

Brain and Cognitive Development Among U.S. Youth With Perinatally Acquired Human Immunodeficiency Virus Infection

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INTRODUCTION

As a result of gradually improving access to care and the favorable impact of antiretroviral therapy (ART) on health and well-being, hundreds of thousands of children living with human immunodeficiency virus (HIV) worldwide are reaching adolescence and young adulthood. Adolescence is noteworthy for significant physical, cognitive, emotional, and social changes as well as continued maturation of brain structure and function well into adulthood [1, 2]. Throughout adolescence, choices regarding education, relationships, sexual behavior, substance use, employment, and health have reciprocal effects upon each other and may have significant ramifications for both current and future well-being. Therefore, adolescence is accompanied by opportunities for positive adaptation and resilience and, conversely, by cognitive and behavioral risk, which may be heightened in the context of perinatally acquired HIV infection (PHIV).

Multiple studies of infants and children with PHIV have demonstrated an impact of HIV on the central nervous system (CNS) as well as upon cognitive and behavioral functioning [3–5]. Early severe HIV disease, even in the presence of immunologic and systemic virologic recovery during childhood, places global cognitive function, motor development, as well as selective aspects of academic and adaptive functioning at increased risk for impairment. However, less is understood about the long-term effects of PHIV and evolving ART on brain maturation and the higher-order cognitive skills that support academic and adaptive development as youth proceed into young adulthood. Until recently, few studies examined neurological and cognitive outcomes

among older adolescents with PHIV who experienced delayed or what is now considered suboptimal ART, severe disease progression, viral compartmentalization within the cerebrospinal fluid, or intermittent or ongoing systemic inflammation and immune activation. Current investigations in countries where ART has been widely available now provide opportunities to examine outcomes such as executive function (EF), memory, and language, along with their associations with brain development, viral suppression, and risk behaviors. Such data are critical to informing interventions that assist youth with PHIV as they navigate typical and unique developmental challenges and strive to reach young adult milestones.

The Pediatric HIV/AIDS Cohort Study (PHACS; <https://phacsstudy.org/>) [6] is a prospective cohort study in the United States that has monitored the health and development of children and adolescents with PHIV since 2007. Between March 2007 and December 2009, children from 15 study sites in the United States and Puerto Rico were eligible for enrollment into the Adolescent Master Protocol (AMP) of PHACS if they (1) were born to HIV-infected mothers, (2) were between 7 and 16 years of age, and (3) were either previously enrolled in another approved longitudinal cohort study, ie, the Pediatric AIDS Clinical Trials Group protocols 219 and 219C; the Women and Infants Transmission Study; or had complete medical histories available since birth, including details of use of antiretrovirals (ARVs), HIV ribonucleic acid concentrations, and lymphocyte subsets. The PHACS/AMP enrolled 451 children with PHIV and 227 HIV-exposed but uninfected children

(PHEU) as a comparison group. The PHACS/AMP monitors HIV-associated metabolic, cardiac, pulmonary, and neurological complications, growth indices, and ARV exposure and treatment, as well as cognitive, adaptive, academic, language, memory, executive functioning, and mental and behavioral health outcomes. Demographic and psychosocial factors are studied to more fully understand the impact of risks conferred by family and structural factors, such as histories of mental illness and learning problems, poverty, violent neighborhoods, and stressful life events, some or all of which may be experienced by families affected by HIV.

In this supplement, we present the results of 4 investigations of cognitive development and brain structure of youth with PHIV who are participants in PHACS/AMP. These investigations offer new insight into (1) associations among brain structures and indices of severe HIV disease, (2) higher-order cognitive functioning, including memory and executive functioning, (3) cognitive underpinnings of academic functioning, and (4) presence and persistence of language impairment among youth with PHIV in the United States. The findings of these investigations clarify and support current priorities of PHIV care, including early HIV diagnosis, early initiation of ART, ongoing adherence support to ensure viral suppression, and culturally sensitive intervention to mitigate cognitive or behavioral risk outcomes. They also highlight the fact that the development and well being of youth affected by HIV, whether perinatally infected or uninfected but HIV-exposed in utero, are significantly influenced by the social and economic contexts in which these youth live, which may be characterized by variable or diminished opportunities or by sociocultural advantages that contribute to resilient outcomes. Finally, these investigations also suggest opportunities for evaluation of ART regimens with high CNS penetration (NeuroCart) as well as behavioral interventions that have proven successful in ameliorating psychosocial and cognitive risk among children affected by HIV or other chronic illnesses across international settings [7–9].

In recent years, magnetic resonance spectroscopy and multimodal neuroimaging studies have examined neuro-metabolite levels and brain structure, connectivity, and volume among small cohorts of children and youth with PHIV across cultures [10–15] and have the potential to improve our understanding of the CNS impact of viral suppression, neuroinflammation, and disease progression across developmental stages. Human immunodeficiency virus infects the CNS early in life in the context of perinatally acquired HIV, thus it is important to identify and understand HIV effects during sensitive periods of brain development and as the brain matures throughout adolescence. In this volume, Lewis-de los Angeles and colleagues [16] describe their investigation of subcortical gray matter in adolescents

with HIV infection enrolled in PHACS/AMP, identifying clusters of shape deformation rather than volume differences for entire subcortical structures, as observed in adults with HIV infection. Importantly, the observed shape deformations were negatively associated with markers of disease severity, including level of peak plasma viremia, which in turn were associated with indices of cognitive functioning. These findings suggest several hypotheses regarding the etiology of structural changes and the mechanisms by which cognitive impairment can occur, which will be explored in future neuroimaging studies by this group. Furthermore, as prevention/intervention strategies are developed and implemented to reduce risk among children, adolescents, and young adults with PHIV, longitudinal neuroimaging studies have the potential to reveal neuroprotective effects of combination ARV intensification and behavioral health interventions across the lifespan.

Executive function refers to higher-order cognitive abilities necessary for behavioral and cognitive regulation, which, if impaired, may limit or complicate attainment of skills necessary for successful adolescent and adult transition. Executive function has been studied among small cohorts of children with PHIV, motivated in part by recognition of the critical role of EF in learning, decision making, and risk taking, but also by observations of EF deficits among adults with HIV infection and the concomitant impact on functional outcomes [17, 18]. In this volume, Nichols and colleagues [19] describe EF among a large cohort of youth with PHIV, enrolled in the Memory/EF substudy of PHACS/AMP, including those with and without an AIDS diagnosis and a comparison group of PHEU youth. Results highlight relative similarities in multiple domains of EF among PHIV youth without early, severe HIV disease complications and PHEU youth, with EF standard scores that range from low average to average. However, results also identify an increased risk for impairment associated with an early AIDS diagnosis and the influential role of family and socioeconomic factors on EF outcomes. These findings underscore the importance of ongoing monitoring of EF, regardless of evidence of viral suppression, to identify stability or change as a function of immune activation, socioeconomic factors, or any experienced EF interventions.

An important concurrent investigation of Nichols' examination of EF is presented by Sirois and colleagues [20]. This paper examines the role of EF and memory in academic and adaptive skill development among youth in the Memory and EF substudy of PHACS/AMP. Youth with PHIV often underperform academically relative to expectations based on their global cognition [21]. Identification of contributing factors, such as EF and memory problems, is crucial to guide interventions and to prevent future negative consequences on employability, mental health, and management of life tasks.

Results reveal that specific aspects of memory and EF are strongly related to academic achievement in both reading and mathematics and, to a lesser extent, with selective aspects of adaptive functioning. Consistent with prior research, caregiver and other sociodemographic factors also had significant effects upon academic and adaptive outcomes regardless of youth HIV status. This investigation highlights the need for ongoing surveillance of children's development throughout their school years and early identification of cognitive and behavioral problems that may be amenable to intervention, such as EF and memory skills. Identification of need and provision of multilevel supports are especially critical for children living in families affected by HIV across the globe, given many families' concomitant exposure to stress, violence, stigma, and poverty, which may exert their own unique toll on learning, health outcomes, and behavior.

Language development, the final topic in this supplement, was identified as an area of vulnerability among children with PHIV early in the HIV/AIDS epidemic [22–24] but has received limited attention with respect to older youth. Redmond and colleagues [25] present one of few longitudinal examinations of language functioning among PHIV and PHEU children and adolescents in the PHACS/AMP cohort. Results indicate that over one third of youth, regardless of HIV status, demonstrated language impairment, with high stability of scores during the 18-month test-retest interval. Among youth with PHIV, disease markers and treatment with combination ART were associated with changes in the trajectory of impairment over time. These results are relevant given the critical role of language comprehension and expression in academic achievement, social interaction, vocational success, and achievement of many adult milestones. Moreover, for youth with PHIV, adequate language skills are particularly important for successful adherence to treatment, healthcare management, and transition to adult healthcare settings. Importantly, Redmond and colleagues identify the contributions of family history of language and/or reading problems as well as other sociodemographic factors associated with risk of language impairment. The authors acknowledge the importance of early identification of language delay, early remediation, and ongoing monitoring of language function not only through childhood, but throughout adolescence, when maintenance of viral suppression for PHIV youth is often challenged due to nonadherence.

THOUGHTS FOR THE FUTURE

Importance of International Research

Eradication of pediatric HIV is a viable goal, particularly in the United States and other countries with adequate

resources. However, in those settings where HIV treatment and prevention efforts were initially absent or delayed, scale-up of ART remains slower than needed and perinatal HIV transmission, while reduced, continues [26]. Worldwide, 150 000 children became newly infected with HIV in 2015 while 49% of children living with HIV were accessing treatment [27]. Fortunately, studies of cognitive, neurological, and behavioral outcomes among children and adolescents growing up with HIV in low-to-middle income countries (LMIC) are increasing in number. Cohort studies such as PREDICT in Thailand and Cambodia [28] provide opportunities to understand the impact of variably timed ART without the confounding effects of in utero drug exposure, which was common in the United States during early years of the HIV epidemic, as well as influences related to cultural variability. Studies in sub-Saharan Africa may reveal neurocognitive differences related to HIV-subtypes that could influence antiretroviral choices and may also identify unique contributions of coinfections, malnutrition, and poverty. Important differences are likely between children with early diagnosis of PHIV and early effective combination ART versus those who experience delayed or inadequate ART and delayed or variable viral suppression. Understanding these differences is necessary to not only prevent or reduce sequelae associated with virological failures, but also to highlight the need for increased financial support for resource-limited environments where the likelihood of delayed diagnosis, insufficient ART scale-up, loss to follow-up, and mortality rates remain unacceptably high.

Unique Challenges

Across LMIC and high-resource settings affected by prevalent HIV, including those represented in this supplement, there are numerous psychosocial factors that likely play critical roles in HIV and treatment complications for youth with PHIV. Stigma, disclosure, family loss, poverty, stressful life events and trauma, and mental health problems have been shown to complicate the lives of children and adolescents with HIV, affecting adherence, academic function, and transition to adulthood and adult care [5]. For example, HIV remains a highly stigmatized condition globally, with multiple consequences. Human immunodeficiency virus-associated stigma may impact families' ability to initiate a disclosure process with their children and may provoke feelings of fear, shame, and doubt during critical periods of identity formation among youth [29–31]. For adolescents, HIV-associated stigma may bring additional burden with regard to peer relationships, medication adherence, and normative sexual activity, reducing the likelihood that HIV disclosure to sexual partners will occur in a safe and timely manner. This may be even more challenging

if higher-order cognitive functioning, communication skills, and familial support are compromised. Furthermore, as a multigenerational disease, HIV may impose loss and grief upon children and adolescents who often have limited access to services that could support recovery. Stigma, delayed disclosure, and loss each may contribute to risk for mental health problems among youth with PHIV, who are also at risk for psychiatric disorders due to HIV itself, familial factors, and negative environmental stressors [32, 33]. Despite remarkable progress in HIV medical care, more progress is needed to address and systematically ameliorate the negative psychological effects of growing up with PHIV.

Significant energy must now be directed towards development and implementation of evidence-informed and culturally valid and reliable prevention services to support youth with PHIV as they adapt to their chronic condition and cope with its implications for their emerging autonomy, social relationships, future goals, and transition to adulthood. Randomized clinical trials in LMIC and high-resource countries have begun to attest to the potential for improved adaptation of youth and their caregivers in the presence of supportive educational, counseling, and economic empowerment programs [8, 34–37]. Programs such as these can have a positive impact on medication adherence, a goal that is often challenged by co-occurring psychosocial conditions during adolescence. For those with cognitive deficits, neurocognitive rehabilitation [9] may offer opportunities for improvement and may reduce the impact of specific deficits on academic and adaptive development, future employment, and health management.

In upcoming years, efforts must continue to understand the biologic basis of structural and functional brain changes, as well as neurocognitive and behavioral sequelae among children, adolescents, and young adults with PHIV across the globe. Current studies provide guarded optimism for the future of PHIV youth, yet many continue to face unknown and unique risks compared with those infected in adulthood. It is unclear, for example, whether early and life-long exposures to HIV and perhaps inconsistent and/or long-term treatment with ART will hasten the biologic aging process via chronic immune activation, with resulting activation of neuroinflammatory processes and cell senescence. Basic determinants studies to identify pathways to risk and resilient outcomes, as well as intervention studies to promote evidence-informed treatment, are also critical. As the work in this supplement underscores, both PHIV and PHEU youth are at risk for deficits in areas of cognitive function critical to adult transition. Efforts to monitor and support youth with PHIV are ongoing, yet PHEU youth warrant attention as well, as studies monitoring their development reveal high rates of mental health problems and sexual risk and substance use behaviors,

which may place them at risk for negative health outcomes, including HIV infection [38].

In sum, determining ways to help HIV-affected youth overcome or cope with challenges while also ensuring their health and growth must be key components of our global response to the AIDS epidemic and its consequences. This special issue identifies critical areas for future research and intervention efforts and will hopefully provoke continued societal dedication to these goals.

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