A study of neuropsychological profile of human immunodeficiency virus-positive children and adolescents on antiretroviral therapy

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INTRODUCTION

According to the UNAIDS global AIDS update 2016, there were 17 million people living with human immunodeficiency virus (HIV) infection on antiretroviral therapy (ART) in the year 2015. The Asia-pacific region saw a rise in ART coverage from 19% (17%–22%) to 41% (35%–47%) in 2015. This heartening trend is believed to be responsible for a 26% decline in global AIDS-related deaths recorded since 2010.[1] In light of India’s contribution to the global HIV/AIDS burden, we are one of the fast-track countries on the way to achieve the goal of ending the global AIDS epidemic by 2030 as envisioned by UNAIDS.

The National AIDS Control Organization reported that the total number of people living with HIV in India in 2015 was 21.17 lakhs (17.11–26.49 lakhs).[2] Children (below 15 years of age) accounted for 6.54% of these. Children are a unique subset of this population for diverse reasons. They are almost always infected perinatally when

ABSTRACT

Aims: The aim is to study the neuropsychological and functional profile of children and adolescents with human immunodeficiency virus (HIV) infection on antiretroviral therapy (ART) and the association between the neuropsychological status and medical illness variables, treatment variables, and functional status in the cases of the sample and compare with normal controls.

Materials and Methods: Forty-two HIV-positive children and adolescents on ART were evaluated and compared with 40 matched controls not known to be HIV-positive. The tools used were the Wechsler Intelligence Scale for Children-III R for neuropsychological evaluation, the Brief Impairment Scale to assess functional impairment, and a semi-structured questionnaire to obtain other relevant details.

Results: There were significant differences between the verbal, performance intelligence quotients (IQs), global IQ score, and several individual subtests between cases and controls. The HIV group was also found to have a significant functional impairment.

Conclusion: Our findings show that HIV infection is associated with significant cognitive and functional impairment. The role of ART in these impairments requires further study. Such understanding can help to introduce wholesome and relatively safer management strategies for youngsters with HIV infection and improve their quality of life.

Key words: Adolescents, anti-retroviral therapy, children, HIV, intelligence
their physiological development itself is incomplete. Hence, the underdeveloped immune system is affected early on. Perinatally transmitted HIV (PHIV) has been found to affect physical health and nutrition directly, interfering with normal growth and development; causing structural and functional brain damage; and disrupting the social environment of affected children.\textsuperscript{\textordfervent{[3-8]}} With increasing availability of ART people with HIV live longer lives than they would have otherwise.\textsuperscript{\textordfervent{[9,10]}} However, ART has also been found to be associated with worsened quality of life (QoL).\textsuperscript{\textordfervent{[11]}} A matter of concern is the impact of prolonged exposure to ART during developmental periods in children. One area of focus is cognitive abilities such as attention, concentration, abstraction, and arithmetic, which are essential for effective communication, self-care, education, training, employment, and leading a fruitful and independent life. Children with PHIV are additionally disadvantaged by susceptibility to early parental losses and significant changes in their primary support groups.

Studies have been conducted across the globe to verify and quantify the occurrence of cognitive and functional impairment among patients with HIV/AIDS using varied tools (e.g., progressive matrices and trail-making tests). The effect of ART on cognitive abilities independent of the disease itself is yet to be determined with certainty. The increasing diagnosis of HIV dementia necessitates a study of the effect of HIV and ART on early cognitive development.

We undertook this study to evaluate the neuropsychological and functional profile of children and adolescents infected with HIV in the Indian context.

\textbf{MATERIALS AND METHODS}

We conducted a cross-sectional case–control study at the department of psychiatry of a tertiary teaching hospital after Institutional Ethics Committee approval. A total of 42 children who were HIV-positive and on ART following up in the HIV outpatient department (OPD) were taken in the study and comprised the “cases.” Forty children not known to be HIV-positive were selected as “controls.”

The inclusion criteria for the cases were age 8–15 years, HIV-positive status, having regular follow-up at the HIV clinic, and receiving ART. For the controls, the criteria were healthy children and adolescents of ages 8–15 years, not known to be HIV-positive who were matched for sociodemographic variables such as age, gender, and medium of education. The exclusion criteria were clinical Stage IV disease of HIV based on the WHO criteria, history of birth complications, delayed milestones, any central nervous system disease, a history suggesting scholastic backwardness, and comorbid neurological disease which may confound our findings. Children/adolescents with the history of chronic medical illnesses or childhood behavior disorders were excluded from the control group.

\textbf{Procedure}

Evaluation of cases: After screening to suit the selection criteria, a written informed consent from the accompanying parent/guardian and assent from the child were obtained for participation in the study. The caretakers were interviewed in the format of a semi-structured questionnaire that was prepared to obtain sociodemographic details, information regarding the illness/physical health of the child, and other relevant details. The Brief Impairment Scale (BIS) based on caretaker interview was used for evaluating and quantifying the childrens’ functional status. Cognitive abilities evaluation of the cases and controls was done by clinical psychologists at the Department of Psychiatry using the Indian (Mahendrika Bhatt) version of the Wechsler Intelligence Scale for Children III R (WISC-III R).

Evaluation of controls: The controls were selected from healthy children and adolescents accompanying patients at the Psychiatry OPD of the hospital. After they were screened to meet the abovementioned criteria, written informed consent and child assent were obtained; followed by caretaker interview to obtain sociodemographic details, evaluation of functional status using BIS. Cognitive abilities assessment was done by the clinical psychologists as described above using the WISC-III R. The data were analyzed using the Statistical Program for the Social Science version 10.0 (SPSS Inc. Chicago, Illinois, USA). The tests used were Chi-square, Student’s \textit{t}-test, and Pearson’s correlation coefficient.

\textbf{The Wechsler Intelligence Scale for Children-III R (Mahendrika Bhatt version for Indian children)}\textsuperscript{\textordfervent{[12]}}

This test is designed for participants aged 6–15 years. The Mahendrika Bhatt adaptation is available in Indian languages – Hindi and Gujarati and was suitable for our participants. Verbal intelligence quotients (VIQ), performance IQ (PIQ), and a composite full-scale IQ (FSIQ) scores can be obtained. Each score has a mean of 100 and a standard deviation of 15. Each major scale consists of 5 required subtests and supplementary subtests. IQ scores are computed from the 10 required subtest scores. Verbal subtests measure cognitive abilities such as general fund of knowledge; logical, abstract thinking, ability to form verbal concepts; computational skills and numerical reasoning; general word knowledge, language development; common sense, awareness of social rules and mores and ability to use past experiences; and short-term auditory memory. Performance subtests measure long-term visual memory, visual alertness, and ability to differentiate between essential and nonessential details; temporal visual sequencing, social awareness, nonverbal reasoning, and planning ability; nonverbal concept formation, ability to analyze a whole into component, visual-spatial organization; anticipation
of part-whole relationships, ability to use sensory-motor feedback, visual-motor speed and coordination and accuracy, short-term visual memory and ability to follow directions; visual planning and ability to follow a visual pattern. In view of the possibility of such a comprehensive evaluation, this test was chosen.

Brief Impairment Scale[13]

The BIS is administered to an adult informant with regard to his or her child/ward. It consists of 23 items scored along three functioning domains: Interpersonal relations, school/work, and self-fulfillment. Score ranges from 0 (no problem) to 1 (some problem), 2 (a considerable problem), and 3 (a serious problem). The time reference used originally in this scale was “the past year,” which however is flexible as per research needs. It shows high internal consistency and test–retest reliability, overall, and in most of its individual items. The original author’s recommendation is that a score of ≥14 be used to identify children impaired and in need of services. However, the scale cannot be used for clinical diagnosis. As there are no cutoff scores affixed for Indian children, in the current study, we did not use any. Instead, the scores obtained were compared between the two groups.

RESULTS

The average age of the participants in our study was 10.71 years among the cases and 11.53 years among the controls (range 8–15 years). Males comprised 69% of the cases and 65% of controls. Primary caregiver included at least one biological parent in 83.3% (n = 35) of the HIV-infected participants, compared to 92.5% (n = 37) among the controls. None of these differences were statistically significant.

The HIV group fared significantly poorly than controls in most of the subtests of the WISC, except arithmetic, picture completion, and mazes [Table 1]. We found no significant differences between the performances of girls and boys within the HIV group.

Evaluation of the BIS scores showed that the HIV group was significantly more impaired than controls on all the areas of functioning [Table 2].

No significant association was found between WISC scores and CD4 cell counts [Table 3]. No significant association was found between WISC scores and duration of ART [Table 4].

A significant negative correlation was found between VIQ and self-fulfillment component of BIS and VIQ and total BIS scores. Similar findings were obtained between FSIQ and self-fulfillment component of BIS [Table 5]. It appeared to suggest that children with better VIQ had significantly lesser difficulties in self-fulfillment and total impairment. There was no significant correlation between the rest of the WISC parameters when compared with the impairment scores.

| Test domain | Mean score (±SD) | P |
|-------------|-----------------|---|
| Interpersonal relations | 1.6±0.24 | 0.007* |
| School/work performance | 2.65±0.29 | 0.0054* |
| Self-fulfillment | 4.14±0.21 | 0.002* |
| Total score BIS | 8.83±0.83 | <0.0001* |

| Test domain | Mean score (±SD) | P |
|-------------|-----------------|---|
| Interpersonal relations | 0.64±0.35 | 0.55±0.50* | 0.0012* |
| Arithmetic | 0.68±0.13 | 0.98±0.20 | 0.0008* |
| Similarities | 0.74±0.13 | 0.10±0.22 | 0.0068 |
| Digit span | 0.86±0.13 | 1.05±0.24 | 0.0007* |
| Vocabulary | 0.98±0.13 | 0.87±0.13 | 0.004* |
| Picture completion | 0.71±0.19 | 0.90±0.14 | 0.032* |
| Picture arrangement | 0.92±0.13 | 1.08±0.13 | 0.512 |

| Variable | Sample size, n (%) | Mean VIQ | Mean PIQ | Mean FSIQ |
|----------|-------------------|----------|----------|----------|
| CD 4 count (cells/cmm) |               |          |          |          |
| <500 | 5 (11.9) | 67.40±19.35 | 95.20±22.30 | 78.60±22.26 |
| >500 | 37 (88.1) | 71.92±20.24 | 93.22±18.94 | 80.00±19.66 |

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DISCUSSION

In our study, children with HIV on ART were found to have scored significantly poorly on the verbal and performance domains of the WISC compared to matched controls. Discussing the findings on the verbal intelligence domain, we found our cases scored significantly low scores on five out of six subtests, that is, general information, comprehension, similarities, digit span, and vocabulary.
Table 4: Comparison of cognitive test scores on Wechsler Intelligence Scale for Children III-revised with duration of antiretroviral therapy

| Variable | n (%) | Duration of ART (years) | Mean VIQ | Mean PIQ | Mean FSIQ |
|----------|-------|-------------------------|---------|---------|----------|
|          |       | <5 (73.8)               | 72.00±20.18 | 91.29±20.32 | 78.94±20.37 |
|          |       | >5 (26.1)               | 69.64±20.19 | 99.55±14.08 | 82.36±18.33 |
| P        |       |                         | 0.7407   | 0.1479   | 0.6087   |

By Student's t-test, P>0.05 Not significant. SD – Standard deviation; ART – Antiretroviral therapy; VIQ – Verbal IQ; PIQ – Performance IQ; FSIQ – Full-scale IQ; IQ – Intelligence quotient

Table 5: Correlation between scores on Wechsler Intelligence Scale for Children III-revised and impairment scores in the human immunodeficiency virus-infected participants (cases)

| WISC-III R domains | BIS domains | Pearson’s correlation coefficient (r) | P  |
|--------------------|-------------|--------------------------------------|-----|
| VIQ                | IPR         | −0.22                                | 0.1613 |
|                    | School performance | −0.20                               | 0.2039 |
|                    | SF          | −0.37*                               | 0.0157* |
|                    | Total BIS   | −0.31                                | 0.0455* |
| PIQ                | IPR         | −0.07                                | 0.891 |
|                    | School performance | 0.01                                | 0.954 |
|                    | SF          | −0.23                                | 0.14 |
|                    | Total BIS   | −0.10                                | 0.96 |
| FSIQ               | IPR         | −0.16                                | 0.3113 |
|                    | School performance | −0.13                                | 0.023 |
|                    | SF          | −0.34                                | 0.0274* |
|                    | Total BIS   | −0.25                                | 0.1101 |

*Significant, by Pearson’s correlation. WISC-III R – Wechsler Intelligence Scale for Children III-revised; BIS – Brief impairment scale; IPR – Interpersonal relations; SF – Self-fulfillment; VIQ – Verbal IQ; PIQ – Performance IQ; FSIQ – Full-scale IQ; IQ – Intelligence quotient

The mean VIQ of this group was 71.38 compared to 90.03 of the control group. These findings indicate deficits in information processing, logical reasoning, abstraction, short-term auditory memory, attentions, language development, social awareness, and judgment in the HIV group.

In her doctoral dissertation, Clark reported that out of 42 HIV-positive children included in her study, 60% had VIQ scores more than one standard deviation below the normative mean (mean VIQ=81.17). In a study of 274 HIV-positive children by Nozyce et al. the mean VIQ was found to be 82 on Wechsler Pre-Primary Scale of Intelligence-Revised (WPPSI-R) and 85 on WISC-III. Although language impairment has been found in children and youth with PHIV, it has also been seen in those who are perinatally exposed to HIV but are uninfected (PHEU-perinatally exposed to HIV but uninfected individuals). This study also found that those who received ART demonstrated resolution of these impairments implying that ART has the potential to improve certain cognitive outcomes in infected youth.

Expressive linguistic deficits were found to occur significantly more than receptive deficits by Wolter et al. among HIV-infected participants. They noted that siblings of infected participants performed significantly better and did not demonstrate discrepancy between the receptive and expressive abilities. These findings indicate that HIV infection or even exposure without infection can interfere with the ability of the affected individuals to communicate effectively.

A similar study involving 20 HIV-infected children on ART with good adherence for 2 years at least, found significant deficits in attention, language, fine motor performance, executive and visuomotor functions, verbal learning, and memory compared to matched uninfected controls. The study included only children with average IQs (i.e., scoring 90 or above) on formal intelligence testing.

The children with HIV in our study scored significantly lower in picture arrangement, block design, object assembly, and coding subtests of the performance IQ test. The final PIQ was also lower compared to controls – mean PIQ-93.45 versus 104.3, respectively. These findings indicated impairment in temporal visual sequencing, nonverbal reasoning, planning, nonverbal concept formation, visual-spatial organization, sensory-motor feedback, visual-motor abilities, short-term visual memory, and ability to follow directions accurately.

Clark reported PIQ was more than one standard deviation below the normative mean in 62% of her sample of HIV-infected children. Nozyce reported a WPPSI-R mean PIQ score of 84 and WISC-III mean of 90, in her sample, which is significantly lower than the American normative mean PIQ. In our study, children with HIV had significantly lower full-scale IQ scores compared to controls – 79.83 versus 96.68, respectively. Similar findings have been recorded by others as well.

Our findings suggest that seemingly normally developing children with HIV on ART lag behind in several areas of cognitive functioning compared to children without HIV. This lag has been seen in children/youth with and without a previous AIDS-defining illness as well as the PHEU. This suggests a possible role of early, intrauterine exposure to HIV and/or ART in resulting in long-lasting cognitive deficits. It is recognized that neuronal invasion by the virus occurs early in the course of infection – a matter of concern with respect to the developing fetal brain.

Neuroimaging studies have demonstrated a high incidence of structural brain abnormalities in children with symptomatic HIV infection, including cortical atrophy and white matter abnormalities. Interestingly, Sarma et al. have reported increases in gray matter volumes in several regions of the brain in HIV-infected youth. They hypothesize that this may be the result of on-going neuronal infection and swelling or...
of the toxicity of ART. Similar studies in adults with HIV have found cortical thinning/atrophy compared to controls. Whether it represents the end stage of neuronal swelling noted in PHIV needs to be determined.

All the participants with HIV in our study were on ART for variable periods of time. Hence, the association of ART with the neuropsychological findings could not be ascertained. It has been found that the cognitive dysfunction in HIV changes from being “subcortical” in nature without ART to a combination of “cortical” and “subcortical” after starting treatment. The influence of ART on cognitive outcome remains ambiguous at best. Widespread availability of combination ART has been associated with decreased incidence of HIV-associated dementia, but milder forms of HIV-associated neurocognitive disorders or HAND, have been found to persist. This phenomenon may be explained by the fact that by the time medications are initiated, immunosuppression has already occurred, corresponding with peak cognitive deterioration, the so-called “legacy effect.” Indeed, there is an evidence to show that nadir CD4 cell count is associated with cognitive impairment, especially in the areas of attention, working memory as evaluated by digit span backward and executive functioning, evaluated by trail-making tests. Choice of medication has also been found to have an impact on cognitive outcomes.

We attempted to evaluate the association between CD4 counts and cognitive functions and found no significant differences in VIQ, PIQ, and FSIQ between the different values. There was no significant difference in cognitive performance between participants with significant immunosuppression (CD4 counts < 500 cells/cmm) and those without, in our study. Performance on neuropsychological tests is found to decrease over time as a consequence of HIV-disease progression. There is research where no significant association was found between stage of HIV/CD4 count and cognitive functioning. As there was no longitudinal evaluation of the children from the beginning of their illness, we were unable to determine the relationship between CD4 cell counts and cognitive functions. Cognitive functions may be influenced by other factors such as the age of onset of illness and type of ART used.

We attempted to find out the association between duration of ART and cognitive functioning. The HIV group was further subdivided into two groups for simplifying comparison-based on the duration of ART: Less than and more than 5 years. No significant differences were found between the two groups when evaluated for VIQ, PIQ, and FSIQ. It may indicate that cognitive dysfunction in HIV occurs early on in the infection and is not significantly affected by duration of treatment. Studies have found early initiation of ART in HIV-infected children may play an important role in preventing or slowing deterioration of cognitive functioning, supporting early treatment commencement. A South-African study reported no significant change in the cognitive performance of their sample of 40 HIV-positive children before and 6 months after commencing highly active ART. Other factors which may contribute to such neuropsychological profile in HIV-infected children/youth are social and educational deprivation associated with HIV, early parental loss, changing social environments, chronic ill-health during critical growth period, nutritional deficiencies, and the presence of psychiatric comorbidities in the children.

QoL in any medical condition is drastically affected by the presence of functional impairments, especially chronic illnesses like HIV/AIDS. Our findings were significant impairments in relating with family and peers, carrying out academic and extracurricular activities and in being self-sufficient among the infected children compared to controls. Studies have found that there are several factors which influence the QoL and functioning in HIV/AIDS and the use of effective ART regimes can improve the cognitive functioning and QoL. Patients with better QoL have better medication adherence which is another extremely important finding, especially as HIV/AIDS is a chronic illness requiring long-term treatment.

We found a negative correlation between mean IQ scores and impairment scores. Better VIQ and FSIQ were significantly associated with lower scores on self-fulfillment. No other statistically significant associations were found. There are limitations of our study. Academic problems may not have been picked up accurately by caregivers, as academic performance is judged by them mainly by marks or grades that the child usually gets at school, which is not necessarily a mirror of his/her cognitive faculties. Subtle motor and sensory deficits in these children may have played a role in negatively impacting extracurricular activities. These factors must be borne in mind while interpreting our findings. Interpersonal relations of infected children can also be affected by the social environment they live in. In our study, 16% of the cases were being cared for by a guardian other than a parent, indicating that burden of care had shifted from parent(s) to other members of the society. Such significant changes in family structure might be associated with impairments in functioning.

Ours is one of few studies performed in the area of pediatric HIV in India. From our findings, a few recommendations/suggestions can be made: (1) Early cognitive assessments and rehabilitation must be made routinely available to this population – by inclusion of clinical psychologists and therapists in the HIV clinics. In areas where such workforce is limited, training of medical and paramedical
staff at the clinics in administration of simple bedside tools of cognitive assessment and cognitive rehabilitation techniques may be considered; (2) Alternatively, tie-ups between neuropsychiatric services and HIV clinics on a consultation-liaison basis in urban areas is feasible; (3) Involvement of the caregiver is key-providing them simple educational materials to understand HIV, ART, and their potential impact on the lives of children, importance of cognitive impairments and their long-term consequences, early identification of cognitive and behavioral problems, etc.; (4) The clinics may consider devising a pathway of care for providing early and intense psychosocial interventions for those in need; 5) An impetus to research in the field of developmental neuropsychology and HIV/AIDS is called for; And (6) Using available scientific information to enhance prevention of parent-to-child transmission strategies, as this is the only way to prevent HIV-induced neuropsychological dysfunction in the generations of the future altogether.

**CONCLUSION**

We conclude that HIV infection in children and adolescents is associated with significant cognitive and functional impairments. Well-designed studies are required to differentiate the roles of HIV itself and ART in these findings.

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**Conflicts of interest**

There are no conflicts of interest.

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