testing.

Caregiver depression symptoms: Self-reported caregiver depression symptoms were assessed using part II of the Hopkins Symptom Checklist (HSCL) at child enrollment [124]. Each question had four response options ("Not at all," "A little," "Quite a bit," and "Extremely," rated 1 to 4, respectively). Responses across all 15 items were averaged to generate depression symptom scores for each caregiver. For caregivers with multiple children in the study (n=49), depression symptoms were measured at the time of each individual child's enrollment.

Covariates: We considered factors suggested by previous literature to be associated with children's perinatal HIV exposure and caregiver depression symptoms [87, 89, 123]. These included socio-demographic information about the primary caregiver, including age, self-reported education level (no education or primary level not completed, primary level completed, or above primary), employment status (no income, informal income, unskilled employment, or driver, skilled worker or professional), and wealth (sum of material possessions: electricity, running water, refrigerator, television, and car) at enrollment. We also considered caregiver

lifetime exposure to traumatic events using the Stressful Life Events Screening Questionnaire (SLESQ), a 14-question instrument with three responses ("no", "yes, only once", "yes, more than once") rated 0-2 [125] as well as caregiver social support using an adaptation of the Duke-UNC Functional Social Support Questionnaire, an 8 question instrument measuring both emotional and instrumental support with four possible responses ("never", "much less than I would like", "less than I would like" and "as much as I would like") rated 0-4 [126]. Information about the primary caregiver, such as relationship to the child and status of the biological mother (deceased or living) was collected through caregiver report or access to medical records at enrollment. We considered the number of children per household as a covariate but decided not to include this variable in analyses due to its role as a potential mediator. Child health covariates were collected to characterize the health of the children and caregivers in the study sample but also were not included in the models due to their potential to operate as mediators. These factors included such health indicators as ferritin (above or below 15 ng/mL [127]) and hemoglobin levels at enrollment(above or below 115 g/L[128]). In addition, CD4 count was available for CPHIV in order to describe the health status of this group. Birthweight was collected from hospital records and additional infections were screened for via stool sample at enrollment (giardia, amoeba, and cryptosporidium). Intrauterine ART exposure information for the child was also collected via interview at enrollment to better characterize the sample.

Analysis Plan

We began by describing the analytic sample according to caregiver and child characteristics at enrollment for all covariates described above. We then examined whether the study covariates varied across the perinatal HIV exposure groups. All scores were normally distributed with the exception of caregiver lifetime stress, which was log-transformed prior to

inclusion in the analysis. We then performed random effects general linear modeling to evaluate the association between children's perinatal HIV exposure status and caregiver depression symptoms (alpha=0.05, two-tailed). The random effect reflected the presence of multiple children per household in the study sample; other factors were entered as fixed effects. We chose this modeling strategy because it allowed us to generate the need to generate one depression symptom score for caregivers who had multiple children enrolled in the study. We then repeated the random effects general linear modeling following adjustment for caregiver age, education, social support, lifetime trauma, and wealth.

We also explored whether the associations between child HIV exposure and caregiver depression symptoms were modified by caregiver social support or wealth. We selected these factors based on literature review and because they may represent modifiable targets for intervention [69, 123, 129]. A cut point of p=0.1 (two-tailed) was used to evaluate statistical significance of interactions due to the exploratory nature of this analysis.

Finally, we repeated all analyses after limiting the sample to children whose caregiver was reported as their biological mother to evaluate whether the mother's own diagnosis drove any findings observed. All analyses were completed using SAS software 9.4 (Cary, NC).

2.3 Results

Caregivers included in the analytic sample were 91% female with a mean age of 39.5 years (Table 1.1). A majority reported no or informal income, while 40% reported having formal employment (skilled or professional). Caregiver education ranged from no education or primary education completed (59%) to above primary (41%). The average caregiver social support score was 1.5 (range 0-3; standard deviation [SD]=0.1) and the average caregiver wealth score was 1.5 (range 0-5; SD=1.2).

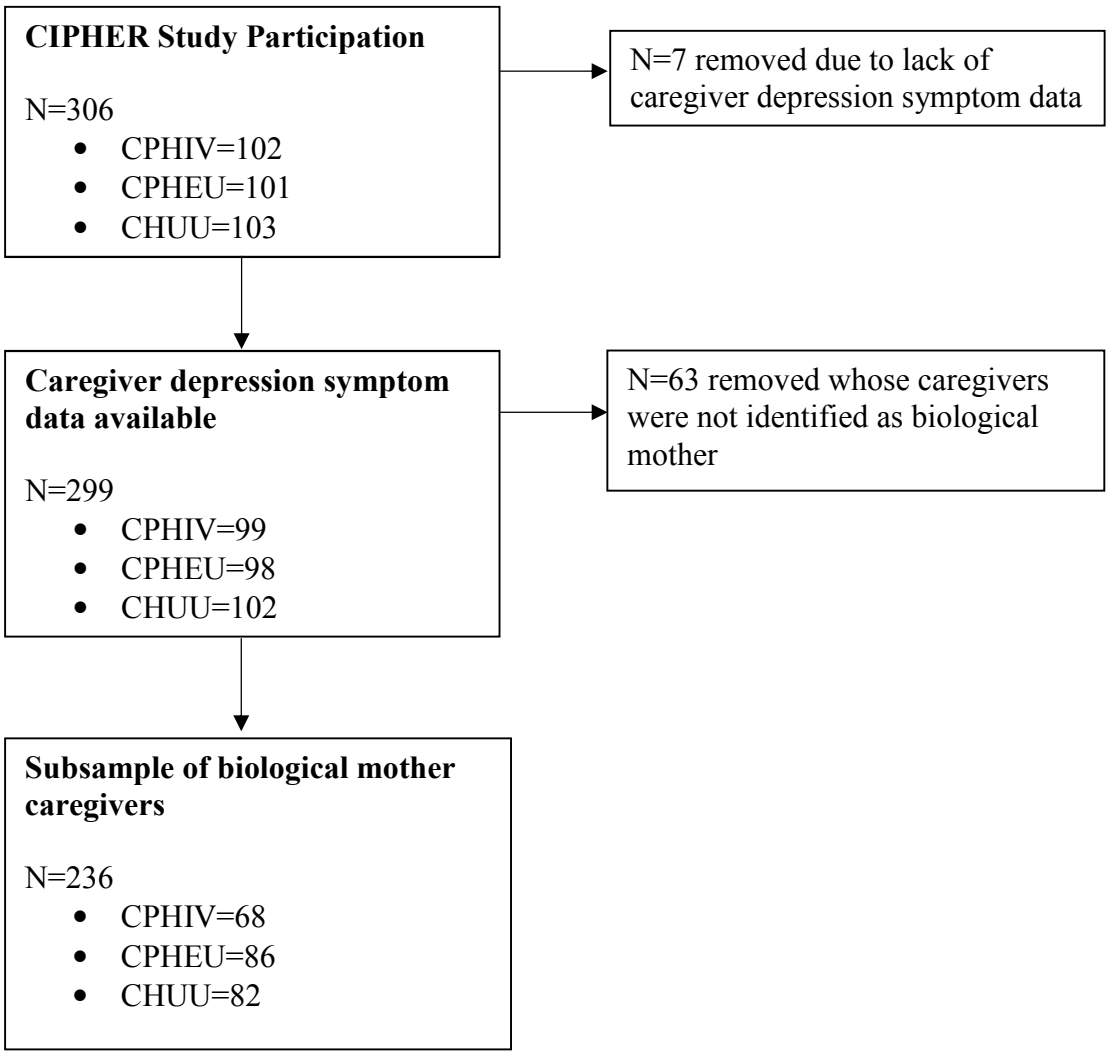
When comparing covariates across child HIV exposure groups, we observed a few key differences (Table 1.1). The CPHIV group experienced the death of their biological mother more frequently (23%) compared to the CPHEU (8%) and CHUU (3%) groups. In addition, CPHEU caregivers reported lower levels of wealth and higher levels of lifetime trauma compared to CPHIV and CHUU caregivers.

We observed that perinatal HIV exposure status was associated with mean caregiver depression symptoms (Table 1.2). Specifically, in unadjusted analyses, depression symptoms were higher among CPHEU compared to CPHIV caregivers (unstandardized beta coefficient [*B*]=-3.5, 95% confidence interval [CI] -5.3, -1.8). This finding was attenuated slightly but remained significant following adjustment for covariates (*B*=-2.2, 95%CI -4.1, -0.4). Depression symptoms did not differ between the CPHIV and CHUU caregivers (*B*= -1.8, 95%CI -3.7, 0.1) or between CPHEU and CHUU caregivers (*B*= 1.7, 95%CI -0.3, 3.37) in unadjusted models.

We also observed that caregiver social support modified the findings above ($p < 0.10$; Figure 1.2). At lower levels of social support, CPHEU caregivers reported higher depression symptoms compared to CPHIV caregivers, the CPHEU slope of *B*=-0.2, (95%CI-0.3,-0.1) represents a significant negative association between caregiver social support and depression symptoms in this HIV exposure group. Wealth did not formally modify associations between child perinatal HIV exposure status and caregiver depression symptoms ($p > 0.10$; Figure 1.3).

We repeated all analyses within the subsample of biological mothers to examine whether their own diagnostic status drove any findings we observed. Our pattern of results remained unchanged. However, we observed slightly larger differences in depression symptoms between the CPHEU and CPHIV caregivers in both the unadjusted and adjusted models (*B*=-4.2, 95% CI -6.4, -2.0 and *B*=-2.8, 95% CI -5.1, -0.6 respectively).

Figure 1.1: Aim 1 analytic sample derivation



CPHIV= Children perinatally HIV exposed, infected
CPHEU= Children perinatally HIV exposed, uninfected
CHUU= Children perinatally HIV unexposed

Table 1.1 Caregiver and child covariates by perinatal HIV exposure status in analytic sample (n=299)

	Analytic sample N=299		CHUU$_1$ N = 102		CPHEU$_2$ N = 98		CPHIV$_3$ N = 99		p^+
	N	%	N	(%)	N	(%)	N	(%)	
Caregiver Characteristics (at enrollment)									
Caregiver sex									
Female	273	(91)	92	(90)	92	(94)	89	(90)	0.54
Male	26	(9)	10	(10)	6	(6)	10	(10)	
Biological caregivers	236	(79)	82	(35)	86	(36)	68	(29)	0.321
Caregiver Education									
No or primary education not completed	116	(39)	31	(30)	47	(48)	38	(38)	0.06
Primary education completed	59	(20)	21	(21)	21	(21)	17	(17)	
Above primary	124	(41)	50	(49)	30	(31)	44	(45)	
Caregiver Employment									
No income	92	(33)	32	(36)	28	(30)	32	(33)	**0.04***
Informal income	77	(27)	21	(23)	33	(35)	23	(23)	
Unskilled employment	59	(21)	16	(18)	24	(26)	19	(19)	
Driver or skilled work	53	(19)	21	(23)	8	(9)	24	(25)	
Caregiver Lifetime Exposure to Traumatic Events (SLESQ)									
Quartile 1 (0-2)	51	(17)	18	(18)	10	(11)	23	(24)	**0.05***
Quartile 2 (3)	57	(19)	44	(45)	37	(38)	34	(35)	
Quartile 3 (4-5)	118	(40)	13	(13)	9	(9)	12	(12)	
Quartile 4 (>5)	66	(23)	23	(24)	41	(42)	28	(29)	
Continuous caregiver variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Caregiver Support (Range 0-3)	1.5	0.1	1.6	0.1	1.5	0.1	1.4	0.1	0.15
Caregiver age (mean)	34.5	8.4	33.6	8.3	35.8	11.7	34.1	11.7	0.16
Wealth Score (Range 0-5)	1.5	1.2	1.7	1.2	1.3	1.7	1.5	1.7	0.07
Child Health Characteristics (at enrollment)									
Child sex									
Female	151	(50)	47	(46)	55	(56)	49	(50)	0.35
Male	148	(50)	55	(54)	43	(44)	50	(50)	
Child ferritin level									
< 15 ng/mL	8	(3)	4	(4)	2	(2)	2	(2)	0.62
≥15 ng/mL	279	(97)	93	(96)	94	(98)	92	(98)	
Child Hemoglobin (Hb) level									
<115 g/L (anemic for 5-11 yr. olds)	24	(8)	5	(5)	7	(7)	12	(12)	0.18
≥ 115g/L (normal)	267	(92)	92	(95)	89	(93)	86	(88)	
Other infection (giardia, amoeba, cryptosporidium)									
Any	24	(8)	9	(9)	7	(7)	8	(8)	0.91
None	266	(92)	89	(91)	87	(93)	90	(92)	
Birthweight									
< 2500g (low)	10	(4)	7	(8)	0	(0)	3	(3)	**0.02***
≥ 2500g (normal)	260	(96)	81	(92)	89	(100)	90	(97)	
In utero (ART) exposure									
Any in utero ART	96	(32)	0	(0)	54	(54)	42	(42)	---
No in utero exposure	101	(34)	0	(0)	44	(45)	57	(58)	
No ART exposure	102	(34)	100	(100)	0	(0)	0	(0)	
CD4									

Table 1.1 (Cont'd)

< 500 Cell/mm^2	--	--	--	--	--	--	32	(34)	--
≥500 Cell/ mm^2	--	--	--	--	--	--	61	(66)	
Continuous child variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Child age	7.7	1.4	7.7	1.4	7.4	2.0	7.9	2.0	0.08
CD4	--	--	--	--	--	--	759	488	--
Ferritin (ng/mL)	87.6	125	74.4	127	117.7	176	70.5	178	0.01*
Hemoglobin (g/dL)	13.1	1.3	13.2	1.3	13.1	1.8	13.0	1.8	0.32

[1] Children Perinatal HIV Unexposed, Uninfected
[2] Children Perinatal HIV Exposed, Uninfected
[3] Children Perinatal HIV Exposed, Infected
[+]Chi squared test for comparisons among HIV exposure groups

[*] $p < 0.05$; [†] $p < 0.10$

Missing data: Caregiver employment (n=18), Caregiver SLESQ (n=7), Caregiver social support (n=8), Ferritin (n=12), Hemoglobin (n=8), Any other infection (n=9), Birthweight (n=29), In utero ART exposure (n=2)

Table 1.2 Unadjusted and adjusted associations of perinatal HIV exposure or infection with depressive symptoms in caregivers (n=299)

	$CHUU_1$		$CPHEU_2$		$CPHIV_3$		$CHUU_1$ vs $CPHIV_3$	$CPHEU_2$ vs $CHUU_1$	$CPHEU_2$ vs $CPHIV_3$
	Mean	(SD)	Mean	(SD)	Mean	(SD)	B (95% CI)	B (95% CI)	B (95% CI)
Full analytic sample	**Max N = 104**		**Max N = 100**		**Max N = 102**				
Unadjusted	26.8	(8.0)	28.6	(7.5)	25.0	(7.1)	-1.8 (-3.7, 0.1)	1.7 (-0.3, 3.7)	**-3.5 (-5.3, -1.8)***
Adjusted[4]	28.9	(15.2)	29.5	(15.0)	27.2	(15.1)	-1.7 (-3.7, 0.3)	0.6 (-1.5, 2.7)	**-2.2 (-4.1, -0.4)***
Biological mothers only	**Max N= 82**		**Max N= 86**		**Max N= 68**				
Unadjusted	27.1	(8.1)	29.2	(7.8)	25.0	(7.3)	-2.1 (-4.5, 0.3)	2.1 (-0.3, 4.5)	**-4.2 (-6.4, -2.0)***
Adjusted[4]	31.9	(17.8)	32.7	(17.7)	29.8	(16.2)	-2.1 (-4.6, 0.3)	0.7 (-1.7, 3.1)	**-2.8 (-5.1, -0.6)***

[1] Children Perinatally HIV Unexposed, Uninfected
[2] Children Perinatal HIV Exposed, Uninfected
[3] Children Perinatal HIV Exposed, Infected
[4] Wealth score, Caregiver age, caregiver employment, caregiver education, caregiver social support, caregiver lifetime trauma (SLESQ)

* $p < 0.05$; † $p < 0.10$

Missing values: lifetime trauma (n=7), social support (n=1)

Figure 1.2: Caregiver depressive symptoms effect modification by caregiver social support

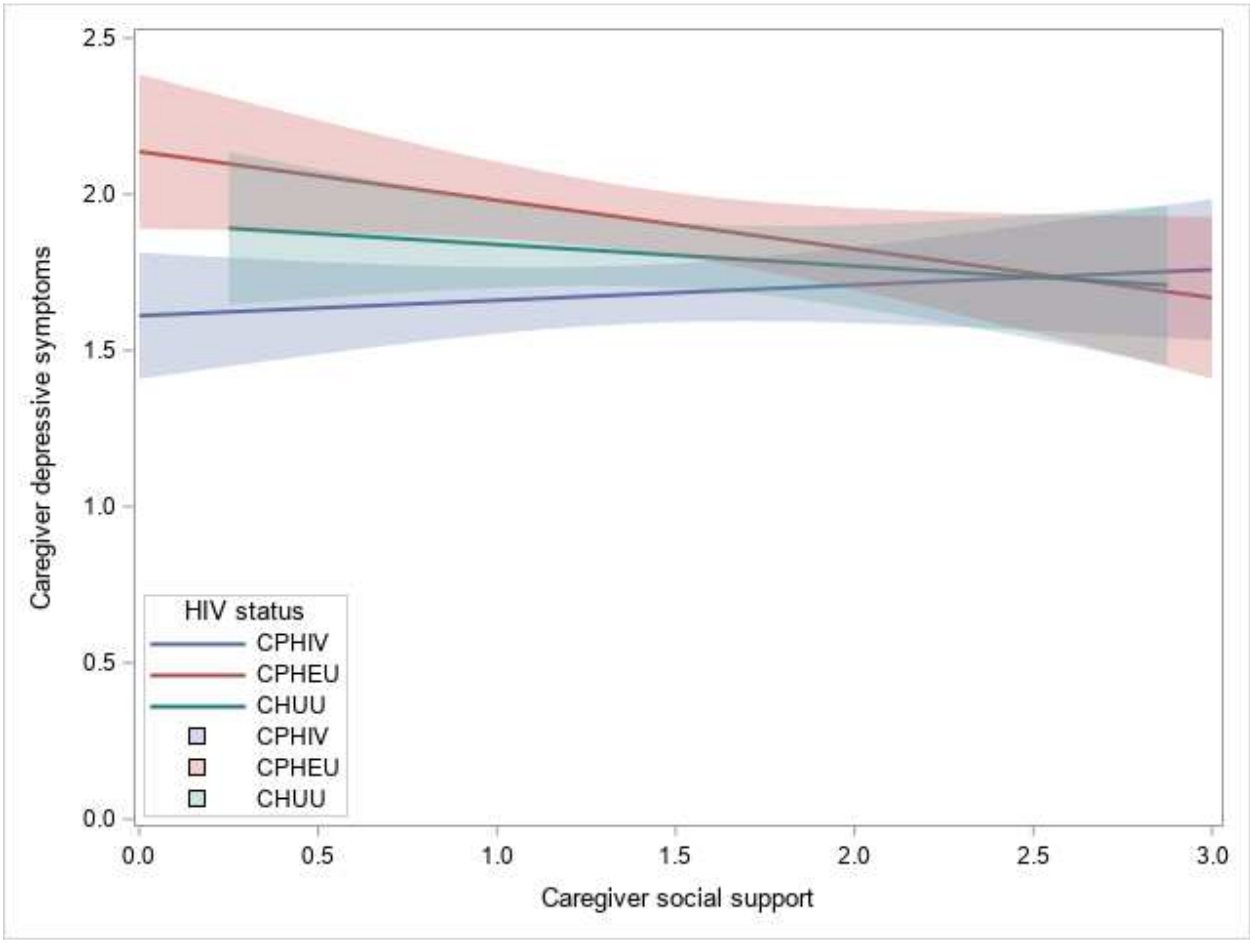
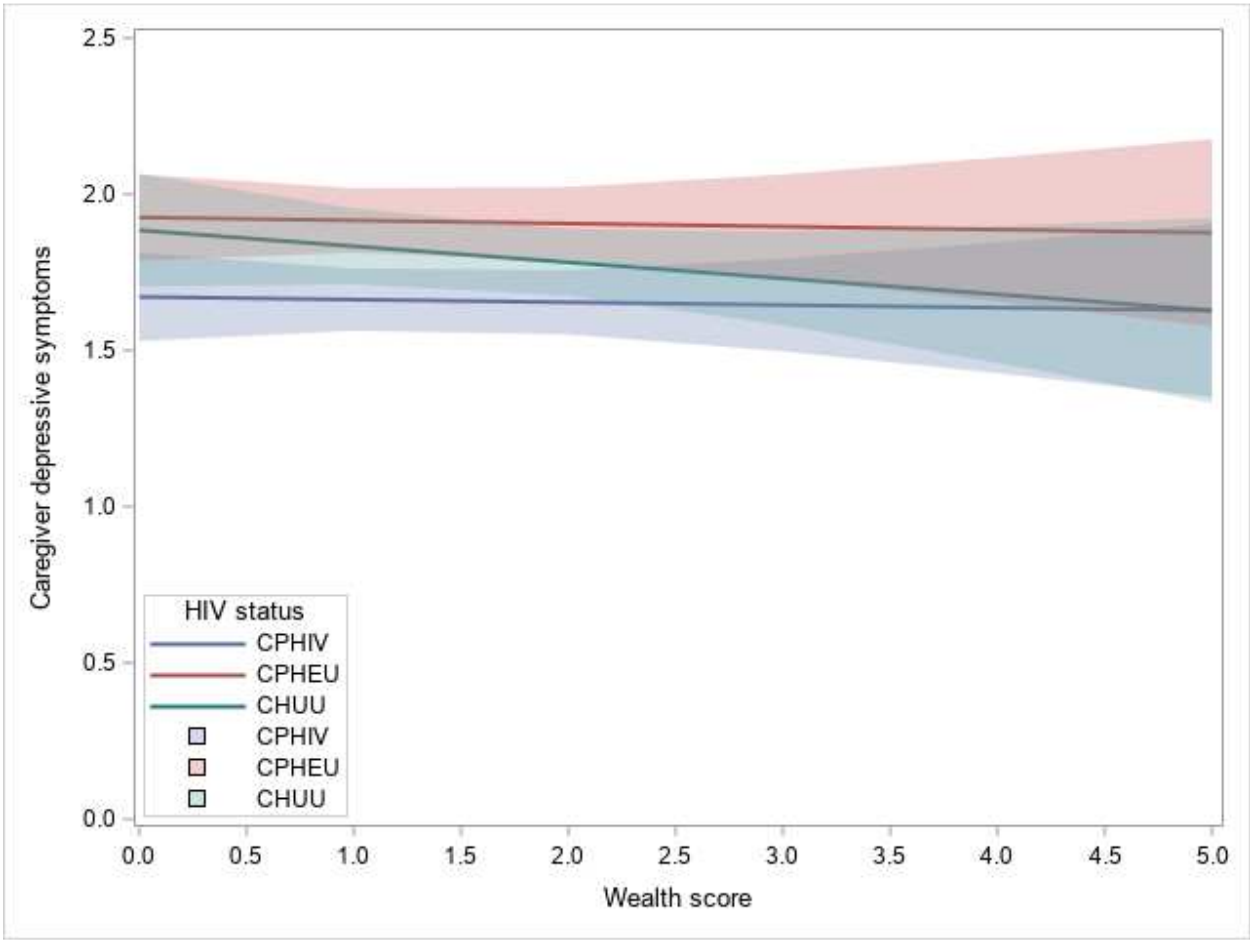


Figure 1.3: Caregiver depressive symptom effect modification by wealth score



2.4 Discussion

We investigated whether perinatal HIV exposure was associated with caregiver depression symptoms among a cohort of children and their primary caregivers in Uganda, a population that is at increased risk for depression due to endemic HIV and environmental factors associated with familial HIV. Unlike many previous studies, we were able to include a full complement of comparison groups to better understand the role of child HIV serostatus in our findings, adjust for various factors associated with caregiver depression, and perform sensitivity analysis limited to biological mothers.

We found that child perinatal HIV exposure was associated with caregiver depression symptoms, with CPHEU caregivers reporting higher levels of difficulties compared to CPHIV and CHUU caregivers. This is consistent with descriptive data from two recent studies that investigated other health outcomes. One, based in Thailand, found CPHEU caregivers reporting higher levels of depression (using the Patient Health Questionnaire (PHQ) 9) compared to CPHIV caregivers; [122] sample sizes were very small and included younger children than our cohort (12-56 months old). The other, a Kenyan-based study, found a similar trend with measures of emotional well-being, a measure strongly associated with depression [130] among caregivers of 12-17-year-olds [89]. In contrast to these findings, a study including participants from four sub-Saharan countries found no difference in caregiver depression symptoms across any of the perinatal HIV exposure groups [119]. However, associations between levels of depression (high vs. low) and child executive functioning were observed across perinatal exposure groups (the primary objective of the study), signaling caregiver depression as an important factor in the caregiving environment for HIV-affected children [119]. Another well-powered study based in South Africa and Malawi (n=989) reported higher levels of depression

symptoms among CPHIV compared to CHUU caregivers, but a CPHEU comparison group was not included [120-122]. Taken together, there is a limited literature that has investigated perinatal HIV exposure with caregiver depression, with our findings corroborated by some studies and not others. Many of these studies were conducted in the post-cART era and better reflect the current environment for HIV-affected families. Nonetheless, our findings warrant replication and continued investigation.

Another important finding from our study was that the difference in caregiver depression symptoms across perinatal HIV exposure groups was minimally attenuated following adjustment for covariates. This represents a major contribution of this work, given that findings summarized in the previous paragraph were derived from studies focused on other health outcomes and were unadjusted. Our results suggest that basic demographics, socioeconomic factors, and the caregiver's lifetime history of trauma do not account for the higher levels of depression symptoms observed among CPHEU caregivers. One thought is perhaps CPHEU caregivers have unmet mental health needs and are not receiving mental health interventions. In Uganda, CPHIV are placed into long-term clinical follow-up when serostatus is confirmed. It is therefore possible that their caregivers maintain a more active connection with health services compared to CPHEU caregivers. Another possibility is that CPHEU exhibit different behavioral profiles than CPHIV or CHUU, and that, in turn, impacts parental well-being or stress [78, 122]. Irrespective of the explanation, the higher levels of depression symptoms among CPHEU caregivers should be better understood in order to reduce the burden on caregiver mental health within HIV-endemic areas.

We also found that caregiver social support acted as an effect modifier between perinatal HIV exposure and caregiver depression symptoms. Specifically, CPHEU caregivers reported

higher levels of depression when they reported lower levels of social support; however, no group differences were observed when caregivers reported higher levels of social support. This suggests that social support may help buffer CPHEU caregivers from depression symptoms associated with their child's exposure status. This explanation is substantiated, in part, by a recent study from South Africa where social support acted as a buffer against the negative effects of caregiver illness-related stressors on depression symptoms. However, this interaction was not significant for caregiver HIV/AIDS illnesses, only non-HIV related illnesses [69]. That said, this study does establish the importance of community support of the caregiver when dealing with their own health issues on top of their caregiving burden.

We also investigated whether our findings changed in a meaningful way when the sample was limited to the biological mother rather than another family member or adult. This allowed us to evaluate whether the mother's experience with her own HIV illness affected any findings observed. Our results were unchanged, though the difference in mean depression symptoms between CPHEU and CPHIV caregivers increased, driven by higher depression symptoms among CPHEU caregivers. This might be because individuals other than the mother who care for HIV-exposed children report lower depression symptoms compared to biological mothers and lowered mean depression symptom levels in the full analytic sample. As shown in Table 1.1, CPHEU and CPHIV were more likely to lose their biological mother relative to CHUU and were being cared for by someone else.

Limitations

While our study provides new insight into the association between perinatal HIV exposure and caregiver depression, we acknowledge several limitations. Due to the cross-sectional nature of our analysis, we were unable to establish temporality between child HIV

exposure and caregiver depression symptoms. This prevents the interpretation of directionality or causality within our study. As discussed in this literature, there may be a bi-directional effect of caregiver mental health on children (and vice versa). Additionally, the CHUU group was recruited from the Kawaala Health Center while the children were accessing treatment for other medical conditions. This sampling approach might have selected children with underlying health conditions that resulted in additional strain for caregivers. As previously stated, caring for chronically ill children is associated with higher caregiver depression [88], and including caregivers to children who are receiving clinical evaluation or treatment might underestimate differences that could have been revealed if a non-clinic-based sample was available. Another limitation is that depression symptoms may not correspond to a clinical diagnosis of major depressive disorder. As a result, it is unclear whether our findings would generalize to this latter diagnosis. Social desirability biases could also lead caregivers to underreport their depression symptoms, though this pressure could not explain our findings if they operated equally across the HIV exposure groups. However, we acknowledge that due to this bias we may have captured less of the caregiver burden than what was actually experienced.

Strengths

Despite these limitations, our study included children from 3 different HIV exposure status groups with detailed information regarding the caregiver's health and resources. This allowed for a more comprehensive set of comparisons within the study. Another strength was that perinatal HIV exposure status was assessed for all children at enrollment and was cross-referenced with medical records documenting perinatal HIV exposure statuses; this reduces the likelihood of misclassification of children across exposure groups. Additionally, we recruited a limited age range of children, allowing for a focused look at one particular phase of child

development without various stages of behavioral maturation complicating the findings. Unlike previous research, we evaluated potential effect modifiers in the association between perinatal HIV exposure and caregiver depression symptoms. This contributes valuable information when identifying potential targets for intervention strategies. Finally, the HIV exposed and/or infected children in our study could represent the "new normal," with both groups of HIV-affected children relatively healthy compared to previous generations of HIV-affected youth. Our study provides a foundation that can inform future work examining the interrelationship of child health and behavioral factors and their caregiver's mental health over time.

Additional future directions include investigating what drives the difference in caregiver depression symptoms between CPHEU and CPHIV caregivers. Moreover, this information would be beneficial in developing interventions targeting the mental health of CPHEU caregivers to reduce the excess depression burden within this population. Also, future studies could investigate if elevated depression symptoms we observed are clinically significant and would lead to an increase in major depressive disorder diagnoses within this population.

CHAPTER 3 (Aims 2 & 3): PERINATAL HIV EXPOSURE AND INFECTION AND CHILD EXECUTIVE FUNCTION

3.1 Introduction

An estimated 75.7 million people have been infected by the human immunodeficiency virus (HIV) since the beginning of the pandemic in the 1980s [1]. While mortality from HIV has been drastically reduced due to the availability of antiretrovirals, government testing, and treatment protocols, new infections are still alarmingly high and the burden of chronic infection remains significant. In 2020, there were 38 million people worldwide living with HIV, 1.7 million of whom were newly infected [1]. Geographically, this burden has been felt predominantly in sub-Saharan Africa, with this region accounting for 59% of new infections [3]. Of the new infections documented in 2020, approximately 160,000 were children 0-5 years old [131]. Women and children are particularly vulnerable to HIV infection due to transmission through sexual contact or by mother-to-child transmission (MTCT) during childbirth.

With access to combination antiretroviral therapy (cART), survival following perinatal HIV infection is possible and perinatal infection can be avoided where treatment is available. However, access to and distribution of cART is uneven where HIV is endemic, and it is important to characterize the physical and cognitive health trajectories to children who were infected or otherwise exposed to HIV perinatally. To this end, factors that are associated with functional outcomes in children entering school represent a particularly important area of research for HIV-affected youths. This includes executive functioning (EF), a set of distinct but overlapping cognitive processes that allow an individual to control and coordinate their thoughts, actions, and behaviors. This aspect of cognitive development is of particular importance to HIV-exposed children due to its association with functional survival behaviors such as adherence to

drug regimes, goal-setting, and risk of HIV transmission [113, 114]. Moreover, specific indices within EF, such as cognitive control, are considered key predictors of success in school [115]. In addition, executive functions (and the brain networks that support them) have protracted developmental trajectories that may be amenable to intervention, thus rendering the understanding of EF outcomes related to HIV exposure early in life important to investigate [132, 133].

Given these considerations, EF in children following perinatal HIV exposure has been investigated for years [92, 111, 134]. However, results to date are mixed. This may be due to the lack of a comparison group that is HIV-exposed but uninfected (CPHEU), wide age ranges among study participants, and variation in EF assessment protocols [92, 113]. For example, most studies to date compare children who were perinatally exposed to HIV (CPHIV) and infected to a group of children who were both unexposed and uninfected (CHUU). In these circumstances, it is unclear whether findings can be attributed to HIV infection itself or correlates of exposure to infection. Compounding this problem is that study sample sizes are often small (particularly for the CPHEU group, if present), and this leads to variably powered analyses across studies. In addition, studies to date also often include wide age ranges for participants. This has the potential to obscure findings specific to a given age due to the protracted developmental trajectory of EF that stems from infancy through the second decade of life [135]. Findings in the literature also vary based on the scope of EF assessment. For example, in a systematic review published in 2009, the majority of studies reported a detrimental effect of perinatal HIV infection on neurocognitive functioning; however, meta-analyses were not performed due in part to the non-comparability of EF measures [92]. Another review yielded similar conclusions, reporting that perinatal HIV infection was associated with lower EF performance, but only among some

subdomains (verbal and visuospatial working memory) and not with global EF [113]. These findings underscore the importance of multidimensional EF assessment in projects that address the impacts of HIV exposure or infection.

In addition to these considerations, few studies have addressed caregiver mental health (e.g., depression symptoms) as a covariate, despite its association with their own HIV status as well as child neurocognitive functioning [94, 101, 105]. Furthermore, the sex of the child is an additional covariate to consider, given that from infancy, males experience more HIV-related complications compared to their female counterparts; in addition, sex differences are also observed in some EF subscales with the direction of the difference dependent upon the specific subscale under investigation [136]. The Socioeconomic Status (SES) of the family is also an important factor to consider due to its role historically as a driver for women to adopt unsafe behaviors that can lead to an increased risk of HIV infection, particularly in sub-Saharan Africa [137, 138]. Family SES and its association with child EF is also well-documented throughout developmental literature [139-141], but research evaluating HIV exposure does not often include group caregivers' relationship to the child, limiting data available to describe confounders between perinatal HIV exposure and EF.

It is similarly unclear whether factors that modify the impact of HIV exposure on morbidity would also modify the association between perinatal HIV exposure and EF. Two factors receiving much attention to this end include the child's biological sex as well as caregiver depression symptoms. For instance, only 8% of studies in a systematic review performed any type of analysis or discussed sex differences in associations between perinatal HIV exposure and EF [92]. Those that did showed no difference between males and females, but most were underpowered to evaluate group differences; all but one was based in North America [92]. In

addition, caregiver depression symptoms are associated with higher EF problems in their children [71, 72, 142], including among children and caregivers affected by HIV [71, 121]. Understanding whether modifiers are instrumental in the association between perinatal HIV exposure and EF could help higher-risk groups of children who could benefit from monitoring and/or intervention.

Our goal is to address these knowledge gaps by evaluating EF in a sample of Ugandan children, a population disproportionately burdened by perinatal HIV exposure. To do this, we will evaluate whether EF (including its multiple dimensions) differs among groups of children defined by their perinatal HIV exposure and infection status at EF assessment. We will also consider how the contribution of covariates not often included or understood in previous work affect the association between perinatal HIV exposure and EF (i.e., household demographics and caregiver psychological functioning) (Aim 2). As part of this process, we will investigate whether any findings observed are moderated by child sex or caregiver depression symptoms (Aim 3).

3.2 Methods

Study Population & Design

We performed a cross-sectional analysis using data from the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) study. The sample includes Ugandan children (6-10 years old) and their primary caregivers enrolled from the Kawaala Health Center (KHC) in the Kawempe Division of Kampala, Uganda. Approximately equal numbers of children with three HIV exposure statuses were enrolled in the study between 3/15/17 and 9/15/18: children with perinatally acquired HIV infection (CPHIV, n = 102), children with perinatal HIV exposure, but no infection at enrollment (CPHEU, n = 101), and children with no perinatal HIV exposure

and no infection at enrollment (CHUU, n = 103). We included children with an available caregiver report of EF in our analysis (n=4 missing reports per HIV exposure group). Multiple children per household were eligible for participation. The study protocol was approved by the research ethics review committees of Michigan State University (IRB Protocol#: 16-828), Makerere University College of Health Sciences, School of Medicine (Protocol REC REF# 2017-017), and the Uganda National Council for Science and Technology (Protocol #: SS 4378). All caregivers gave written informed consent and all children provided assent for study participation.

Measures

Perinatal HIV exposure and infection: Perinatal HIV exposure was ascertained from and verified through KHC medical records. For the CPHEU and CPHIV groups, serostatus was monitored through 18 months of age using DNA-polymerase chain reaction tests. Serostatus at enrollment was assessed using HIV-rapid diagnostic testing.

Executive Functioning (age 6-10): Child executive functioning (EF) was assessed by caregiver report using the Behavior Rating Inventory of Executive Function (BRIEF) at enrollment. The BRIEF is a questionnaire developed for parents and teachers to evaluate different aspects of executive functioning in school aged children. A trained research assistant at the KCHC administered the BRIEF to parents in trailers separate from the general patient area [112]. The original 86-item instrument was shortened to 24 questions, translated, and culturally adapted for use in this study setting [112]. The BRIEF evaluates eight subscales of EF that in turn form 3 EF domains. The inhibit, shift, and emotional control subscales combine to create the Behavioral Regulation Index (BRI) and initiation scale, working memory, plan/organize, organization of materials, and monitor subscale create the Metacognition Index (MCI) [143]. The

BRI and MCI then combine to form an overall Global Executive Composite (GEC) [143]. Age- and sex- standardized z-scores were derived for all BRIEF measures using the CHUU group as the referent [112]. We modeled all BRIEF scores as continuous variables.

Covariates: We considered factors that the literature suggests are associated with perinatal HIV exposure and EF. This included socio-demographic information about the primary caregiver, such as self-reported education level (no education or primary level not completed, primary level completed, or above primary), employment status (no income, informal income, unskilled employment, or driver, skilled worker or professional), and wealth (sum of material possessions: electricity, running water, refrigerator, television, and car) at enrollment. We also considered caregiver depression symptoms (Hopkins Symptom Checklist; normal $\leq$ X 1.75, high > 1.75 [144], both of which were assessed via interview at enrollment [124]. Information about the biological mother (deceased or living) was collected at enrollment through medical records or by caregiver report. Child health indicators at enrollment such as ferritin level (above or below 15 ng/mL [127]) and hemoglobin level (above or below 115 g/L [128]) also were collected as part of a series of laboratory tests from blood drawn at enrollment for child participants. Ferritin and anemia levels were used to characterize the health of the children in the study but were not included in adjusted models due to their potential to operate as mediators. Intrauterine ART exposure information for the child was also collected via interview at enrollment to better characterize the sample.

Analysis Plan

We began by describing the analytic sample according to caregiver and child characteristics at enrollment. We then examined whether the study covariates varied across the perinatal HIV exposure groups. We evaluated the distribution of the GEC as well as the BRI and

MCI subscales for normality; no transformations were needed. We then performed unadjusted analyses for each of the 3 domains and 8 subscales of EF. We used random effects general linear models to account for the presence of multiple children per household included in the study sample. We employed an alpha of 0.05 (two-tailed).

We then repeated these analyses following adjustment for the covariates described above. The first adjusted model included household characteristics (biological mother mortality status, caregiver education, caregiver employment, and wealth score), and the second adjusted model retained these covariates and added caregiver depression symptoms.

We then evaluated whether any findings observed were modified by child sex and caregiver depressive symptoms. We selected these factors based on literature review that identified their importance as modifiers or potential modifiers of the association between perinatal HIV exposure and EF [71, 92, 119]. A cut point of p=0.1 (two-tailed) was used to evaluate statistical significance due to the exploratory nature of this analysis. All analyses were completed using SAS software 9.4 (Cary, NC).

3.3 Results

Caregivers included in the analytic sample were 92% female between the ages of 19 and 67 years at enrollment (Table 2.1). Approximately one-third of households had two or more children who participated in this study. The average caregiver depression score was a 1.81 (on a scale from 1-5), and the average perceived stress score was 21.7 (on a scale from 0-40). A majority of caregivers reported having no income or informal income, while 41% reported having formal employment (skilled or professional). Caregiver education ranged from no education or primary completed (57%) to above primary (42%). Only 9% of children included in

the study were categorized as anemic due to hemoglobin (Hb) levels below 115g/L at enrollment, and 2% had a ferritin level below 15 ng/mL.

When comparing covariates across child HIV exposure groups, we observed a few key differences (Table 2.2). The CPHIV group experienced the death of the biological mother more frequently (23%) compared to the CPHEU (8%) and CHUU (3%) groups, but experienced lower levels of caregiver depression symptoms relative to children from the other groups. Socio-demographic factors also differed across HIV exposure groups, with the CPHEU caregivers reporting lower levels of wealth and higher rates of informal income and unskilled employment compared to CPHIV and CHUU caregivers.

In our unadjusted analyses, perinatal HIV exposure was not associated with the GEC and MCI scores (Table 2.3). However, for the BRI, the CPHIV group had lower levels of problems relative to the CHUU and CPHEU groups (*B*= -0.40, 95% CI -0.77, -0.03, *B*=-0.40, 95%CI -0.76, -0.02 respectively). This finding was driven by lower levels of problems on the shift subscale (*B*=-0.40, 95% CI -0.77, -0.02, *B*=-0.38, 95%CI -0.76, -0.01). Adjustment for household socio-demographic factors did not affect comparisons for the BRI domain and shift subscale between the CPHIV and CHUU groups (*B*=-0.44, 95%CI -0.85, -0.04, *B*=-0.48, 95% CI -0.89, -0.07 respectively), but comparisons with the CPHEU group were attenuated to trend levels (*B*=-0.38, 95%CI -0.78, 0.02, *B*=-0.39, 95%CI -0.80, 0.10 respectively). All remaining findings were attenuated to non-significance following adjustment for depressive symptoms. We also observed that the CHUU group had: 1) lower functioning on the plan/organize subscale than the CPHEU group, and 2) lower functioning on the monitor subscale relative to the CPHIV group. Only the latter remained significant in the fully adjusted model (*B*=0.029, 95%CI 0.05, 0.78).

We observed that the child's sex modified the findings described above. Specifically, BRI scores differed between the CHUU and CPHIV groups among males (Figure 2.1) (*B*=-0.84, 95%CI -1.41, -0.27), but not among females (Figure 2.2) (*B*=0.06, 95%CI -0.46, 0.59). This same pattern of findings was observed with the shift and working memory subscales.

Caregiver depression symptoms also modified the association between HIV status and the shift subscale of child EF. For caregivers with high levels of caregiver depressive symptoms (Figure 2.3), the CPHEU group tended to have higher levels of MCI problems compared to the CHUU group (*B*=0.49, 95%CI -0.16, 1.15). Among caregivers with lower levels of depression symptoms (Figure 2.4), the CPHIV group exhibited lower levels of BRI problems compared to the CHUU group, also trending toward significance (*B*=-0.47, 95%CI -0.98, 0.04).

Table 2.1 Caregiver and child characteristics in the CIPHER dataset and analytic sample (EF z scores)

	CIPHER Study N = 306		Analytic Sample N = 294		P- value
	N Mean	(%) SE	N Mean	(%) SE	
Caregiver Characteristics					
Caregiver Sex					
Female	279	(91)	270	(92)	0.691
Male	27	(9)	24	(8)	
Caregiver Education					
No education or primary education not completed	116	(39)	110	(38)	0.931
Primary education completed	59	(20)	56	(19)	
Above primary	125	(42)	124	(42)	
Caregiver Employment					
No income	92	(33)	91	(33)	0.974
Informal income	77	(27)	72	(26)	
Unskilled employment	59	(21)	59	(22)	
Driver, skilled worker, or professional	54	(19)	51	(19)	
Wealth score	1.49	0.07	1.50	0.07	0.923
Caregiver Depression Score	1.81	0.03	1.81	0.03	0.976
Child Characteristics					
Child HIV Exposure					
$CPHIV_1$	102	(33)	99	(34)	0.990
$CHEU_2$	101	(33)	97	(33)	
$CHUU_3$	103	(34)	98	(33)	
Child sex					
Female	154	(50)	150	(51)	0.813
Male	152	(50)	144	(49)	
Child ferritin level					
< 15 ng/mL	8	(3)	7	(2)	0.799
≥ 15 ng/mL	286	(97)	276	(98)	
Child Hemoglobin (Hb) level					
<115 g/L (anemic for 5-11yr. olds)	25	(8)	25	(9)	0.845
≥115 g/L (normal)	273	(92)	262	(91)	
Early ART exposure					
Any in utero ART	99	(32)	97	(33)	0.112
Not exposed in utero	103	(34)	98	(33)	
No early ART	104	(34)	99	(34)	
Child Executive Functioning Score					
Global Executive Composite	-0.09	0.07	-0.09	0.07	1.0
Behavioral Regulation Index	-0.13	0.08	-0.13	0.08	1.0
Metacognition Index	0.08	0.09	0.08	0.09	1.0

1 HIV Unexposed, Uninfected
2 Perinatal HIV Exposed, Uninfected
3 Perinatal HIV Exposed, Infected

* $p < 0.05$

Missing data CIPHER sample: Caregiver education (n=4), caregiver employment (n=24), wealth score (n=9), caregiver depression (n=7), Ferritin (n=12), Hemoglobin (n=8), GEC (n=12), BRI (n=12), MCI (n=12)

Missing data analytic sample: Caregiver education (n=4), caregiver employment (n=21), wealth score (n=5), caregiver depression (n=10), child ferritin (n=11), child hemoglobin (n=7)

Table 2.2 Child perinatal HIV exposure and caregiver and child covariates in analytic sample (n=294)

	CHUU[1] N = 99		CPHEU[2] N = 97		CPHIV[3] N = 98		P-value
	N Mean	(%) SE	N Mean	(%) SE	N Mean	(%) SE	
Caregiver Characteristics (at enrollment)							
Caregiver sex							
Female	89	(90)	91	(94)	90	(92)	0.606
Male	10	(10)	6	(6)	8	(8)	
Caregiver Education							
No education or primary education not completed	28	(29)	45	(47)	37	(38)	0.057
Primary education completed	21	(21)	20	(21)	15	(16)	
Above primary	49	(50)	31	(32)	44	(46)	
Caregiver Employment							
No income	32	(37)	27	(30)	32	(34)	**0.014***
Informal income	18	(21)	32	(35)	22	(23)	
Unskilled employment	15	(17)	25	(27)	19	(20)	
Driver, skilled work or professional worker	22	(25)	7	(8)	22	(23)	
Wealth Score (Range 0-5)	1.73	0.12	1.30	0.17	1.46	0.17	**0.041***
Caregiver Depression Score	1.82	0.05	1.92	0.07	1.67	0.07	**0.003***
Child Health Characteristics (at enrollment)							
Child ferritin level							
< 15 ng/mL	4	(4)	2	(2)	1	(1)	0.356
≥ 15 ng/mL	90	(96)	93	(98)	93	(99)	
Child Hemoglobin (Hb) level							
<115 g/L (anemic for 5-11 yr. olds)	5	(5)	7	(7)	13	(13)	0.127
≥ g/L (normal)	89	(95)	88	(93)	85	(87)	
Early ART exposure							
Any in utero ART	0	(0)	54	(56)	43	(43)	**<0.001***
Not exposed in utero	0	(0)	42	(44)	56	(57)	
No HIV to treat	104	(100)	0	(0)	0	(0)	

[1] HIV Unexposed, Uninfected
[2] Perinatal HIV Exposed, Uninfected
[3] Perinatal HIV Exposed, Infected

* $p < 0.05$

Missing data: Caregiver education (n=4), caregiver employment (n=21), wealth score (n=5), caregiver depression (n=10), child ferritin (n=11), child hemoglobin (n=7)

Table 2.3 Unadjusted and adjusted associations of perinatal HIV exposure or infection with parent-reported EF (z scores) in Ugandan children (age 6-10 years)

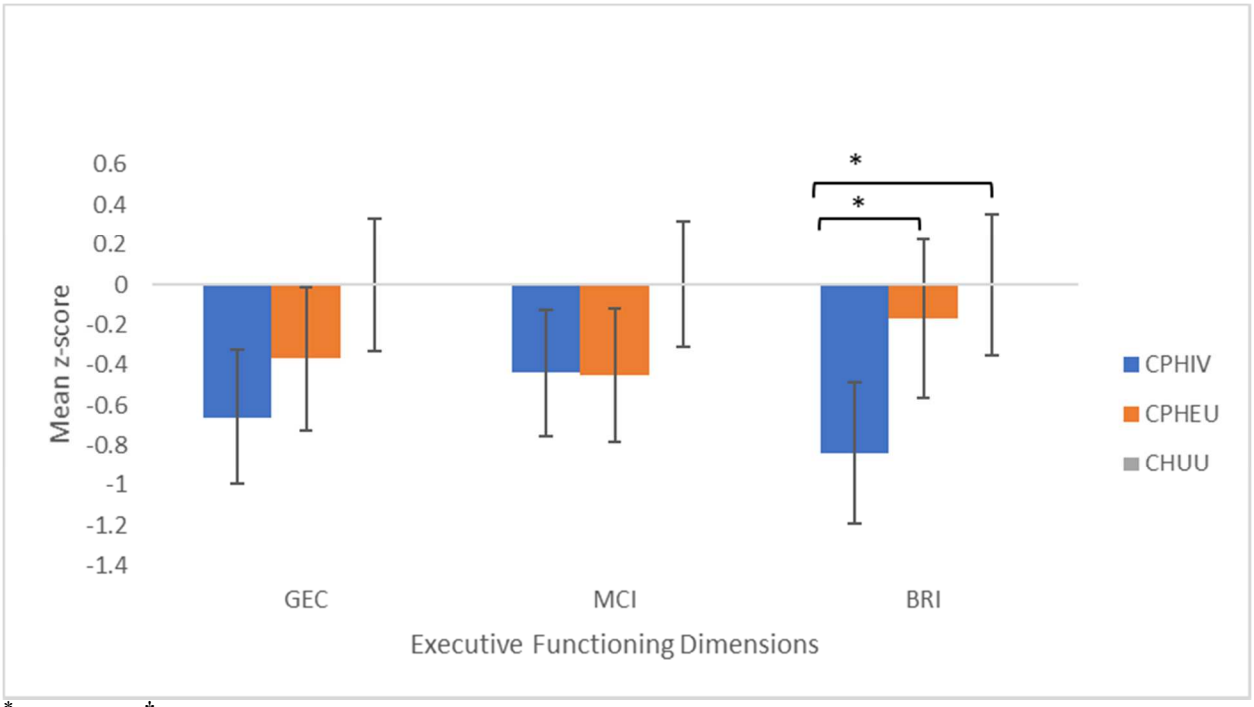
	CHUU[1]		CPHEU[2]		CPHIV[3]		CHUU[1] vs CPHIV[3]	CHUU[1] vs CPHEU[2]	CPHEU[2] vs CPHIV[3]
	Mean	(SE)	Mean	(SE)	Mean	(SE)	P-value	P- value	P- value
	Max N = 98		Max N = 97		Max N = 99		3 vs 1	3 vs 2	2 vs 1
Global Executive Composite (GEC)									
Model 1: Unadjusted	0	(0.12)	-0.04	(0.12)	-0.23	(0.12)	0.195	0.825	0.282
Model 2: Household characteristics[4]	0.26	(0.18)	0.11	(0.17)	-0.07	(0.15)	0.078†	0.425	0.317
Model 3: Model 2 + Caregiver depression	0.25	(0.17)	0.01	(0.16)	0.02	(0.14)	0.189	0.167	0.955
Behavior Regulation Index (BRI)									
Model 1: Unadjusted	-0.001	(0.13)	-0.01	(0.13)	-0.40	(0.13)	0.037*	0.969	0.040*
Model 2: Household characteristics[4]	0.09	(0.20)	0.03	(0.19)	-0.36	(0.16)	0.033*	0.769	0.059*
Model 3: Model 2 + Caregiver depression	0.07	(0.18)	-0.10	(0.18)	-0.26	(0.15)	0.091†	0.385	0.399
Metacognition Index (MCI)									
Model 1: Unadjusted	0.002	(0.16)	0.23	(0.16)	0.03	(0.16)	0.901	0.319	0.381
Model 2: Household characteristics[4]	0.35	(0.24)	0.44	(0.23)	0.24	(0.19)	0.655	0.732	0.424
Model 3: Model 2 + Caregiver depression	0.33	(0.24)	0.32	(0.23)	0.32	(0.19)	0.958	0.968	0.989
BRI Subscales									
Inhibit									
Model 1: Unadjusted	0	(0.12)	0.07	(0.12)	-0.05	(0.12)	0.770	0.694	0.494
Model 2: Household characteristics[4]	0.23	(0.17)	0.22	(0.16)	0.06	(0.14)	0.325	0.928	0.364
Model 3: Model 2 + Caregiver depression	0.22	(0.17)	0.15	(0.16)	0.11	(0.14)	0.528	0.712	0.792
Shift									
Model 1: Unadjusted	-0.01	(0.14)	-0.02	(0.14)	-0.40	(0.13)	0.039*	0.951	0.045*
Model 2: Household characteristics[4]	0.08	(0.20)	-0.003	(0.19)	-0.40	(0.16)	0.022*	0.669	0.056*
Model 3: Model 2 + Caregiver depression	0.06	(0.19)	-0.10	(0.19)	-0.34	(0.16)	0.054†	0.440	0.236
Emotional Control									
Model 1: Unadjusted	-0.01	(0.11)	0.08	(0.11)	-0.11	(0.10)	0.506	0.565	0.205
Model 2: Household characteristics[4]	0.02	(0.16)	0.03	(0.15)	-0.09	(0.12)	0.481	0.961	0.441
Model 3: Model 2 + Caregiver depression	0.01	(0.15)	-0.06	(0.14)	-0.03	(0.12)	0.802	0.627	0.806
MCI Subscales									
Initiation									
Model 1: Unadjusted	0	(0.13)	0.13	(0.13)	-0.12	(0.13)	0.495	0.482	0.168
Model 2: Household characteristics[4]	0.27	(0.19)	0.36	(0.18)	0.08	(0.16)	0.343	0.639	0.155
Model 3: Model 2 + Caregiver depression	0.27	(0.19)	0.27	(0.18)	0.15	(0.15)	0.562	0.990	0.554
Working Memory									
Model 1: Unadjusted	-0.02	(0.13)	-0.12	(0.14)	-0.20	(0.13)	0.368	0.619	0.691
Model 2: Household characteristics[4]	0.27	(0.21)	-0.004	(0.20)	-0.06	(0.17)	0.122†	0.204	0.780
Model 3: Model 2 + Caregiver depression	0.24	(0.20)	-0.11	(0.19)	0.01	(0.16)	0.269	0.089†	0.537
Plan/ Organize									
Model 1: Unadjusted	-0.01	(0.18)	0.54	(0.18)	0.16	(0.18)	0.515	0.037*	0.141†
Model 2: Household characteristics[4]	040	(0.28)	0.76	(0.26)	0.39	(0.22)	0.968	0.225	0.205
Model 3: Model 2 + Caregiver depression	0.39	(0.27)	0.67	(0.26)	0.46	(0.22)	0.800	0.326	0.466
Materials/ Organize									
Model 1: Unadjusted	-0.03	(0.13)	0.11	(0.13)	-0.08	(0.13)	0.763	0.444	0.287
Model 2: Household characteristics[4]	0.32	(0.20)	0.32	(0.19)	0.11	(0.16)	0.319	0.978	0.298
Model 3: Model 2 + Caregiver depression	0.31	(0.20)	0.27	(0.19)	0.15	(0.16)	0.436	0.819	0.581
Monitor									
Model 1: Unadjusted	-0.02	(0.11)	-0.08	(0.11)	0.17	(0.11)	0.245	0.690	0.123†
Model 2: Household characteristics[4]	0.16	(0.17)	-0.02	(0.16)	0.27	(0.14)	0.539	0.298	0.098†
Model 3: Model 2 + Caregiver depression	0.17	(0.17)	-0.07	(0.16)	0.31	(0.14)	0.423	0.183	0.037*

[1] Children HIV Unexposed, Uninfected reference category
[2] Children Perinatal HIV Exposed, Uninfected
[3] Children Perinatal HIV Exposed, Infected

[4] Household characteristics= biological mother alive, caregiver education, caregiver employment and wealth score

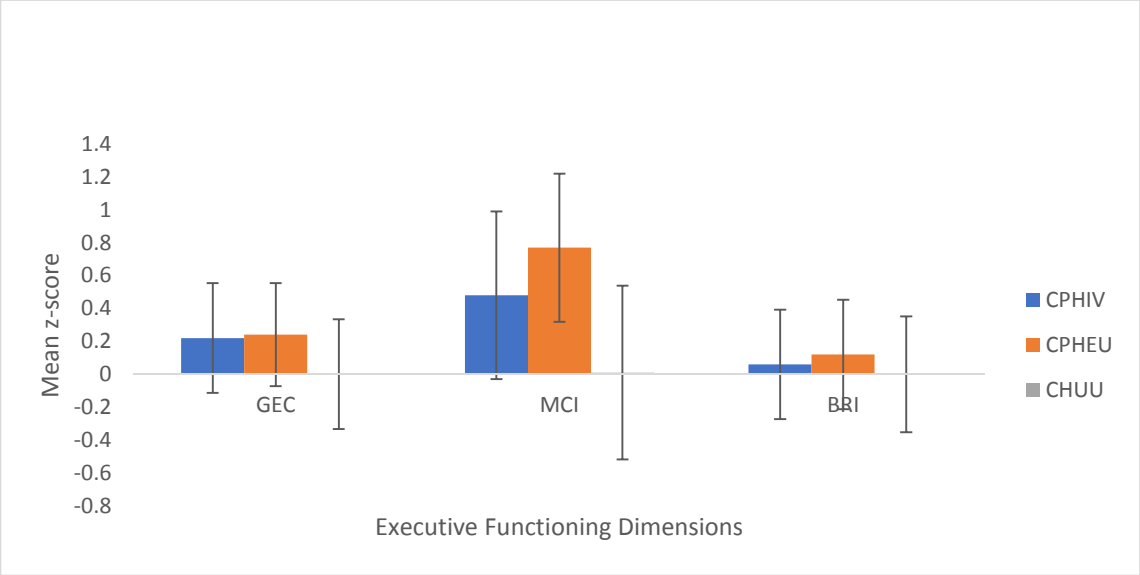
* $p < 0.05$; † $p < 0.10$

Figure 2.1: Executive functioning scores by perinatal HIV exposure status in males



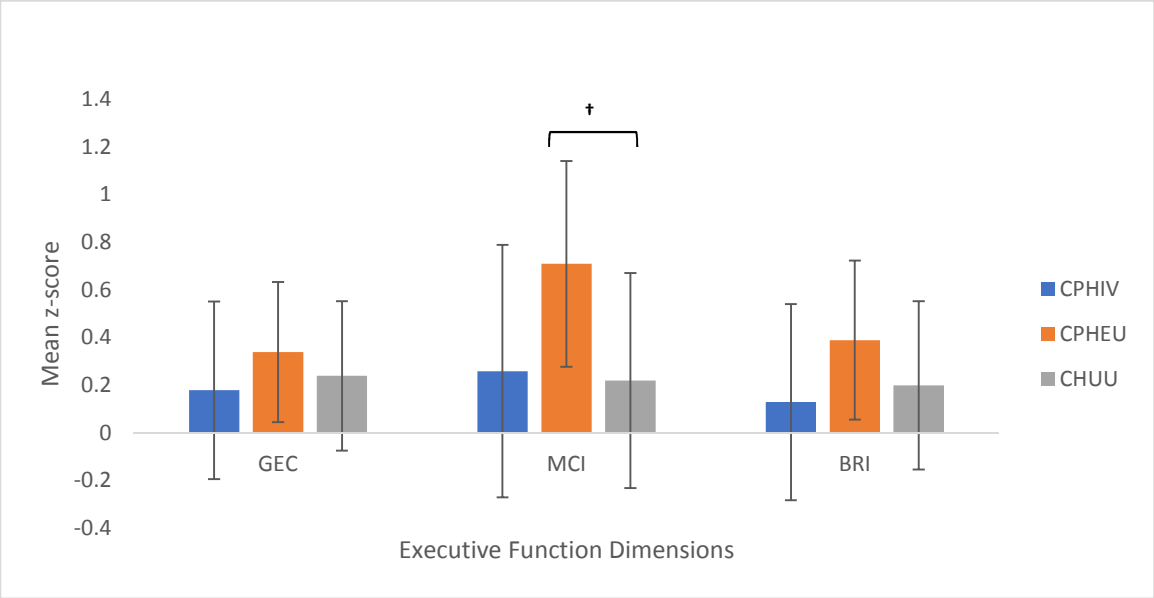
* $p < 0.05$; † $p < 0.10$

Figure 2.2: Executive functioning scores by perinatal HIV exposure status in females



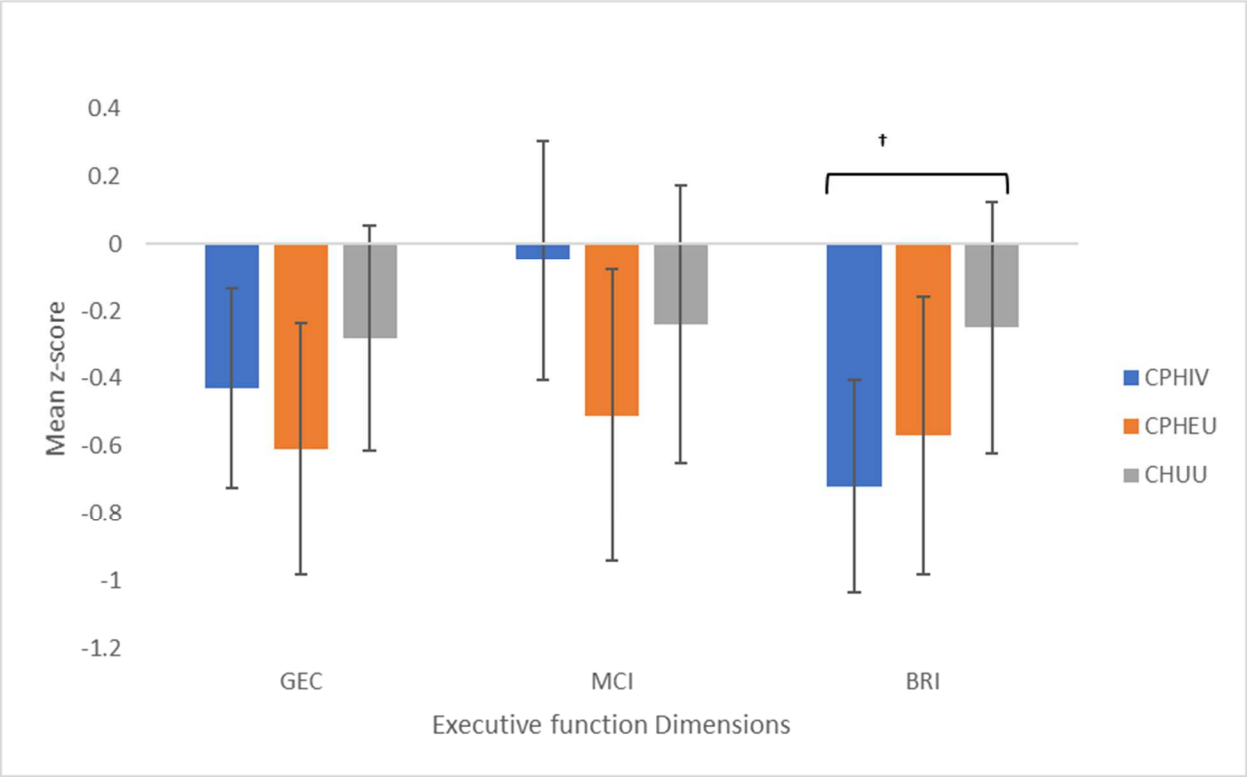
* $p < 0.05$; † $p < 0.10$

Figure 2.3: Executive functioning scores by EF dimension in children with high depressive symptom caregivers



* $p < 0.05$; † $p < 0.10$

Figure 2.4: Executive functioning scores by EF dimension in children with low depressive symptom caregivers



* $p < 0.05$; † $p < 0.10$

3.4 Discussion

We investigated whether perinatal HIV exposure was associated with caregiver-reported EF among children in sub-Saharan Africa, a population disproportionately affected by perinatal exposure and infection. As part of this process, we adjusted for covariates not often included in previous research (e.g., caregiver mental health; child health indices) and examined whether caregiver depression symptoms or child sex modified any associations observed. Unlike many studies on the topic, this sample included a full complement of comparison groups in an attempt to disentangle impacts linked to perinatal HIV exposure vs. infection.

We found no association between perinatal HIV exposure and child EF when using the BRIEF global composite score. This differs from a 2009 systematic review reporting that perinatal HIV exposure and infection were associated with lower levels of cognitive functioning [92]. A more recent meta-analysis focused exclusively on EF and included two sub-Saharan African-based studies; both found that CPHIV had higher, though non-significant, EF problems compared to CPHEU and CHUU [92, 112, 113, 145]. These findings may differ from ours due to cohort-specific differences in HIV testing and treatment among pregnant women in children. During the years in which our cohort participants were born, significant improvements were achieved in the reduction of perinatal mother-to-child transmission (PMTCT) within middle and lower-income countries, with 45% of HIV-infected pregnant women in 2008 receiving at least some treatment, up from 10% in 2004 [146]. Testing of pregnant women giving birth in sub-Saharan African was also rapidly improving, from 6% in 2004 to 28% in 2008 [146]. Early intervention is critical to improving short- and long-term health outcomes among children with HIV [147, 148], and this may contribute to the null finding for the global EF score observed in our study, despite having larger sample sizes than seen in previous work.

However, we did corroborate a pattern of limited associations between perinatal HIV exposure and individual EF dimensions. This included lower levels of problems on the BRI for the CPHIV group compared to the CPHEU and CHUU groups in unadjusted models. Effect sizes were small (Cohen's d = 0.3), with the shift subscale driving these differences. It is not immediately clear why the CPHIV group would have the lowest level of EF difficulties. One reason may be that in Uganda, CPHIV children are enrolled and connected to clinical care for life once HIV status is confirmed in order to continue to monitor their health status. It is also possible that because caregivers are aware of the child's serostatus, their ratings of EF were differentially impacted across the perinatal HIV exposure groups. However, whether these differential impacts would result in higher scores for CPHIV compared to the other groups requires further examination. The use of performance-based EF tasks may be helpful in this regard. Finally, the specific configuration of findings we observed may be due to chance given the large number of comparisons we performed without correction. That said, the CPHIV group was consistently found to have fewer problems across EF dimensions which may somewhat mitigate this concern.

Another important finding from our study was that any associations we observed were attenuated to non-significance following the inclusion of caregiver depression symptoms in the fully adjusted models. This may suggest that caregiver mental health may be a potential confounder or mediator of the association of HIV exposure and child EF. Indeed, one longitudinal study in sub-Saharan Africa found that children whose caregivers reported higher levels of depression symptoms had higher levels of EF problems compared to children whose caregivers reported lower levels of symptoms regardless of HIV status [145]. However, another study reported that although there was no difference between CPHIV and CPHEU in behavioral

or cognitive measures, higher caregiver depression scores were related to higher caregiver-reported problems with EF among CHUU, but not CPHEU [71]. This suggests that HIV status of the child may operate as a moderator between caregiver depression symptoms and EF. These studies, combined with our findings, highlight the importance of considering caregiver mental health when evaluating child EF within the context of HIV infection.

That said, maternal depression symptoms may induce spurious associations between perinatal HIV exposure and some dimensions of EF by operating as a collider. Parenting a child with a chronic illness like HIV and living with HIV themselves increases the risk for poor mental health, particularly depression [88, 105, 149]. Additionally, while child behavior problems have been shown to negatively affect parental mental health, these studies have been predominately based in non-HIV-affected countries [71, 150, 151]. Nonetheless, better understanding that caregiver mental health has an important effect on child EF can inform future research that investigates how interventions aimed at caregiver psychological functioning may improve child EF for children with HIV. While this work is relatively new, there have been successful trials that improved child EF through caregiver training interventions in a similar cohort [152, 153]. In addition to caregiver depression symptoms, our study also showed evidence of effect modification by child's biological sex. Specifically, we found no association between perinatal HIV exposure and EF among females, but higher levels of EF problems among CPHEU males. If replicated in future work, findings such as these may help target at-risk subgroups of children who could benefit from interventions to improve EF, particularly during a time when the underlying neural structures are particularly plastic.

Limitations

While our study provides insight into the association between HIV infection and child EF, we acknowledge several limitations. For example, the CHUU group was recruited from the Kawaala Health Center while they were accessing treatment for other medical conditions. Although the EF measures were collected after the child had recovered, this sampling approach might have selected children with other underlying health issues that resulted in poorer scores. In addition, this cohort was born as HIV treatment and testing were evolving and thus represents diverse exposure to early ART. This is reflected in our study population, with some children born to HIV-positive mothers having no intrauterine ART exposure (44% of CPHEU and 57% of CPHIV) and others receiving exposure to combination treatment (56% of CPHEU and 43% of CPHIV). Due to the varied cART regimens present in the sample, we were unable to rigorously evaluate the impact of this factor on our findings. Our EF assessment also relied upon one modality (caregiver report), and using one proxy-reported EF measure may be insufficient to capture the complexity of the construct. However, unlike performance-based tests, the BRIEF attempts to measure the "real world" effects of EF problems and is thus considered to have better external validity [143, 154].

Strengths

Despite these limitations, our study included children from 3 different HIV exposure groups with a larger sample for each group than observed in previous studies. This allowed for a more comprehensive set of comparisons with additional power. Another strength was that perinatal HIV exposure status was assessed for all children at enrollment, which in combination with medical records documenting perinatal HIV exposure status, reduces the likelihood of misclassification of children across exposure groups. Additionally, we recruited children from a

limited age range, focusing on a time of life where EF has been linked to academic outcomes and may be responsive to intervention [132, 133]. This limited age range allows for a focused look at one particular phase of child development without the finding being complicated by the various stages of normal EF maturation. In addition, unlike previous studies, our analyses considered the primary caregiver's psychological functioning. This allowed us to better understand the contribution of the caregiver's mental health to our findings. Finally, as previously stated, this cohort of HIV exposed and/or infected children could represent the "new normal", having greater opportunities to be exposed to HIV treatment and thus increasing their chances of survival and decreasing potential sequelae than previously studied cohorts. Our study allowed us to observe how, moving forward, children perinatally exposed to HIV but also cART may function cognitively in middle childhood.

Future directions for this research include further investigation into the association of perinatal HIV exposure and child EF in the context of caregiver depression symptoms. This is particularly important given that HIV + women are found to report greater depression symptoms compared to than HIV- women, [155, 156] and that caregiver mental health is associated with child EF, particularly when EF is reported by a caregiver [71, 119]. Additionally, it will be imperative to investigate how our findings relate to outcomes linked to EF, such as academic achievement and behavioral problems. This would help establish the importance of EF as a potential intervention target to improve school readiness.

CHAPTER 4: DISCUSSION

The three aims presented in this dissertation explore how perinatal HIV infection and exposure can affect caregivers and school-age children. First, we found that perinatal HIV exposure status was associated with caregiver depression symptoms. Specifically, symptoms were higher among CPHEU compared to CPHIV and CHUU caregivers. We also observed that the support that caregivers perceive is an important modifier in this association and that at lower levels of social support, CPHEU caregivers report higher levels of depression than caregivers to CPHIV and CHUU. These findings were unaffected when the sample was limited to biological mothers, suggesting that the burdens associated with the caregiver's positive serostatus could not explain the findings. Second, although there were no associations between perinatal HIV exposure status and overall GEC through the BRIEF, we found that perinatal HIV exposure status was associated with individual EF dimensions, specifically behavioral regulation in children. There were lower levels of behavioral regulation reported by the caregivers of CPHIV compared to CPHEU and CHUU, even after adjustment for sociodemographic factors and caregiver mental health indicators. Third, within our cohort, child biological sex and caregiver depression symptoms appear to modify the association between perinatal HIV exposure group and behavioral regulation in children.

Although these findings are cross-sectional, they suggest that environments experienced by families affected by HIV are important to consider when evaluating key indicators of functional survival, such as caregiver mental health and child EF. Historically, we expect CPHIV and their caregivers to experience more negative consequences compared to the CPHEU and CHUU due to HIV infection and associated health care and psychological burdens [92, 112, 113, 145]. However, we found that CHUU and CPHEU and their caregivers experience more negative

outcomes than CPHIV. While not the first time that CPHEU groups have been observed experiencing poorer functional outcomes compared to CPHIV [122, 157], it is an intriguing finding because we cannot immediately explain this configuration of findings due to perinatal exposure to chronic viral infection. This prompts us to reexamine what might explain the group differences we observed, including potential mediators and effect modifiers.

Previous studies have identified high levels of depression in people living with HIV; however, the differences in outcomes between caregivers to CPHEU and CPHIV in our study cannot be explained by the mother's HIV status alone. Finding that social support modified the relationship between HIV exposure group and caregiver depression within our study signals that networks and support received by caregivers play an even larger role in maternal mental health apart from what they experience managing their own chronic health condition. One hypothesis for the difference between CPHIV and CPHEU caregiver depression symptoms may include unmeasured aspects of the larger environment (meso- and macro-systems). For example, Uganda has a national program that enrolls HIV+ children into follow-up monitoring and clinical care for life, directly linking the children and caregivers to healthcare providers. We are unaware of similar programs to support CPHEU caregivers, and perhaps this differential access to healthcare services contributes to the finding we observe here.

We also found that CPHEU themselves had more caregiver-reported executive functioning problems than CPHIV, again signaling that chronic infection may not be the most significant factor in how perinatal HIV exposure affects this outcome in children. Previous research on biomarkers in CPHEU has also found elevated inflammatory markers, fewer T-cells, and lower levels of maternal IgG transferred from their mother than CPHIV, [49] making responses to infections more difficult early in life and perhaps identifying an indirect pathway in

which HIV exposure in this group could contribute to negative functional outcomes differently than CPHIV. Additionally, our cohort was born as HIV treatment and testing protocols were evolving and represent diverse exposures to early ART. Recent studies have shown single-dose nevirapine together with two NRTIs (sdNVP) + zidovudine (ZDV) + lamivudine (3TC) regimens might be associated with greater behavioral and EF dysfunction in CPHEU compared to CPHEU who did not receive in utero/peripartum antiretrovirals [158]. Further investigating the impacts of prenatal antiretroviral exposure (frequency, dose, duration, and type of regimen) would be an excellent target for future research.

With CPHEU groups in our study having more caregiver-reported EF problems, this finding also raises the possibility that the higher levels of EF problems among CPHEU could be contributing to the higher levels of depression symptoms observed among their caregivers relative to the other perinatal HIV exposure groups. Indeed, maternal mental health and child behavior have been shown to influence each other [80, 81], and further exploring these relationships within an HIV context is important. That said, we did include maternal depression symptoms as a covariate in our Aim 2 analyses and found that findings attenuated to non-significance following adjustment for caregiver depressive symptoms. This raises the possibility that maternal depressive symptoms may contribute to links between perinatal HIV exposure and child EF. Future directions should include collecting longitudinal measures of child EF and caregiver depression symptoms to interrogate the plausibility of this explanation as well as whether child EF drives associations between perinatal HIV exposure and caregiver mental health. Inclusion of diagnostic-level assessments of mental health would also provide an important context for interpreting any findings observed.

We also worked to understand effect modifiers to the association between perinatal HIV exposure and EF in children in order to identify higher-risk groups and investigate potential intervention targets through modifiable factors. In Aim Two, we found effect modification by child's biological sex, with higher levels of EF problems among CPHEU males, but not among females. Findings like these may assist in identifying subgroups of children at particular risk for EF problems during a time when the neural systems underlying these processes are still developing. Furthermore, we found caregiver depression symptoms modified the association between perinatal HIV exposure and specific dimensions of EF, with CPHIV having lower levels of behavioral regulation problems compared to CHUU among caregivers with lower levels of depression symptoms. Continued exploration into potential effect modifiers like these in the perinatal HIV exposure/ child and caregiver functional outcomes literature will be important for future studies and for tailoring specific interventions to high-risk groups.

Limitations

While this dissertation provides insight into the association between perinatal HIV exposure and caregiver depression and child EF, we acknowledge several limitations. The cross-sectional nature of our analysis did not allow us to establish temporality between caregiver depression symptoms and child EF. As discussed, these associations may be bi-directional. Additionally, the CHUU group was recruited from the Kawaala Health Center as they were being treated for non-HIV-related conditions. This sampling approach might have introduced bias by selecting children with underlying health conditions that resulted in additional strain for caregivers. This cohort also represents a diverse exposure history to cART given that the protocols and treatment were evolving as the children in the study were born; thus, we were unable to rigorously evaluate the impact of specific regimens on our findings, particularly given

our sample size. Furthermore, while we collected data on salient aspects of caregiver and child functioning, these are highly complex, multifaceted phenomena. Therefore, it will be crucial to determine whether the findings reported here are observed with respect to other outcomes in these domains. Finally, the analyses were not corrected for multiple comparisons, and as a result, some of the findings we report may reflect Type I errors. Replication is warranted and encouraged.

Strengths

Despite these limitations, our study included a full complement of groups (CHUU, CPHEU, and CPHIV) allowing for comprehensive comparisons. HIV exposure status was also assessed for all children at enrollment and confirmed with medical records reducing the likelihood of misclassification between exposure groups. Importantly, we recruited children from a narrow age range, allowing us to focus on a specific phase of child development without the findings being complicated by the inclusion of children at various stages of typical EF maturation. Unlike previous studies, we considered the contribution of caregiver's mental health to our findings to better characterize the environment in which CHUU, CPHEU, and CHUU are developing. Lastly, with our cohort representing a "new normal" for HIV-exposed and infected children, our study allows us to observe how children may function cognitively in middle childhood after HIV exposure to or infection of HIV in the post-cART era.

Ultimately, this dissertation endeavors to gain insight into the pathway from perinatal HIV exposure and infection to and caregiver mental health outcomes and child functioning. We conclude that there are differences between these exposure groups and that important environmental factors may be critical to understanding the impacts on the functional survival of caregivers and their children.

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