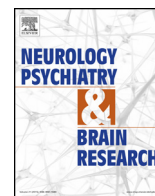




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Abundance of psychiatric morbidity in perinatally HIV infected children and adolescents with comparison to their HIV negative sibling

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ABSTRACT

Human Immunodeficiency Virus (HIV) impairs the physiological, behavioral and social development of the infected-children. With the advent of better antiretroviral-therapies (ARTs), the infected children are surviving well beyond adolescence accompanying with complicated ramification of management with bio-psycho-social factors. Presently, 76 children (53 perinatally HIV+ and 23 of their HIV- sibling) are screened for psychiatric-morbidities with Developmental-Psychopathology-Check-List (DPCL) which is a modified version of widely used protocol 'Child Behavior Check List (CBCL)'. Positively screened for psychopathology was regarded as psychiatrically morbid. In South-East Asian perspective, this type of investigation is scanty. Here, we investigate and report the psychiatric-morbidity status of vertically HIV infected children with a longitudinal comparison to their HIV- sibling. The present results suggest that 42.1% of the study-population suffers from psychiatric morbidity. Among the HIV+, 45.28% suffer from psychiatric-morbid constituting emotional-disorder, 41.67%, conduct-disorder, 37.50%, somatization 33.33%, learning-disorder, 29.16%, whereas in the HIV- group, 34.79% suffers from psychiatric morbidity mainly with emotional disorder [87.50%]. The age as an independent variable is noticed to be associated significantly ($p < 0.001$) with psychiatric-morbidity. Other variables amongst sex, CD4+ count, living-status of parents, caregiver-status was found to have certain extent of association with psychiatric-status. The present comparison with the more reliable control like HIV- sibling will help for the first time, to characterize better the infection association of psychiatric-morbidity of the HIV+ children. Advances should be espoused for the better survival of HIV infected children with improved ARTs application incorporating with advanced psychiatric-services.

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1. Introduction

The Human Immunodeficiency Virus (HIV) epidemic was identified in 1980 & since then it has become a global challenge for the psychological health of the young children of HIV infected mothers. The report reveals that more than 22 million people have perished from this disease, and it is today the seventh-leading cause of death in the United States (Benton, 2010). Several countries in South East Asia also experience a sharp rise in HIV

infection in the last decade which has not been focused very much (Sugimoto et al., 2014). The vulnerability of a large number of infected children begins before their mother's dieing and extends after her death (Pelton & Forehand, 2005). Evidence suggests that anti-retroviral therapy (ART) has been successfully implemented worldwide, including the Southeast Asian region for last few years. As a result, the quality of life (QOL score), which is an important ART outcome, became lower in HIV-infected children (Bunupuradah et al., 2013). Past research has demonstrated that young children affected by maternal HIV, manifest with elevated stress/anxiety and negative well-being. The most important factor for the psychiatric morbidity is the children's worry about their mothers' health and possibility of her death. This situation initiates intense feelings of bereavement in the child's mind. Other factors include feelings of secrecy/stigma associated with HIV/AIDS and increased burden of adult responsibilities/care giving etc. (Murphy, Roberts,

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& Herbeck, 2013a). The neuro-psychiatric anomalies in the children include a range of developmental delays, learning problems, and behavioral, emotional, language and cognitive issues (Belman et al., 1996; Chase et al., 2000). The HIV+ individuals demonstrate a poorer attention/processing speed (Nagarajan et al., 2012). More language impairment is shown in perinatally HIV infected children than HIV uninfected but exposed children (Rice et al., 2012). The HIV+ children manifest a major deficit in perceptual performance. The socioeconomic status has been shown to influence their cognitive efficacy (Kandawasvika et al., 2014). This efficacy is impaired with a symptom of compromised executive function and slowed information processing (Koekkoek, de Sonnevile, Wolfs, Licht, & Geelen, 2008). Traumatic brain injury (TBI) has been recognized in HIV/AIDS affected population (Jaffe, O'Neill, Vandergoot, Gordon, & Small, 2000). Nevertheless, the cognitive and behavioral factors are differentially involved in the sensitivity and severity of the traumatic brain injury of the adolescents (Donders, DenBraber, & Vos, 2010). Individuals with HIV and a history of blow (TBI) to the head reported a higher number of total symptoms which suggests an influence of HIV on it. In addition to the cognitive and behavioral factors, there are few more factors like physical and meta-cognitive also found to be involved (Donders et al., 2010; Jaffe et al., 2000). A WHO sponsored multi-centric study in four developing countries, including India, finds that 12–29% of children attending primary health care facilities has identifiable psychiatric disorders (Weiland, Pless, & Roghmann, 1992). In the present Indian scenario, there has been a significant maternal and pediatric adherence to ART (De & Dalui, 2012), which may throw some positive influences on psychiatric outcome.

The improvement of child-mother communication, HIV/AIDS knowledge, reducing anxiety (particularly related to transmission) and lessening the stigmatizing situations might develop the psychological health of HIV+ or HIV- children of a positive parent (Murphy, Marelich, Graham, & Payne, 2013b). The depression in AIDS orphan is so intense and transmissible that even their caregivers are more likely to meet the clinical threshold for depression than the caregivers of non-orphaned children (Kuo, Operario, & Cluver, 2012). One investigation also indicates an association between caregiver mental health and child emotional and behavioral functioning (Mellins, Brackis-Cott, Dolezal, & Abrams, 2006).

The neuropsychiatric sequelae of HIV as it relates to the effect of the disease on the brain are an understudied area of research. In the present experimental setting, we made an attempt to delineate the common psychiatric morbidity and its magnitudes in perinatally HIV infected children with a comparison to their HIV- siblings.

2. Methods

This cross-sectional study was conducted in the Apex Referral Centre (National AIDS Control Organization, NACO and World Health Organization, WHO recognized) for pediatric HIV, Medical College and Hospital, Kolkata which is regarded as an ART clinic of excellence. The rest part of the work viz data analysis was done at the same Department and in the Cell and Molecular Therapeutics Laboratory, Postgraduate Dept Biochemistry and Biotechnology, OIST affiliated to Vidyasagar University.

2.1. Participants

The study population was the children of seventy six (53 HIV+ and 23 HIV-, sibling of this HIV+ group). The HIV status was concluded with the results of 3rd generation HIV-ELISA assay-kit of

three different make. The study period was February 2007–August 2008.

2.2. Inclusion and exclusion criteria

The inclusion criteria were (i) >3 years age (ii) no history of blood transfusion before diagnosis of HIV status (iii) reliable caregiver/informant available (iv) perinatally infected with HIV (or un-infected; sibling) and (v) willing to participate in the study. The exclusion criteria were (i) active opportunistic or serious infection and the children who can not move or walk alone (ii) Incapacitating involvement of central nervous system (HIV-encephalopathy) or sequel of HIV infection (tubercular-meningitis) (iii) overt mental-retardation (iv) other illnesses that affect the brain, such as: toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, or cytomegalovirus encephalitis, brain tumor (eg., primary central nervous system lymphoma).

2.3. Procedures

Psychiatric morbidity status of the children was studied using the Developmental Psychopathology Check List (DPCL) (Kapur, Barnasus, & Reddy, 1994). The DPCL screening protocol is an Indian adaptation akin to the versions of widely used 'Child Behavior Check List (CBCL)' developed by (Achenbach & Edelbrock, 1983). It was developed at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India 2000 and Indian Council of Medical Research (ICMR). It contains interviewer-rated items/responses on hyperkinesis, conduct-disorder, autism, hysteria (somatic), emotional-disorder, learning-disorder and psychosis. Screen positive for psychopathology was regarded as positive for psychiatric morbidity as exhaustive diagnostic schedule either for ICD-10 or DSM-IV-TR was not applied.

Presently studied other variables (clinical and psychosocial) were; CD4+ count, ART and caregiver status and the living-status of the parents.

The study was conducted by the post graduate students and registered health professionals in the Govt. hospitals. This study adhered the regulatory affairs regarding this type of study. And the present investigation was approved by the Committee of the College reviewing thesis work of postgraduate students.

2.4. Statistical analysis

The data were analyzed by the software SPSS 13.00 for Windows (SPSS Inc., Chicago, USA) for assessment of correlation between psychiatric morbidity, socio-demographic and clinical variables. Descriptive analysis was done using Pearson's chi-square and Student's *t*-test. To compare different variables and psychiatric status, one way ANOVA with Tukey's post hoc test is used. Pearson correlation $p < 0.05$ was considered as statistically significant. Logistic regression analysis was done to assess the correlation amongst socio-demographic and clinical variables and psychiatric morbidity.

3. Results

In the present investigation, 76 children (39 male, 53 HIV+ and 23 HIV- who are sibling of HIV+, ($p < 0.01$)) are screened with Developmental Psychopathology Check List (DPCL) for psychiatric morbidities. Socio-demographic profile of the study area is noted. Positively screened for abnormal psychology was regarded as psychiatrically morbid. The psychiatric morbid positive (Psy+) is 32 when non morbid (Psy-) is 44 in number ($p < 0.001$) (Fig. 1a). Psychiatric morbidity is appreciably higher in HIV+ of both male and female. And the same is also higher in HIV- female (50%). Due

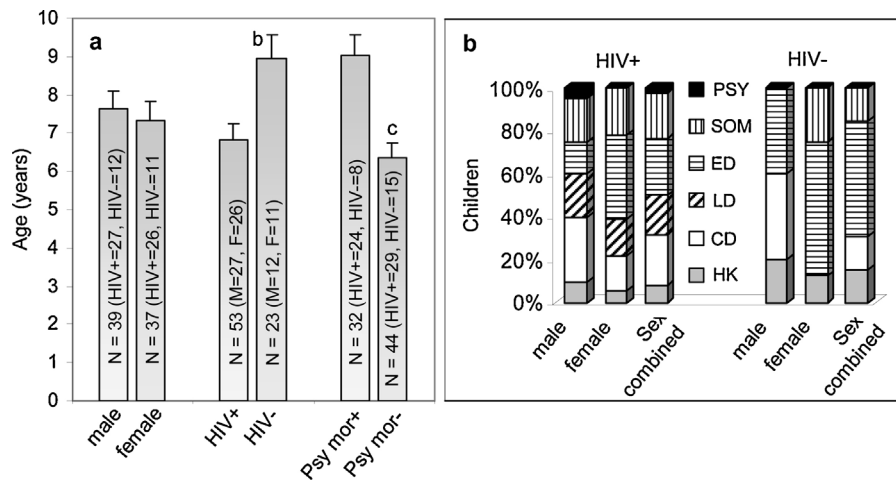


Fig. 1. (a) Distribution patterns of total participant children in relation to gender, HIV status and psychiatric morbidity status. Average age of children distributed in different groups. Bar represent mean \pm SE. Significant differences between corresponding groups ^b $p < 0.01$, ^c $p < 0.001$. (b) Distribution patterns of HIV+ and HIV- children group in different category of psychiatric disorder. PSY- psychosis, SOM-somatization, ED- emotional disorder, LD- learning disorder, CD- conduct disorder, HK- Hyperkinetic disorders.

to a lower sample size the difference of psychiatric morbidities in HIV+ to that of HIV- is not statistically significant: Chi Square is 0.73, $p = 0.3944$; (Fisher's exact test: $p = 0.4552$). But, the odd ratio showed that there were 1.552 times (95% CI: 0.563–4.279) chances of the HIV+ children to be suffering from psychiatric morbidity than the non-HIV infected children. The relative risk of 1.302 (95% CI: 0.691–2.452) also supported that there was an association between HIV infection and psychiatric morbidity.

The present results indicate that within studied population, 42.1% suffers from psychiatric morbidity. Among the HIV+, 45.28% suffer from psychiatric morbidity constituting emotional disorder [ED] 41.67%, conduct disorder [CD] 37.50%, somatization [SOM] 33.33%, learning disorder [LD] 29.16%, whereas in the HIV- group, 34.79% suffers from psychiatric morbidity mainly with emotional disorder [ED] 87.50% (Fig. 1b). The proportion of psychiatric morbidity is shown gender wise in HIV+ or HIV- children (Fig. 2a). The independent variable that is significantly related to psychiatric morbidity is age. In our study, >9 years group was found to be significantly associated with psychiatric morbidities ($p < 0.001$)

(Fig. 2b). Some other variables amongst sex, CD4+ count, living status of parents, caregiver status were found to have certain extent of associated with psychiatric status. This is may be due to the lower sample size and/or inter-individual variability in relation to these factors. The interactive role of these factors may also disqualify the impact of a single factor.

Age wise distribution suggests when more HIV+ participants of both genders occupy <6 and 6–9 years group than a high number of HIV- belongs to 6–9 and >9 years categories. It is also noticed that the number of Psy+ and HIV- is higher in <6 years than the 6–9 and >9 years group (Fig. 2b). A significant number of HIV- are grown under the care of a grandmother or mother, whereas, almost 90% foster care children are found to be HIV+ (Fig. 2c). Similarly, in terms of percentage, a significant number of psychiatric morbid negative patients are grown under the care of a grandmother or mother (Fig. 2d). But almost 50% HIV+, who grows under foster care, belong to the psychiatric morbid positive category (Fig. 2d). In relation to the living status of parents, in the case of father alive, 60% are evaluated to be psychiatric morbid negative and father-

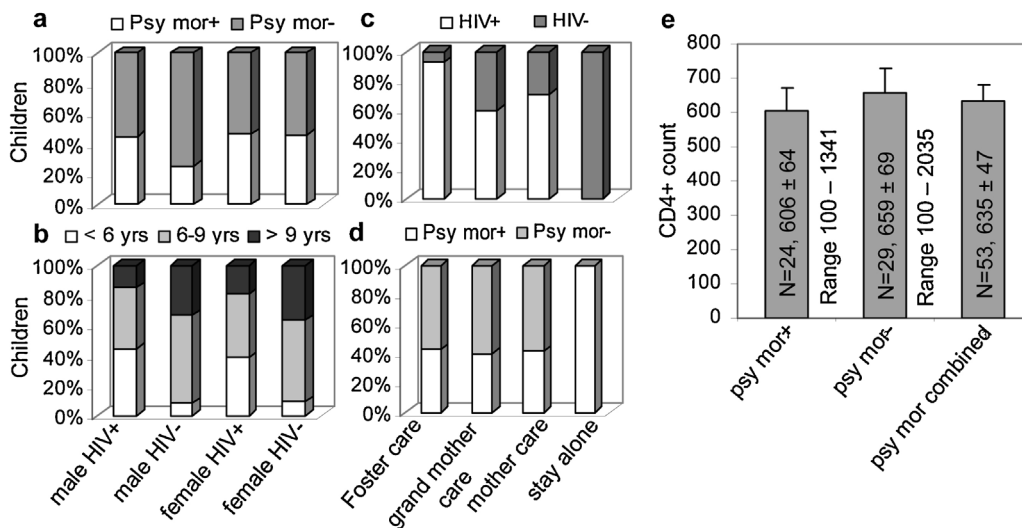


Fig. 2. Gender-wise distribution patterns of psychiatrically morbid positive or negative children in HIV positive or HIV negative category (a) Age-wise distribution patterns of HIV positive or HIV negative male and female children (b). Distribution patterns of HIV+ or HIV- children based on their caregiver status (c). Distribution patterns of psychiatrically morbid positive or negative children based on their caregiver status (d). CD4+ count in the HIV infected children (e).

dead result in ~42% psychiatric morbid positive status. In case of mother living state, ~56% are Psy- or dead state, ~53% are found to be in a Psy+ state (data not shown).

The CD4+ count was performed in 53 HIV+ children (psychiatric morbidities positive 24 and that negative 29). It is noticed that the average CD4+ count is 10% lower in Psy+ than Psy- patients and when the range for Psy+ is found at (100–1341) the same is found as 100–2035 in the Psy- children (Fig. 2e). When we evaluate the different forms of psychiatric disorder, it is noticed that HIV+ male are 50% in CD, but female 58% in ED group. In HIV- group male, 66% in CD/SOM group and 100% female in ED group (Fig. 1b). ART application data suggest that ART was given to 29 (55%) HIV+/Psy+ children and ART is given to 24 (45%) HIV+/Psy-children. The Chi-squared Automatic Interaction Detector, popularly known as

exhaustive CHAID algorithm statistics was utilized to prepare a brief classification tree for the canonical representation of the current data analysis (Fig. 3). Taking PSYCHOMORBSTAT (psycho morbidity status) as the dependency variable tree was prepared in relation to the independent variables e.g. Age, sex, CD4+, caregiver and parents' living status. The statistical analysis is summarized in the tree with adjusted *p* values.

4. Discussion

It is difficult to distinguish pure virus effects and other neuropsychological developmental effects generated from infection, illness, death and social ramifications. Infant grows up. So, this list further may encompass the treatment concern, care,

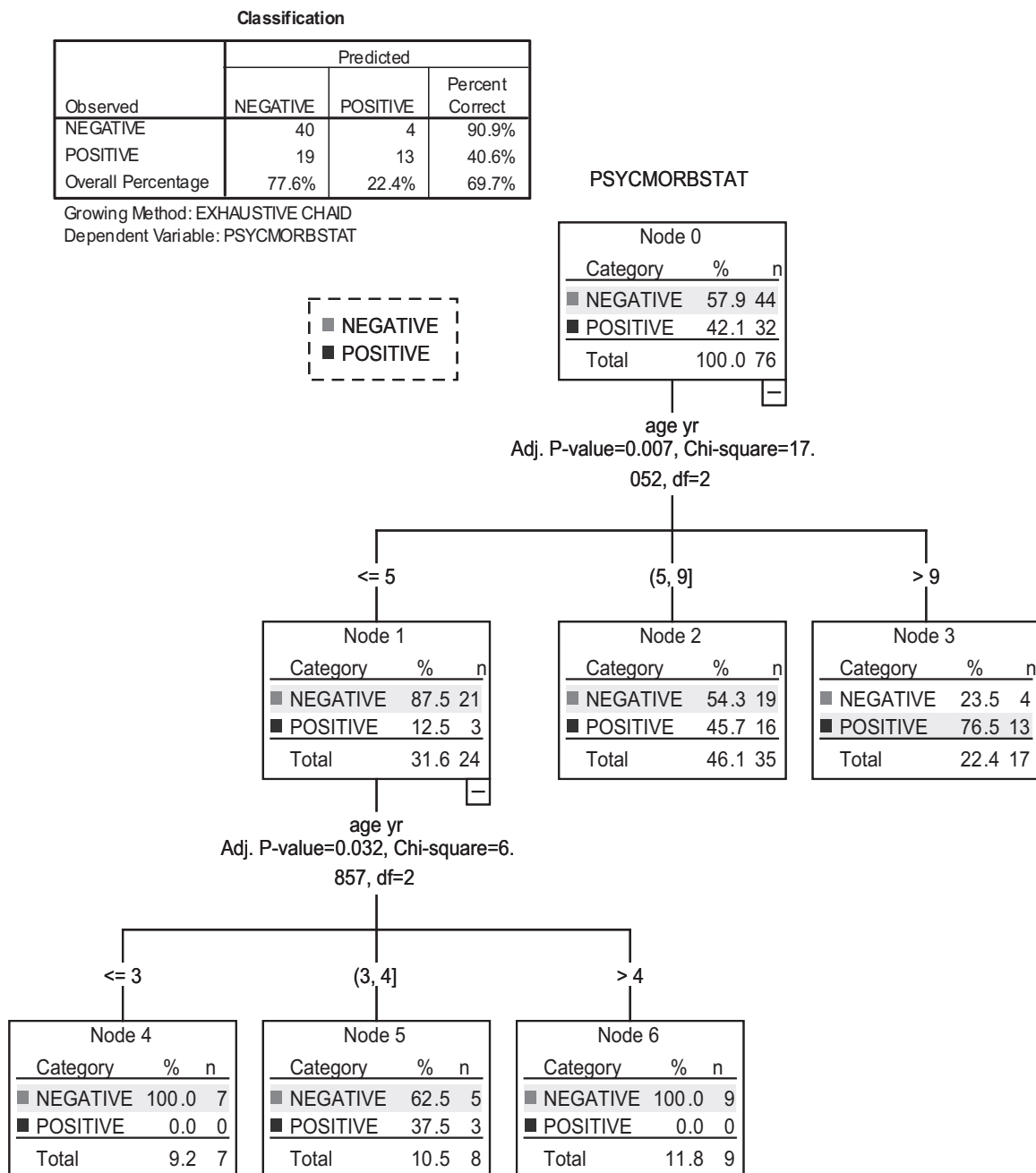


Fig. 3. Classification tree. Taking PSYCHOMORBSTAT (psycho morbidity status) as the dependency variable tree was prepared in relation to the independent variables e.g. Age, sex, CD4+, caregiver and parents' living status. The statistical analysis is summarized in the tree with adjusted *p* values.

disclosure, stigma and emerging sexuality, mainly at the onset of adolescence (Chase et al., 2000; Murphy, Forsyth, & Adnopez, 2002; Sherr, Mueller, & Varrall, 2009). The prudent appreciation of being HIV positive before the advancement towards a personal relationship is very much important for better psycho-social adjustment of the adolescent (Greenhalgh, Evangelii, Frize, Foster, & Fidler, 2013). So, to characterize the individual and interactive role of different factors a suitable control is needed to study the child neuropsychological development. Illness caused by HIV/AIDS as well as stigma and social circumstance may trigger a widespread emotional trauma. In the present study, this is an ideal setting to investigate the bio-psycho-social model rendering the dynamic role of different factors (Engel, 1980). Our present results unequivocally indicate the higher psychiatric morbidity (with its differential form) in the HIV+ children with comparison to the most reliable control of HIV- children who are the sibling of those HIV+ groups.

The literature suggests that HIV itself can affect the development as a patho-physiological consequence (Belman et al., 1996; Murphy et al., 2002; Sherr et al., 2009). It is substantiated by our result of more HIV+ children showing Psy+ status with a notably lower CD4+ count. An early autopsy study in HIV+ children pointed their (90%) significant neurological abnormalities like cerebral atrophy (Belman et al., 1996). In this type of human epidemiological studies the influence of other factors on the studied factor can not be completely negated. And the experimental settings and the availability of the proper sample and reasonable control is not under the choice of the investigator. The report on these issues from Asia and especially from the Indian subcontinent is very rare. In this aspect the present work is important. A report suggests that ethnicity and culture have an impact on the cognitive development and the neuropsychological assessment of the children (Byrd, Arentoft, Scheiner, Westerveld, & Baron, 2008).

It is hypothesized that the non-disclosure of a pregnant woman's HIV status to her partner is associated with non-optimal prevention of detectable viral load at delivery, mother-to-child transmission, initiation of antiretroviral therapy and lack of neonatal prophylaxis (Jasseron et al., 2013). The report reveals a significant neuro-developmental delay in the children with an HIV infection (Bruck, Tahan, & Cruz, 2001). That is evidenced from our present result of higher learning and conduct disorder in HIV+ group. HIV type 1 infection has been suggested to manifest an abnormal neurological status and delayed motor development (Drotar et al., 1997).

Several clinical reports suggest that HIV+ children are at higher risk for anxiety, depression, behavioral and subjective distress and psychiatric morbidity than the non-exposed or sero-reverted children (Havens, Whitaker, Feldman, & Ehrhardt, 1994). Infected children had significantly lower scores on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) (Nozyce et al., 2006). Primarily, though the present outcomes solely pertain to the children concern; notwithstanding the maternal HIV positive status negatively affects family and the child's psychological perceptions. In addition, mother's psychological stress and anxiety relate to the risk of HIV transmission even through breastfeeding (Trocmé et al., 2013). In connection to our early paragraph, the parental awareness and psychological adjustment regarding their HIV status also instigate their child's psycho-pathology. Regarding gender relation, our results demonstrate that while male are more associated to conduct disorder, female are more associated with emotional disorder in both HIV+ children and their sibling control group. An investigation suggests that the HIV+ children comprise attention deficit hyperactivity-disorder (28.6%), anxiety disorder (24.3%) and depression-disorder (25%) (Scharko, 2006).

The median age of the studied children was 7.2 years and the median CD4+ cell count was 665 cells/mm³ (Nozyce et al., 2006).

This finding is in line of the agreement of our present findings. We noticed a 10% decline in CD4+ cell count Psy+ than those negative children. Evidence suggests that children with a CD4+ count of <660 cells/mm³ were more likely to manifest a conduct problem (22% vs. 11%; P=0.02) (Nozyce 2006). The report reveals that lower CD4+ count at the disease entry result in behavioral disorder while higher RNA viral load at disease entry result in depression symptoms (Nachman et al., 2012).

Our present investigation suggests that the ART was given to 55% HIV+/Psy+ children and that were given to 45% HIV+/Psy- children. Adherence to combination ART (cART) is vital for HIV infected adolescents for survival with quality of life. Stigma and inadvertent disclosure of HIV status hamper adolescent self esteem and social recognition (Mutwa et al., 2013). Children with higher viral load had a poorer cognitive and neurological signs and behavioral problem (Brackis-Cott, Kang, Dolezal, Abrams, & Mellins, 2009). Inversely, the children with the neuropsychological dysfunction (low IQ), motor dysfunction and cortical atrophy had the highest risk for later HIV disease progression (Pearson et al., 2000). An infection associated patho-physiology of the neural circuitry of the HIV+ children is apparent and evident in our study in the form of impaired learning ability. When, in HIV- control, the emotional disorder is found to be the main clinical outcome. Having been influenced by the same environmental and parental component, the HIV+ and HIV- children are compared in a more reliable manner to focus exclusively on the infection association in the psycho-pathology in the present study.

In a search for the possible remedial/preventive management, some reports are available. The proxemic communication (i.e. Axis, contact behavior, visual code, and tone of voice) between the mother-child is an important determinant of adolescent psychiatric development (Rebouças et al., 2012). Young Citizens Program (YCG) is recognized as a structural and health promotional approach through which an adolescent self-efficacy and child collective efficacy are generated (Carlson, Brennan, & Earls, 2012). It offers a conducive environment for better sustenance. A covariance structure analysis of the "Parents and Adolescents Coping Together" (PACT) model is suggested to evaluate the effect of family cohesion on child/adolescent outcomes (Murphy, Marelich, & Maternal, 2009). The report reveals that worldwide, a significant number of HIV infected children do not know their status. Hence, strategic disclosure of this information may strengthen children's mental stability (Pinzón-Iregui, Beck-Sagué, & Malow, 2013). Natural mentoring care seems more beneficial to ameliorate the distress, mental health in AIDS-orphaned children (Onuoha & Munakata, 2010). It is supported by our results of better psychiatric outcome in parents-alive status or when the children are under the care of mother/grand mother. This state, possibly increases the ability to cope up the psycho-social adversity resulting in a sustainable resilient. It is advantageous in current day; that pediatric neuropsychology has emerged as a distinct subspecialty area with related education, training, and clinical expertise (Baron, Wills, Rey-Casserly, Armstrong, & Westerveld, 2011).

As there is little or no data regarding the psychiatric problems of HIV infected children in South-East Asian setting, this study will serve an important purpose of fulfilling the void. The psychosocial environment of impaired adult love/concern and support, poverty, child trafficking, migrant population, exploitation in terms of gender and labor may result in the delayed growth and development, late puberty, stunting/wasting and malnutrition of the kids (Tomalski & Johnson, 2010). All these may impart the synergistic effect on psychopathology in case of HIV infection. A large number of sample studies with proper control is required to specify the single factorial association on the HIV-related psychopathology. The interactive role of multiple factors may also disqualify the impact of a single factor. Further investigation is

required to make some conclusive remark. Nondisclosure of female HIV+ status to her partner resulting in a HIV+ birth outcome may be an independent risk factor for child depression in the future and disbelief towards its parents. Further work is required to explore the potential causes for the lack of connection between a trusting relationship and some internalizing symptoms such as anxiety and depression in HIV affected children (Zhao et al., 2011). Our present finding may aid in the understanding of the different associations of psychosocial and patho-physiological determinants. While some study has been conducted on adults, comparing HIV+ children with their HIV- siblings is a powerful way to address whether psychiatric features are related to the disease process within the brain vs. other external factors. The present investigation would be a major contribution to the literature on the neuropsychiatric features of HIV. Because, the appropriate settings are scanty in number, where, investigators have availability to this type of data, which highlights the importance of this paper.

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