RESEARCH PAPER

Development, Cognition, Adaptive Function and Maladaptive Behavior in HIV-infected and HIV-exposed Uninfected Children Aged 2-9 Years

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Objectives: To compare development/cognition, adaptive function and maladaptive behavior of HIV-infected and HIV-exposed uninfected children between 2 to 9 years with HIV-uninfected controls. **Methods**: This hospital-based cross-sectional study was conducted from November, 2013 to March, 2015. 50 seropositive HIV-infected, 25 HIV-exposed uninfected and 25 HIV-uninfected children between 2 to 9 years were administered Developmental Profile 3, Vineland Adaptive Behavior Scale 2, and Child Behavior Checklist for assessing development, adaptive function and maladaptive behaviour, respectively. Additional data were obtained by history, examination and review of records. **Results**: Significant developmental/cognitive impairment was observed in 38 (76%), 16 (64%) and 6 (24%) HIV-infected, HIV-exposed uninfected, and HIV-uninfected children, respectively. Significant impairment in adaptive function was found in 12 (24%) and 2 (8%) HIV-infected and HIV-exposed uninfected children, respectively. Maladaptive behavior was not seen in any group. **Conclusions**: High magnitude of impaired development/cognition and adaptive function in HIV-exposed and HIV-infected children warrants assessment of these domains during follow-up of these children, and incorporation of interventions for these deficits in standard care for this group.

Keywords: *Acquired immunodeficiency disorder, Developmental delay, Neurocognition, Outcome.*

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The eco-biodevelopmental framework of child development conceptualizes that interactions between ecology (social and physical rearing environments) and biologic processes (heath), determine developmental trajectories of early childhood. These influence cognition, adaptive function (skills used in activities of daily living) and behavior, the effects of which persist in late childhood, adolescence and even adulthood [1]. Human Immunodeficiency virus (HIV)-infected children from low- and middle-income countries (LMICs) are exposed to more adverse factors than high-income countries. These include non-detection or late detection in pregnancy and infancy, unavailability of timely anti-retroviral therapy (ART), adverse environmental (malnutrition, micro-deficiencies, decreased opportunities, poor nurturing care, etc.) and social (*i.e.* poverty, parental morbidity, mortality and poor literacy) factors [2,3]. HIV-exposed uninfected children are a less recognized, but equally vulnerable population who lack HIV-related biological risk factors, but otherwise face similar adversities.

Previous studies studying development, adaptive function and behavior of these children from high-income countries displayed differences varying from no impairment [4] to significant impairment [5,6]. These discrepancies were explained by heterogeneous objectives, methodology, participants (age, staging, timing of ART, CNS drug penetration) and psychometric testing [7]. There is still paucity of data from LMICs – the available Indian data is restricted to older children and adolescents [8,9]. As ART policy changes and improving health care translates into more survivors, there is a need to detect potential developmental or mental health issues in childhood, for timely intervention.

This study compared development/cognition, adaptive function and maladaptive behavior of perinatally-acquired HIV-infected and HIV-uninfected exposed pre-school and school-aged children with HIV-uninfected (HU) controls. Their correlation with specific clinical and environmental factors was determined.

METHODS

This hospital-based cross-sectional study was conducted from November, 2013 to March, 2015, after obtaining Institutional ethics committee approval. Cases included children aged 2-9 years who were either HIV-

infected (seropositive on three consecutive ELISA rapid tests) or HIV-exposed but uninfected (HIV negative siblings, or children born to seropositive patients), recruited from the ART centre of our hospital. Children of the same age-group, presenting with minor illnesses, were enrolled as controls and considered to be HIV-uninfected. Exclusion criteria were significant perinatal events requiring hospitalization, previous neurological infections, and known neurodevelopmental or chronic disorders. Sequential enrollment continued till a pre-decided sample size of convenience (based on ART center attendance of the previous year) was attained. Parental informed consent was obtained; however, assent of older children was not taken to avoid inadvertent disclosure.

Locally developed, provider-completed, Hindi translations of Developmental profile-3 (DP 3) [10], Vineland Adaptive Behaviour Scale, 2nd edition (VABS 2) [11] and Child Behavior Checklist (CBCL) [12] were administered by a trained pediatrician. The parental questionnaire DP 3 assesses physical, adaptive, social-emotional, cognitive and communication domains from birth to 12 years. It computes standard scores (SS) for domains and an overall General Development Score (GDS), which are rated as Delay, Below average and Average. GDS represents development in children younger than five years and cognition in older children. VABS 2 is a parental interview that measures adaptive function in socialization, daily living skills, communication, and motor domains. Adaptive Behavior Composite (ABC) and SS rate overall and domain-wise performance as Low, Moderate low, and Adequate. Maladaptive Behavior Index and Maladaptive Critical Index is assessed in children ≥3 years. CBCL is a parental interview that categorizes behavior and rates them as Normal, Borderline and Clinical, based on standardized T scores.

History, examination and records were reviewed after which psychometric tests were scored. Primary outcome measures included significant impairment in development/cognition (delay), adaptive function (low) or maladaptive behavior (significant MBI, MCI or T scores).

Statisticial analyses: SPSS version 20.0 was used for statistical analyses. Unpaired t-test and Chi square test were used for inter-group comparisons. Pearson's coefficient of correlation (*r*) was determined by univariate analysis between individual clinical (staging, nutritional status, CD4 status, ART, central nervous system (CNS) penetration) and environmental covariates (socio-economic status, family composition, parental literacy, HIV and ART status, and death) and primary outcomes (VABS-2, DP-3 and CBCL scores). Since development is affected by the cumulative effect of multiple factors, multivariate analysis was applied between combined clinical and environmental covariates with the primary outcomes. Strength of association was measured by multiple correlation coefficient (R).

RESULTS

Of the 113 eligible children, 8 were excluded (3, epilepsy; 4, significant perinatal events; 5, developmental disorders; and 1, meningitis). The study population comprised of 50 HIV-infected children (HI group), 25 HIV-exposed uninfected children (HEU group) and 25 HIV-uninfected (HU group). The mean (SD) age was 4.9 (2.2), 6.1 (1.9), 5.1 (2.2) years and male: female ratio 2.8, 1.1 and 1.1, respectively in the three groups. ***Table* I** displays baseline participant details in the three groups. Distribution of WHO clinical staging in HI group was 24 (48%) T1, 12 (24%) T2, 8 (16%) T3 and 6 (12%) T4; 14 (28%) had CD4 percentage <25% while 15 (30%) had CD4 counts <350µl. Forty five (90%) were on ART; 22 (48.9%) with high CNS penetration and 23 (51.1%) medium CNS penetration. Mean (SD) duration of ART was 1.2 (0.9) years in children aged 2-5 years and 2 (2) years in those between 5 and 9 years. None had microcephaly or focal neurological signs.

Significant development/cognitive impairment was observed in 38 (76%) HI, 16 (64%) HEU, and 6 (24%) (SD) HU children. Mean (SD) GDS of HI and HEU children was significantly lower than HU; 59.2 (16.9), 70.1(13.4) and 77.4(13.4), respectively. Significant adaptive impairment was seen in 12 (24%) HI and 2 (8%) of HEU children. Mean (SD) ABC of HI group was significantly lower than HEU group and HU group [75.3 (8.9) *vs* 85.5 (7.3), $P<0.05$].

Distribution of levels of development/cognition and group [75.3 (8.9) *vs* 85.4 (7.3), $P<0.05$] adaptive function is depicted in ***Fig.* 1**, and domain-wise performance in ***Web Table* I**. Significant maladaptive behavior was not observed in any group. Mean (SD) MBI was 11.7 (1.9), 11.4 (1.1) and 11.2 (1.1) in the HI, HEU and HU group, respectively. The mean (SD) CBCL T score of HI group [29.2 (6.1)] was significantly higher than HEU group [26.0 (1.7)] and HU [26.6 (1.8)] children, but not clinically relevant.

No single independent clinical or environmental covariate had a strong correlation with GDS, ABC or T scores in HI group. Combined clinical covariates displayed strong and significant ($P<0.05$) association with GDS (R=0.84), ABC (R 0.81) and T scores (R 0.73). Association between combined environmental

TABLE I BASELINE CHARACTERISTICS OF CHILDREN ENROLLED IN THE STUDY (*N*=100)

Characteristics		*HI (n=50)*	*HEU (n=25)*	*HU (n=25)*
Parental education	Mother ≤ primary	27 (54)	20 (80)	7(28)
	Father ≤ primary	10 (20)	8 (32)	7 (28)
Child education	No informal (<5 y)	23/30 (77.7)	5/7 (71.4)	7/11 (63.6)
	No school (>5 y)	7/20 (35)	14/18 (77.7)	11/14 (78.5)
[#]Socioeconomic status (SES)	Lower middle	11 (22)	11 (44)	9 (36)
	Upper lower	36 (72)	14 (56)	12 (48)
Family status	Nuclear family	31 (62)	20 (80)	23 (92)
	Maternal death	4 (8)	1 (4)	0
	Paternal death	11 (22)	2 (8)	0
	Both death	4 (8)	1 (4)	0
Anti-retroviral therapy	Antenatal	7 (14)	3 (12)	-
	Maternal	36 (85.7)	6 (14.2)	-
	Paternal	30 (88.2)	9 (26.5)	-
Nutritional status	Severe stunting (<5 y)	19/30 (63.3)	0/11	0/7
	Severe thinness (>5 y)	1/20 (5)	3/18 (16.7)	4/14 (28.6)

HIV: Human Immunodeficiency, HEU: HIV-exposed uninfected, HI:HIV-infected, HU: HIV-uninfected; Significant differences (P <0.05) noted in the following intergroup comparisons: P<0.05 for children not attending school, Lower Middle SES, parents on ART and severe s between HI and HEU, Maternal education, children not attending school, Upper lower SES, nuclear families and severe stunting – between HI and HU; and maternal education between HEU and HU; [#]Using modified Kuppuswamy socioeconomic status scale (1 child each in Upper strata in HI and HU groups, and 2 and 3 children in Upper middle strata in HI and HU groups, respectively).

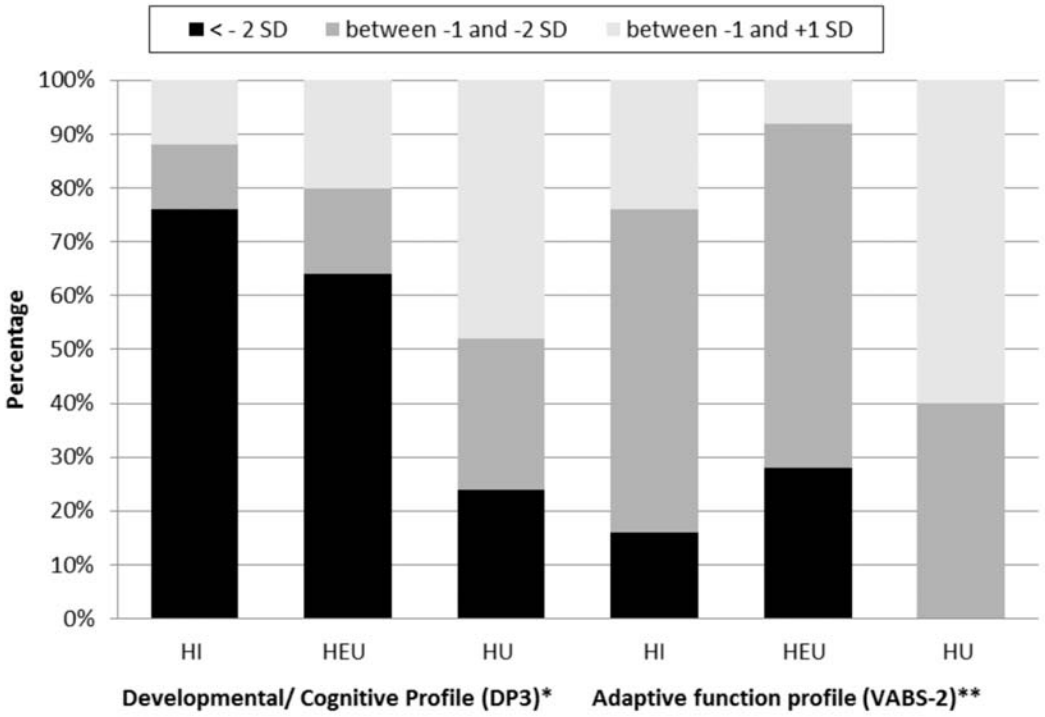

FIG. 1 *Distribution of levels of performance of development/cognition and adaptive function in HIV-infected (HI), HIV-exposed and uninfected (HEU) and HIV-uninfected (HU) groups.*

WHAT THIS STUDY ADDS?

- Impairment in development/cognition and adaptive function was found in HIV-infected and HIV-exposed uninfected children aged 2-9 years.

covariates and GDS was strong in HI (R=0.73, $P<0.05$) and HEU (R=0.74, $P<0.05$), moderate with ABC in HI (R=0.59, $P<0.05$) and HEU (R=0. 66, $P<0.05$), and weak with ABC in HU (R= 0.45, $P<0.05$).

DISCUSSION

We found that the group as a whole had poor maternal literacy, low pre-school/ school attendance, and thinness. A strong and significant association was found between combined environmental factors and overall development (GDS). The high prevalence of impairment in our controls is less than the estimated 43% of children under five years from LMIC who are not expected to attain their developmental potential [13].

Significant cognitive impairment and low scores in developmental and adaptive function was seen in HIV-infected children. Studies from LMIC [4,5,14] have reported this earlier, attributing it to delayed ART (more severe and pervasive neurological damage) and adverse ecological and biological factors [15]. Neurodevelopmental outcomes are better when ART is started in infancy, as it decreases irreversible CNS damage [5]. Though 90% of children in this study were receiving ART, initiation in infancy had not been universal due to the then existing ART policy. Adaptive function in HI children is affected by co-morbid illnesses, increased dependence on caregivers, decreased opportunities, and poor parental support, besides CNS dysfunction [16]. This explains the significant differences between HIV-infected and HIV-exposed uninfected children with respect to proportion, severity of impairment and strength of association between environmental factors and ABC.

Children in HEU group had more cognitive impairment than controls, and a strong association with combined environmental covariates. This was also observed by Bass, *et al*. [2] in Ugandan children. Surprisingly, few studies from high-income countries report equal or even higher impairment in HEU group than HIV-infected children [8]. This phenomenon is explained by HI group children receiving high quality medical, nutritional, and social support, while HIV-exposed but uninfected counterparts remain unsupported. The increased maladaptive behavior reported in older HIV- infected children and adolescents [8,16-19] is attributed to psychological responses to debilitating illness and disclosure. The absence of maladaptive behavior in our study may be attributed to less severe disease in the majority, non-disclosure and good medical care (90% on ART, good adherence to therapy, nutritional support and regular follow-up), all of which promote resilience [4].

Though the Hindi translations of the psychometric tools have not been validated in Indian community, they are routinely used in clinical practice and research. The lack of Indian norms was addressed by including a demographically-matched control group. Other limitations were small sample size (being single centric) and lack of blinding. An attempt was made to decrease information bias by interpreting the tests after collection of clinical data. An adequately powered, multi-centric, longitudinal study with age stratification is recommended to provide deeper insight.

In India, ART became universally available to all HIV-infected children after a policy change in 2014 [20]. Its clinical implications are earlier initiation of ART and more children surviving till adolescence and adulthood. Though biological HIV-related risk factors may decrease, the ecological adverse influence will remain with their associated impact of cognition, adaptive function and behavior. We suggest that the National AIDS Control Organization consider incorporating their assessment in standard care of all HIV-exposed children, whether infected or not.

Contributors: SBM,AS: conceptualized the study and will stand as guarantors; SD,SBM: did the literature search; SD: was trained to administer the psychometric tools by SBM and SS and collected the data; SBM,SD,SS: interpreted and analyzed the data; SM: drafted the manuscript which underwent a critical appraisal by SD,AS,SS. All the authors approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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WEB TABLE I PERFORMANCE ON DEVELOPMENTAL PROFILE-3 (DP3) AND VINELAND ADAPTIVE BEHAVIOR SCALE-2 (VABS-2) AMONG HIV-INFECTED, HIV-EXPOSED UNINFECTED AND HIV-UNINFECTED CHILDREN.

Tool	*Domain*	*Parameter*	*HI (n=50)*	*HEU (n=25)*	*HU (n=25)*
*DP3	Physical	Delay, *n* (%)	16 (32)	4 (16)	3(12)
		Mean SS (SD)	70.8 (15.1)	85.7 (15.4)	87.5 (14.1)
	Adaptive	Delay, *n* (%)	25 (50)	11 (44)	7 (28)
		Mean SS (SD)	65.8 (14.1)	68.7 (13.9)	75.9 (13.1)
	Social emotional	Delay, *n* (%)	12 (24)	4 (16)	3 (12)
		Mean SS (SD)	76.0 (17.4)	80.8 (12.5)	85.1 (12.1)
	Cognitive	Delay, *n* (%)	19 (38)	5 (20)	3 (12)
		Mean SS (SD)	71.7 (17.8)	84.1 (16.9)	85.7 (12.3)
	Communication	Delay, *n* (%)	29 (58)	13 (52)	2 (8)
		Mean SS (SD)	68.3 (12.2)	73.8 (14.4)	84.4 (11.2)
#VABS 2	Communication	Low *n* (%)	14 (28)	2 (8)	0
		Mean SS (SD)	76.6 (9.9)	83.5 (9.7)	91.5 (9.0)
	Daily Living Skills (DLS)	Low *n* (%)	6 (12)	1 (4)	0
		Mean SS (SD)	82.5 (10.9)	91.8 (11.5)	90.8 (11.2)
	Socialization	Low *n* (%)	1 (2)	1 (4)	0
		Mean SS (SD)	78.1 (7.9)	81.7 (6.6)	84.2 (5.2)
	Motor	Low *n* (%)	16 (32)	4 (16)	0
		Mean SS (SD)	74.7 (12.1)	82.9 (12.1)	84.1 (8.3)

HIV: Human Immunodeficiency Virus; HEU: HIV exposed but uninfected; HI: HIV infected; HU: HIV uninfected; SS: standard score; Interpretation.

DP3 scores; SS <70 delay, 70-84 below average and 85-115 average; Interpretation VABS-2 scores: SS <70 Low, 70–84 Moderate Low and 85-115 Adequate.

Significant differences (P<0.05) noted between HI and HEU: Physical and cognitive (DP3), Communication, DLS and Motor (VABS-2); and between HI and HU: all domains (DP3), all domains (VABS-2); and between HEU and HU: Communication (DP3), Communication and Motor (VABS-2).