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Original article

Neurocognitive Functioning in Antiretroviral Therapy–Naïve Youth With Behaviorally Acquired Human Immunodeficiency Virus

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A B S T R A C T

Purpose: Youth living with human immunodeficiency virus (HIV) account for over one third of new HIV infections and are at high risk of adverse psychosocial, everyday living, and health outcomes. Human immunodeficiency virus–associated neurocognitive disorders (HAND) are known to affect health outcomes of HIV-infected adults even in the era of combination antiretroviral therapy. Thus, the current study aimed to characterize the prevalence and clinical correlates of HAND in youth living with HIV. Here, we report baseline neurocognitive data for behaviorally HIV-infected youth enrolled in a prospective study evaluating strategies of antiretroviral treatment initiation and use.
Methods: A total of 220 participants, age 18–24 years, who were naive to treatment (except for prevention of mother-to-child HIV transmission; n = 3), completed a comprehensive neurocognitive, substance use, and behavioral health assessment battery.
Results: Sixty-seven percent of youth met criteria for HAND (96.4% were asymptomatic and 3.5% were syndromic); deficits in episodic memory and fine-motor skills emerged as the most commonly affected ability areas. Multivariable models showed that lower CD4 count, longer time since HIV diagnosis, and high-risk alcohol use were uniquely associated with neurocognitive deficits.
Conclusions: Over two thirds of youth with behaviorally acquired HIV evidence neurocognitive deficits, which have modest associations with more advanced HIV disease as well as other factors. Research is needed to determine the impact of such neuropsychiatric morbidity on mental health and HIV disease treatment outcomes (e.g., nonadherence) and transition to independent living responsibilities in HIV-infected youth, as well as its long-term trajectory and possible responsiveness to cognitive rehabilitation and pharmacotherapy.
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IMPLICATIONS AND CONTRIBUTION

Youth with behaviorally acquired human immunodeficiency virus demonstrate high rates of cognitive impairment. Impairment in certain domains is related to human immunodeficiency virus disease severity and to alcohol use. This impairment could have implications for functional and behavioral outcomes, and raises concerns about subtle central nervous system changes early in infection.

Adolescents and young adults experience the highest risk for human immunodeficiency virus (HIV) infection of any age group, accounting for 39% of new infections [1]. This population also presents unique clinical and public health challenges because of higher rates of poor medication adherence [2] and sexual and

[1] Dr. Garvie's role on the project was initiated while on faculty at St. Jude Children's Research Hospital. At the time of manuscript submission, Dr. Garvie's continued participation was as a contracted consultant.

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substance risk behaviors [3]. Interventions and changes in treatment recommendations for behaviorally infected youth living with HIV (YLWH), such as initiation of combination antiretroviral therapy (cART) at the time of diagnosis, have been implemented in the absence of knowledge regarding their neurocognitive functioning. Cognitive and functional impairments, whether HIV-related or due to other risk factors, may have implications for intervention development and long-term disease and treatment monitoring specifically tailored for adolescents.

The potential public relevance of neurocognitive impairment among YLWH is supported by over 2 decades of clinical research in adults [4] and children with perinatally acquired HIV (pHIV) or HIV acquired through blood products used to treat hemophilia [5,6]. Approximately 30%–50% of HIV-infected adults demonstrate HIV-associated neurocognitive disorders (HAND); in fact, the prevalence of mild-to-moderate neurocognitive deficits has increased in the cART era among persons with less advanced HIV disease [7]. Consistent with its preferential effects on the fronto-striato-thalamo-cortical systems, HIV infection is marked by deficits in executive functions (e.g., planning), memory, and psychomotor speed, with relative sparing of basic language and visuoconstruction skills [4]. Human immunodeficiency virus–associated neurocognitive disorders (HAND) have been linked to a variety of clinical factors, including alcohol and substance abuse [8,9], lower nadir CD4 counts [10], and lower cognitive reserve [11]. Human immunodeficiency virus–associated neurocognitive impairment increases risk of dependence in activities of daily living (ADL), including cART nonadherence [12]. Children and youth with pHIV show a different neurocognitive profile, with impairments in language and global functioning in addition to those seen in adults [6]. Those with HIV acquired postnatally through hemophilia treatment showed declines over time in nonverbal skills, memory, language, and academics that correlated with immunological changes [5].

The authors are unaware of any large-scale neurocognitive studies of adolescents and emerging adults with behaviorally acquired HIV to date. One study of behaviorally infected YLWH that included measures of cognition [13] found impairments in word knowledge and delayed development of abstract reasoning. The potential implications of cognitive impairments in YLWH differ from those in adults, which emphasizes the need for studies targeting this age group. Adolescence and young adulthood are developmental periods characterized by acquisition of skills essential for successful transition to independent adulthood occurring simultaneously with increased experimentation and risk taking. Both of these occur in the context of ongoing brain development, including frontostriatal systems vulnerable to HIV [14]. Furthermore, youth may differ from adults in their profile of substance use and psychiatric and other comorbidities. Here, we report cross-sectional data regarding neurocognitive functioning in treatment naive youth with behaviorally acquired HIV and exploratory analyses of its relationship to HIV disease severity, demographics, substance use, and psychiatric comorbidity.

Methods

Participants

Youth aged 18–24 years with behaviorally acquired HIV infection were enrolled from among clinical patients observed at 15 Adolescent Medicine Trials Network for HIV/Acquired Immunodeficiency Disease (AIDS) Interventions and 12 International Maternal Pediatric Adolescent AIDS Clinical Trials sites across the United States and Puerto Rico into a prospective cohort study evaluating neurocognitive functioning in participants with different illness severity and indications for treatment. At the time this study was initiated, the United States Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents* (*Guidelines*) recommended starting cART in patients whose CD4-positive T-cells were <350 or HIV RNA >100,000 copies/mL plasma, in the absence of clinical or psychosocial contraindications. Participants enrolled into four groups: two groups not yet meeting *Guidelines*, half of whom were randomized to initiate early ART within a treatment strategy study; and two groups who met *Guidelines* and either started treatment or did not because of patient preference or provider concerns about adherence. For the present analysis of baseline neurocognitive functioning, all groups were combined and CD4-positive count was treated as a continuous variable. All participants were treatment naive except for <6 months ART to prevent mother-to-child HIV transmission ($n = 3$). Self-reported English or Spanish fluency was required. Exclusion criteria included prior ART experience other than preventing mother-to-child HIV transmission, current pregnancy, active substance use or dependence judged likely to interfere with study requirements, psychosis, or significant non–HIV-related cognitive or motor impairment (e.g., cerebral palsy, severe traumatic brain injury; milder comorbidities including learning disabilities and attention-deficit/hyperactivity disorder were allowed). The study was approved by the institutional review board at all participating institutions; participants provided written informed consent in accordance with local institutional review board requirements.

Study evaluations

Neurocognitive functioning. The assessment battery included neurocognitive measures with previously demonstrated sensitivity to HAND in adults [15]. Domains included memory (Hopkins Verbal Learning Test–Revised [16,17]; Brief Visuospatial Memory Test–Revised [17,18]), motor skills (grooved pegboard [19], timed gait [20]), attention (Wechsler Adult Intelligence Scale–III [WAIS-III] [21], digit span, and letter/number sequencing), and executive functions (verbal fluency [19], Stroop interference [17,22], and trail making test [23,24]). Measures of general cognitive functioning (WAIS-III [21]), reading ability (Wide Range Achievement Test–4 [25]), everyday functioning (activities of daily living (ADL) [26], and Behavior Rating Inventory of Executive Function–Adult [27]) were included to describe the cohort and/or serve as covariates. Standard scores were computed using published normative standards, with adjustments for age and, where available, race, Hispanic ethnicity, education, and/or gender [17]. Scores within domains were converted to *z*-scores and averaged for analytic clarity and to reduce the number of regression analyses performed. In addition, neurocognitive performance was summarized using an approach developed in the adult HAND literature [15,28], which weights the presence and severity of neurocognitive impairment [29]. Deficit scores, computed using T-score conversions and ranging from 0 (T-scores > 39) to 5 (T-scores < 20; higher deficit scores reflect greater impairment), were averaged to derive a global deficit score (GDS). A GDS cut point of ≥.5 was used to classify individuals with global

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