Original Article

Clinically Directed Selective Screening for HIV Infection in Hospitalized Children

Sandeep B. Bavdekar and Rinku Agarwal

From the Department of Pediatrics, Seth G.S. Medical College & K.E.M. Hospital, Parel, Mumbai 400 012, India.

Correspondence to: Sandeep B. Bavdekar,Flat No. 9, A2, Worli Seaside CHS, Pujari Nagar, K.A.G. Khan Road, Worli, Mumbai 400 018, India.

Background: *As HIV infection presents with several manifestations, none of which is specific, several children are subjected to HIV testing. Very few studies have examined the issue of probability of HIV infection with a given clinical manifestation.* ***Aim:*** *To determine the probability of HIV infection when a child is hospitalized with at least one of the selected manifestations.* ***Material and Methods:*** *Children aged 18 mo and above, admitted to a tertiary care center in Mumbai, India with chronic diarrhea, severe malnutrition, persistent cough, generalized lymphadenopathy, oral thrush, hepatomegaly, repeated common infections, generalized dermatitis, chronic parotid swelling, recurrent bacterial infection, disseminated tuberculosis and/ or Pneumocystis carinii pneumonia were enrolled in a prospective study after obtaining informed consent. They were subjected to HIV testing using WHO-UNAIDS strategy II. The data obtained was analyzed using the Statistical Package For Social Sciences (SPSS) software program.* ***Results:*** *Twenty-three (20%) of the 115 children enrolled tested positive for HIV. The seropositivity rate for various features ranged from 9.1% for chronic diarrhea to 83.3% for chronic dermatitis. Oral thrush, generalized dermatitis and generalized lymphadenopathy were the significant independent clinical risk factors for predicting HIV seropositivity. The probability of HIV infection was higher in children who had higher number of risk factors present concomitantly* ***Conclusions:*** *The probability of HIV infection in a child is dependent upon the nature and number of manifestations present.*

Key words: *HIV infection, Selective screening.*

CHILDHOOD HIV infection becomes clinically apparent after a widely variable asymptomatic period that could span upto 8 years. These children exhibit a variety of manifestations, which amongst others, include recurrent or opportunistic infections, lymphadenopathy, prolonged or persistent diarrhea and hepatosplenomegaly. However, children without HIV infection also get admitted to hospital with diseases that have similar clinical features. This phenomenon is probably related to high prevalence of malnutrition, poor hygiene, inadequate sanitary facilities and preponderance of infectious diseases in our country. Although tests (such as ELISA, rapid tests and simple tests) that are used in the diagnosis of HIV infection in children over the age of 18 months are comparatively inexpensive, they do impose a considerable burden on the country's healthcare system.

Although, several studies have been carried out to determine the likelihood of HIV infection with a given clinical feature in the

African countries(1-5), there are very few studies that have investigated this aspect in Indian children(6,7). Hence, a prospective study was carried out to determine the probability of HIV infection when a child is hospitalized with at least one of the selected manifestations. These manifestations were chosen either for their commonality amongst children seeking medical help or as these features have been reported to be associated with high seroprevalence rate in other studies or are considered to be highly specific manifestation for HIV infection(4,8,9).

Subjects and Methods

This prospective hospital-based study was carried out in the general Pediatric wards of King Edward VII Memorial hospital, a tertiary care hospital in Mumbai, India after obtaining permission from the institution's Ethics Committee for research in human subjects. Two hundred subjects were sought to be enrolled on the basis of a formula used for the estimation of sample size for single population: $n = Z^2 P (1 – P) / d^2$ [wherein, n= sample size; Z = 1.96 for power of 0.8; P = expected proportion *i.e.*, 0.08 (based on findings in a pilot study) and d = absolute precision *i.e.*, 5%].

Consecutive patients aged between 19 mo and 12 years, admitted as inpatients between September 2003-May 2004, with any of the clinical risk factors enumerated and defined in *Table I* were enrolled in the study, after obtaining an informed consent from the parents or guardians. Pre-test counseling was provided and this consisted of information on the link between the high-risk behavior and HIV infection, technical aspects of screening and on the possible personal, medical, social, psychological and legal implications of being found either positive or negative.

After recruitment, details of demographic data, history and examination findings were recorded in a pre-designed proforma. Five ml of blood was collected by venepuncture and the blood sample was sent to the laboratory for HIV testing by ELISA. The ELISA kits Comb Aids and Microlisa were used. These detected antibodies to both HIV-1 and HIV-2 viruses. The diagnosis of HIV infection was confirmed as per WHO- UNAIDS strategy II(10). The parents of children who were sero-positive, were offered post-test counseling, which included providing support and exploring the possibility of achievable solutions to personal problems. The data obtained was analyzed using the Statistical Package For Social Sciences (SPSS) software program. For the chi-square (X^2) analysis, Fischer exact test was used. Wherever appropriate (with bivariate analysis), the relative risk estimate was measured using odds ratio and 95% confidence interval (CI) was estimated around Odd's Ratio. Two-tailed P values less than 0.05 were considered significant.

Results

This prospective study enrolled 115 children (69 boys, 46 girls; M: F= 3:2) aged 19mo-12years. The mean age of the study population was 55.0 ± 31.3 months with a median of 48 months. The maximum number of children (51, 44.3%) was in the age group of 19months-3years. Prolonged fever for over a month's duration was the commonest symptom (53%) noted in the study group and hepatomegaly was the commonest sign (67%) found on the clinical examination. Severe malnutrition was seen in 50% of children. None of the children had chronic parotid swelling or pneumocystis carini pneumonia. The provisional primary diagnoses on admission included tuberculosis, bacterial pneumonia, gastroenteritis, probable immuno-deficiency disorder, typhoid, malaria, cirrhosis of liver, leukemia, lymphoma, collagen

TABLE I–*Definition of Clinical Risk Factors Studied*

Clinical risk factor	Description
Fever for more than a month	Documented fever (Axillary temperature more than 37.8ºC) over a month
Chronic diarrhea	Presence of two or more loose stools per day for a period exceeding one month
Severe malnutrition	The presence of grade III protein energy malnutrition as defined by Gomez's classification, namely 60 percent or less of expected weight for age using the 50th percentile of the NCHS standards as the reference.
Persistent cough	History of cough for more than one month
Generalized lymphadenopathy	Presence of enlarged lymph nodes (diameter of lymph nodes more than 1 cm in axilla and cervical region and more than 1.5 cm in inguinal region) in two or more non- contiguous sites for more than 3 months.
Oral thrush	Presence of whitish plaques in the oral cavity which could not be easily removed and when removed showed an erythematous base.
Hepatomegaly	Liver span more than 4-7 cm (depending upon patient's age) as detected clinically
Repeated common infections	Two or more episodes of infections such as upper respiratory infections and gastro-enteritis in the last 6 months
Generalized dermatitis	Which includes eczema, disseminated maculopapular dermatoses.
Chronic parotid swelling	Swelling of at least one of the parotid glands for a minimum period of 3 months
Recurrent bacterial infections	Occurrence of more than two episodes of serious bacterial infections such as pyogenic meningitis and pneumonia in two year period
	Pyogenic Meningitis: Diagnosed on the basis of clinical history, signs of meningial irritation and results of CSF examination
	Pneumonia: Diagnosed on the basis of clinical findings and results of radiological studies
Disseminated tuberculosis	Miliary tuberculosis (diagnosed on the basis of miliary mottling on the chest radiograph) or
	CNS tuberculosis (diagnosed on the basis of CSF findings and / or results of neuroimaging studies in relevant clinical settings) or
	Pulmonary tuberculosis in conjunction with abdominal tuberculosis (diagnosed on the basis of results of radiological, bacteriological and cytological studies in clinically relevant settings)
Pneumocystis carinii pneumonia	Diagnosed on the basis of clinical features (fever, cough, respiratory distress), results of arterial blood gas analysis, findings on chest radiographs and microbiological studies

NCHS: National Center for Health Statistics, USA.

vascular disease, systemic onset JRA, protein energy malnutrition, nutritional anemia and bronchial asthma amongst others.

Relation between risk factors studied and HIV seroprevalence rate

In the study population, 23 (20%) children were found to be sero-positive. The information regarding the number of subjects with the defined manifestation and the distribution of sero-status related to each manifestation are depicted in *Table II*. The seropositivity rate for the various manifestations varied from 9.1% for chronic diarrhea to 83.3% for generalized dermatitis. For three commonest manifestations, fever for more than one month, severe malnutrition and hepatomegaly, the probability of sero-positive rates were 18%, 26.1% and 20.8% respectively. As shown in *Table III*, oral thrush, generalized dermatitis and generalized lymphadenopathy were the significant independent clinical risk factors for predicting HIV seropositivity. Children with oral thrush had 13.7 times greater risk of being HIV seropositive compared to those who did not have oral thrush. Children with persistent generalized lymphadenopathy had 6.3 times

TABLE II–*HIV Serostatus in Relation to each Clinical Feature*

Clinical manifestations	HIV sero-positive	HIV sero-negative	χ^2	*P*	Odds ratio and (95% confidence interval)	Sensitivity (%)	Specificity (%)
Fever for more than one month (n=61)	11 (18.0)	50 (82.0)	0.31	0.750	0.77 [0.31-1.92]	47.8	45.7
Chronic diarrhea (n = 11)	1 (09.1)	10 (90.9)	0.91	0.373	0.37 [0.05-3.07]	4.3	89.1
Severe Malnutrition (n = 50)	13 (26.0)	37 (74.0)	1.99	0.100	1.93 [0.77-4.87]	56.5	59.8
Persistent cough (n = 28)	7 (25.0)	21 (75.0)	0.58	0.364	1.48 [0.54-4.07]	30.4	77.2
Oral thrush* (n = 4)	3 (75.0)	1 (25.0)	7.64	0.004*	13.65 [1.35-138.1]	13.0	99.0
Generalized lymphadenopathy* (n=20)	10 (50.0)	10 (50.0)	13.68	0.001*	6.30 [2.19-18.09]	43.5	89.1
Hepatomegaly (n = 77)	16 (20.8)	61 (79.2)	0.09	0.464	1.16 [0.43-3.11]	69.6	33.7
Repeated common infection (n = 13)	5 (38.5)	8 (61.5)	3.12	0.257	2.90 [0.85-9.9]	21.7	91.3
Generalized dermatitis* (n = 6)	5 (83.3)	1 (16.7)	15.87	0.002*	25.27 [2.78-229.45]	21.7	98.9
Disseminated tuberculosis (n = 22)	5 (22.7)	17 (77.3)	0.13	0.633	1.23 [0.39-3.763]	21.7	81.5
Recurrent bacterial infection (n = 2)	1 (50.0)	1 (50.0)	1.15	0.263	4.13 [0.24-68.70]	4.3	98.9

Figures in parentheses indicate percentages; * Statistically significant: p > 0.05.

TABLE III–*HIV Seropositivity in Relation to the Number of Risk Factors Present*

Number of Risk Factors Present	HIV- positive Cases (n= 23)	HIV- negative Cases (n= 92)
One, n= 20	2 (10.0)	18 (90.0)
Two, n= 44	6 (13.6)	38 (86.4)
Three, n= 29	5 (17.2)	24 (82.8)
Four, n= 14	4 (28.6)	10 (71.4)
Five, n= 5	4 (80.0)	1 (20.0)
Six, n= 3	2 (66.7)	1 (33.3)

Figures in parentheses indicate percentages.
χ^2= 18.48, $p < 0.05$ (significant).

greater risk of being HIV seropositive compared to those who did not have generalized lymphadenopathy. Children with generalized dermatitis had a 25 times greater risk of being HIV seropositive as compared to those who did not have generalized dermatitis. Though recurrent bacterial infection was not a significant independent risk factor for predicting HIV seropostivity; children with recurrent bacterial infection had 4.1 times greater risk of being HIV seropositive compared to those who did not have this clinical risk factor.

Table III depicts the relationship between number of risk factors that were concomitantly present in a child and sero-positive rate. As the number of risk factors increased the probability of HIV sero-positivity also increased significantly. The rate of seropositivity was 80% in those who had five clinical risk factors. This is in contrast to lower figures obtained with lesser number of risk factors.

Discussion

HIV infection has become one of the greatest pandemics ever. It is in the process of nullifying all the good work done in the field of child survival. Early diagnosis of HIV infection in a child is helpful in providing supportive care and in instituting prophylactic therapy. At the same time, undertaking work up for the diagnosis of HIV infection means spending of community's precious resources. Although, antibody-based tests for the diagnosis of HIV infection are comparatively inexpensive, the costs involved in the associated process of counseling can be enormous. Counseling is also considered to be time consuming and is emotionally draining on the staff(11). In addition, the parents have to undergo tremendous psychological stress till a negative test result is obtained. Routine HIV testing is not a feasible option considering the economic and psychological costs involved. Clinically directed selective screening to diagnose HIV infection is the only way out to achieve the dual objective of diagnosing the maximum number of subjects without wasting resources in an undue manner. However, for this the physicians should be aware about the quantum of risk of HIV infection associated with a particular manifestation in the community that they serve. However, such data regarding Indian children is scarcely available.

In our study, the overall sero-positive rate was 20%. This high rate cannot be considered to reflect the seropositive rate in the population or even in childhood population. It would be much lower. However, the high rate found indicates that the selectively directed screening has been able to facilitate the diagnosis of HIV infection in hospitalized children. We selected 13 risk factors that included common clinical features seen in admitted children (prolonged fever, severe malnutrition, persistent cough, dermatoses, repeated common infections, generalized lymphadenopathy and hepatomegaly), features that were considered highly specific of childhood HIV infection (pneumocystis carinii pneumonia, chronic parotid swelling and recurrent bacterial

Key Message

- Oral thrush, generalized dermatitis and generalized lymphadenopathy were the significant independent clinical risk factors for predicting HIV seropositivity.

infections), and the features that were reported to be associated with higher seropositive rate of HIV infection (chronic diarrhea, oral candidiasis and disseminated tuberculosis). We did not encounter even a single case with parotid swelling or *Pneumocystis carinii* pneumonia (PCP). This indicates that these signs are uncommon in admitted children, whether HIV positive or otherwise. The fact that we only studied children over the age of 18 months and reluctance of physicians to undertake invasive diagnostic procedures for confirming the diagnosis of PCP may also have contributed to our inability to diagnose even a single case of PCP in our series. Although, manifestations such as severe malnutrition, persistent cough, repeated bacterial infections, recurrent minor infections, disseminated tuberculosis and hepatomegaly were associated with seropositive rate in excess of 20%; only oral candidiasis, generalized lymphadenopathy and generalized dermatoses were significant independent risk factors for prediction of HIV infection ($P < 0.05$). This means that severe malnutrition, persistent cough, recurrent minor infections, disseminated tuberculosis and hepatomegaly without being HIV-associated diseases are common manifestations in sick children who require hospitalization in our community.

It is noteworthy that Karande, *et al.*(6) also found that oral candidiasis was a significant risk factor in a study conducted in children from Mumbai, India. Other investigators from Africa have identified different independent risk factors for childhood HIV infection. These include malnutrition(5), oral candidiasis(5,12), pneumonia(13), adenopathy(5) and chronic diarrhea(12,14). In our study we did not find that chronic diarrhea was as a significant risk factor for HIV seropositive status. This indicates that the significant risk factors could vary from community to community. This makes it imperative that studies are carried out to determine these factors in different communities and in different geographical areas. It was also noted that the probability of HIV infection increased progressively and significantly ($\chi^2 = 18.48$, $P < 0.05$) as the number of risk factors concomitantly present in the child increased. A child with more severe disease or with greater immunosuppresion may have more manifestations and this phenomenon could be responsible for the trend referred to above.

The study had its share of limitations. The study was carried out in hospitalized children who were having symptoms and signs of some illness. Hence, these results would also not be applicable to screening of asymptomatic children. In addition, we did not include children aged 18 months and younger as diagnosing HIV infection in them would have entailed performance of HIV DNA PCR. This was not possible due to financial constraints. Despite these limitations, the study was able to identify that oral candidiasis, generalized lymphadenopathy and generalized dermatitis that showed significant association with HIV infection in children. The study also showed that the probability of diagnosing HIV infection increases with the increase in the number of risk factors present in a child. Pediatricians and physicians working in

similar situations could use this data to undertake clinically directed screening to diagnose HIV infection in children.

Acknowledgements

Authors thank Dr. Nilima Kshirsagar, Dean, Seth G.S. Medical College and K.E.M. Hospital, Mumbai for permission to publish this article and Dr. Nithany Gogtay, Associate Professor of Clinical Pharmacology for providing valuable inputs.

Contributors: SBB: Concept and design, critical revision of the draft, act as guarantor of the manuscript RA: Collection, analysis and interpretation of data, preparation of the first draft.

Funding: None

Competing Interests: The paper was presented at the International Pediatric Update held in Mumbai in October 2004 and the abstract of the paper was published in the Proceedings of the meeting brought out on the occasion.

REFERENCES

1. Esamai F, Buku GM. HIV seropositivity in children admitted with diarrhoea at Eldoret District Hospital, Kenya. E Afr Med J 1994; 71: 631-634.
2. Lepage P, Van de Perre P, Nsengumuremye F, Van Goethem C, Bogaerts J, Hitimana LG. Bacteremia as predictor of HIV infection in African children. Acta Paediatr Scand 1989; 78: 763-766.
3. Pallangyo K, Hakanson A, Lema L, Arris E, Mteza I, Palsson K, *et al*. High HIV seroprevalence and increased HIV-associated mortality among hospitalized patients with bacterial infections in Dar es Salaam, Tanzania. AIDS 1992, 6: 971-976.
4. Matee MLN, Lyamuya EF, Mwinula JH, Mbena EC, Samaranayke LP, Scheutz FF. Clinical predictors of HIV-1 infection among preschool children in Dar es Salaam, Tanzania. East Afr Med J 1995; 72: 694-698
5. Prazuck T, Tall F, Nacro B, Rochereau A, Traore A, Sanou T, *et al.* HIV infection and severe malnutrition: a clinical and epidemiological study in Burkina Faso. AIDS 1993; 7:103-108.
6. Karande S, Bhalke S, Kelkar A, Ahuja S, Kulkarni M, Mathur M. Utility of Clinically-directed selective screening to diagnose HIV infection in hospitalized children in Bombay, India. J Trop Pediatr 2002; 48:149-155.
7. Merchant RH, Shroff RC. HIV seroprevalence in disseminated tuberculosis and chronic diarrheas. Indian Pediatr 1998; 35: 883- 887.
8. Lodha R, Singhal T, Jain Y, Kabra SK, Seth P, Seth V. Pediatric HIV infection in a tertiary care center in North India: Early Impressions. Indian Pediatr 2000; 37: 982-986.
9. Emodi IJ, Okafor GO. Clinical manifestations of HIV infection in children at Enugu, Nigeria. J Tropical Pediatr 1998; 44:73-76.
10. National AIDS Control Organization. National AIDS Prevention and Control Policy, New Delhi, Ministry of Health and Family Welfare and National AIDS Control Organization, 2001, P 24.
11. Colebunders R, Ndumbe P. Priorities for HIV testing in developing countries? Lancet 1993; 342: 601-602.
12. Akpede GO, Ambe JP, Rabasa AI, Akuhwa TR, Ajayi Akoma MA, Bukbuk DN, *et al*. Presentation and outcome of HIV-1 infection in hospitalized infants and other children in North Eastern Nigeria. E Afr Med J 1997; 74: 21-27.
13. Mann JM, Francis H, Davachi F, Quinn TC, Baudoux P, Nzilambi N, *et al.* Risk factors for HIV seropositivity among children 1-24 months old in Kinshasa, Zaire. Lancet 1986; 20: 654 -656.
14. Thea DM, St. Louis ME, Atido LI, Kanjinga K, Kembo B, Matondo M, *et al*. Prospective study of diarrheas and HIV-1 infection among 429 Zairian infants. New Engl J Med 1993; 329: 1696-1702.