"Spectrum of HIV-TB Co-Infections In Paediatric Patients"

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ABSTRACT: Tuberculosis (TB) is the most common AIDS-defining opportunistic infection worldwide. Tuberculosis co-infection with HIV is becoming a global emergency especially in India. Its diagnosis is notoriously challenging in countries, with poor resources and with limited diagnostic facilities. The main objective of the research study was to determine the prevalence, pattern and risk factors for TB in HIV co-infected children in Bowring and lady Curzon hospitals, India A cross sectional study, five years retrospective cohort of HIV- children co infected with TB was carried out at the Centre of excellence from April 2004 to Dec 2009. SAS-6.50 version software was used to analyze data. Univariate analysis was employed to draw the significant inference. Of a total of 60 HIV-infected children observed during the review period, 16(26.66%) were diagnosed as having co-existing TB. Among these, their mean age, weight, CD4 cell count and CD4 percentage at the time of diagnosis were 6.3 ± 2.4 years, 14.3 ± 3.4 kg, 262 ± 28.0 cells/ml, and 9.9%, respectively. Pulmonary TB accounted for 14.60% of all TB cases seen, while disseminated form was seen in 3.00%, TBM (5.0%) and TB Bone (2.5%). TB defaulter at 2 months, six months and eight months was 0.86%, 1.10% and 2.56% respectively. Weight loss, severe cough was the clinical features found to have a fairly good sensitivity (88.9%) and specificity (88.6%) for TB in co-infected children (No censored data), with a positive predictive value of 23.0%. While immune reconstitution syndrome (IRIS) occurred in 3 (5.00%) of the patients, two death (3.34%) was recorded among the co-infected children. HAART initiation with low CD4 count is highly associated (r=0.75) with TB. The logistic regression model is very easy to predict the relation between CD4 count and HIV-TB co infection.

Key words: CD4, HIV-TB, HAART, AIDS, LRA, SAS, IRIS

INTRODUCTION:

AIDS is characterized by a number of opportunistic infections which are responsible for high morbidity and mortality. In fact, even before the discovery of the causative virus, cases of AIDS were defined as those having certain opportunistic infections. The spectrum and distribution of opportunistic infections in AIDS patients is ever-expanding. This spectrum varies from continent to continent as also between children and adults. There are differences in the pattern of opportunistic infections in AIDS patients depending upon the risk group. From the limited studies conducted, it is quite apparent that tuberculosis is the single most important opportunistic infection associated with AIDS in our country. It is estimated that an HIV-infected individual is six times at higher risk of acquiring tuberculosis than an HIV-negative individual. In AIDS patients, the incidence of extra pulmonary tuberculosis increases and that of smear positive pulmonary tuberculosis decreases - making the diagnosis of the disease much more difficult, unless good diagnostic tools are available. The centre of Excellence for HIV Care, Bowring and Lady Curzon hospitals has conducted Five year co hort studies in HIV-infected children since 2005 and through these studies has collected cross sectional data on the immunologic status of these patients and recorded complications, including infectious diseases, related to HIV infection and its treatments. Therefore data were analyzed from co hort data, performed after treatment with highly active antiretroviral therapy (HAART) was given, to determine the rates of various infectious complications and the immunologic correlates, specifically CD4 cell counts, associated with these diseases.

EQUATIONS.

A Cross sectional five year co hort study was conducted at ART Centre Bowring and Lady Curzon hospitals, a total 60 HIV-infected children observed during the review period from 2005-2010 , Demographic-Age ,sex, Family history ,occupation ,economic status ,educational status and HIV serpositivity of the parents were included ,clinical profile-type of regimen, duration of the regimen ,WHO Clinical stage , Types of OI's ,onset of OI's to Start of HAART ,complication and illness , anthropometric parameters – Growth parameters ,Immunological marker like CD4 (µ/dl)count at base line , Cd4(µ/dl) count at onset of TB and progressive serial CD4(µ/dl) count were considered. Collected data was analysed using SAS& SPSS-16.50 version .Logistic regression and Univariate analyses were used to draw the significant inference.

LOGISTIC REGRESSION MODEL:

In a present study setting, an outcome might be presence/absence of OI'S disease. The focus of this document is on situations, in which the outcome variable is dichotomous, although extension of the techniques of LRA to outcomes with three or more categories (e.g., improved CD4 Count, CD4 remains same or consistently maintained, or worse) is possible, (Hosmer & Lemeshow, 1989,). In this section, we review the simple regression model and, then, present the model for LRA. The fundamental model underlying logistic regression analysis (LRA) poses that a continuous outcome variable is, in theory, a linear combination of a set of predictors (Age, sex,CD4 Count etc.,) and errors. Thus, for an outcome variable, Y, and a set of p predictor variables, X1,...,Xp, the LRA model is of the form

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots \beta_P X_P + \epsilon$$

$$Y = \alpha + \sum_{J=1}^{r} \beta_j X_j + \epsilon$$

Y= is the intercept, β_j is a multiple regression co efficient, ϵ -errors associated

$$E(Y/X_1X_2 \ \ X_P) = Y^1 = \alpha + \sum_{j=1}^{r} \beta_j X_j$$

$$Loge\left[\frac{\pi}{1-\pi}\right] = \alpha + \sum_{j=1}^{r} \beta_j X_j$$

$$Loge\left[\frac{\pi}{1-\pi}\right] = \alpha + \beta_1 X_1 + \cdots \beta_P X_P.$$

"Y "variable coded 0 &1, 0, 1 represented Ois with or without present,

ODD ratio of OI's $=Loge\left[\frac{\pi}{1-\pi}\right]$

TABLES AND FIGURES:

Tab (1): Descriptive statistics of HIV Infected Peadiatric patients on HAART demographic and laboratory profile**.**

	Categorical variable	Male	Female
1.	Age(Years)	6.2±3.4	5.63±4.80
2		38(63.33%)	22(36.66%)
I.	**Family history**		
a)	**Parents-Education status**		
b)	Illiterate:	32(84.21%)	15(68.10%)
c)	Literate	06(15.78%)	07(31.81%)
III.	**Economic status**		
a)	Low income group	22(36.66%)	12(20.00%)
b)	Medium Income group	09(15.00%0	06(10.00%)
c)	High Income group	07(11.66%)	04(6.66%)
IV.	**Occupation**		
a)	Employed	15(25.0%)	07(11.66%)
b)	Un employed	19(31.66%)	12(20.00%)
c)	Un known	04(6.66%)	03(5.00%)
V.	**Residence**		
a)	Urban	07(11.66%)	05(8.33%)
b)	Rural	29(48.33%)	15(25.00%)
c)	Not Known	04(6.66%)	02(3.33%)
V.	**WHO-Clinical staging**		
a)	Stage-I	05(8.33%)	01(1.66%)
b)	Stage-II	08(13.33%)	04(6.66%)
c)	Stage-III	07(11.66%)	07(11.66%)
d)	Stage-IV	18(30.00%)	10(16.66%)
VI.	**Regimen.**		
	S+L+N	13(21.66%)	09(15.0%)
	S+L+E	09(15.0%)	03(5.0%)
	Z+L+N	12(20.0%0	06(10.0%)
	Z+L+E	04(6.66%)	04(6.66%)
VII.	**Immunological marker**		
	CD4 (%)	8.36	7.65(P≤0.05)

Of a total of 60 HIV-infected children reviewed during the five years period, 15(25.26%) were diagnosed as having co-existing TB. their mean age, weight, CD4 cell count and CD4 percentage at the time of diagnosis were 6.3 ± 2.4 years, 14.3 ± 3.4 kg, 262 ± 28.0 cells/ml, and 9.9%, respectively. Pulmonary TB accounted for 14.60% of all TB cases seen, while disseminated form was seen in 3.00%, TBM (5.0%) and TB Bone (2.5%). TB defaulter at 2 months, six months and eight months was 0.86%, 1.10% and 2.56% respectively. And a mean CD4 cell count/percentage of 261.6 ± 28.0 cells/ml and 9.9%, signifying severe immune suppression Tab (1). There was no statistical significant difference in the characteristics of male and female co-infected children at recruitment (P≤0.05).

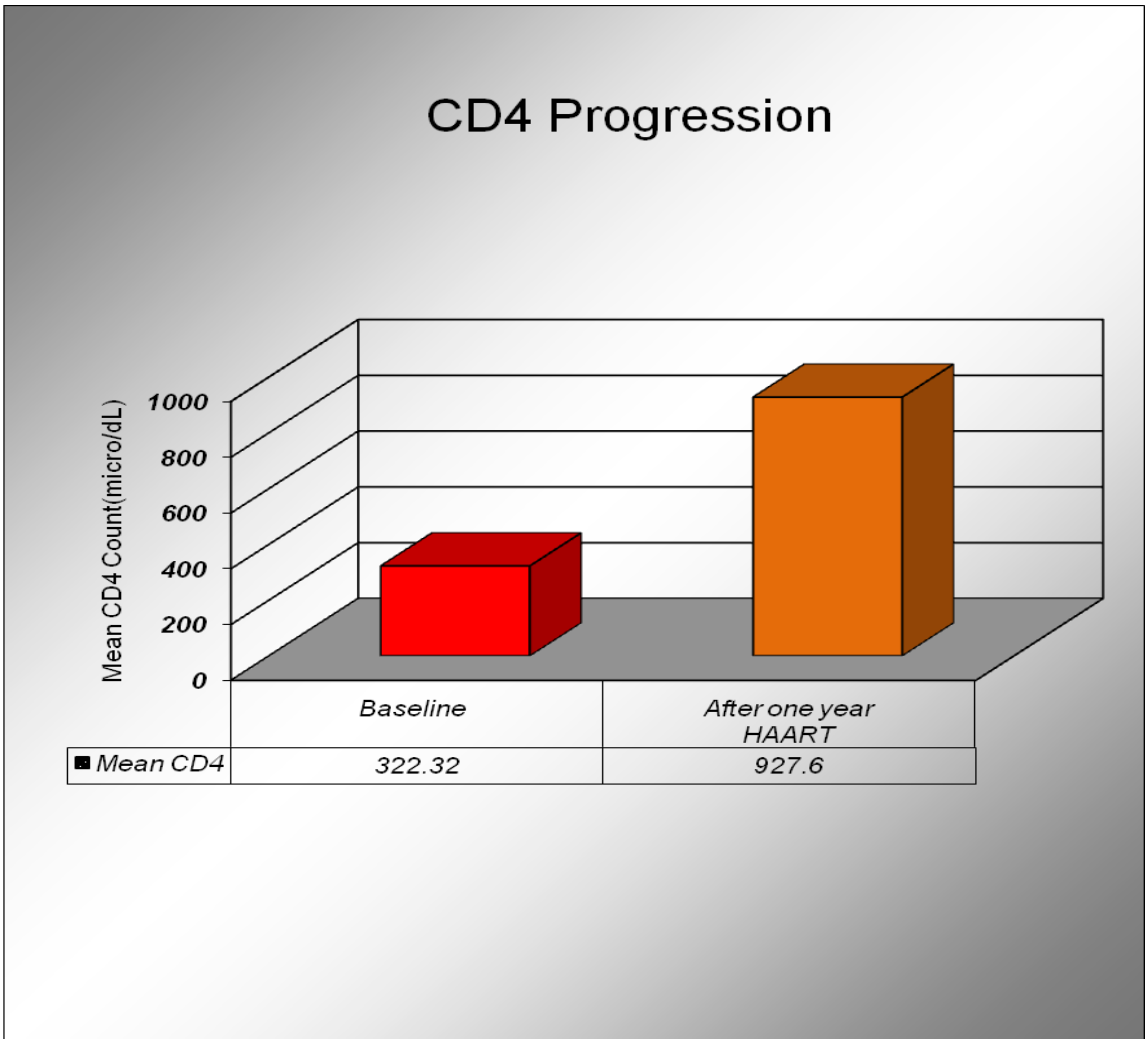
Tab (3): TB sites and WHO clinical stage.

SL	Sites of TB	(%)	WHO Clinical stage	CD4 Cell count	CD4(%) age	P-Value
1.	**Pulmonary TB**	**08(13.33%)**	**3**	**242**	**8.2**	**<0.05**
2.	**Disseminated**	**02(3.33%)**	**4**	**08**	**4.8**	**<0.05**
3.	**TBM**	**03(5.00%)**	**4**	**146**	**6.3**	**<0.05**
4.	**Lymph node**	**01(1.66%)**	**3**	**310**	**11.9**	**<0.05**
5.	**Bone**	**02(3.33%)**	**4**	**102**	**5.1**	**<0.05**
6.	**Total**	**16(26.66%)**	**4**	**161**	**7.2**	**<0.05**

Tab (3): Age wise distribution and site of TB in co infected children.

SL	Age(Yrs)	PTB	Disseminated	TBM	Lymph node	Bone
01	**0-1 yrs**	02	0.0	02	0.0	0.0
02	**>1-2yrs**	02	01	01	01	01
03	**>2-5yrs**	01	01	0.0	0.0	01
04	**>5-10yrs**	02	0.0	0.0	0.0	0.0
05	**>10-15yrs**	01	0.0	0.0	0.0	0.0
06	**>15-17yrs**	00	00	0.0	0.0	0.0
	Total	**08**	**02**	**03**	**01**	**02**

Children in younger age group were more susceptible to TB and were detected Sputum positive (7.60%), In Tab (2), children in the age group of 1-2 years and 2-5 years were statistically significant (P≤0.05) and had TBM and disseminated (3.33%).Environment in which the children live and CD4 count are two important factors affecting the HIV-TB Co infection. HAART was started at a lower CD4 count (<10.62%) and high viral load, TB manifestation was highly associated with lesser CD4 count.



Fig(1): Trend of CD4 Count in paediatric TB-HIV Co infected.

Tab (4): Sensitivity, Specificity and +Ve predictive value for various methods used for diagnosis of TB co infected children.

Sl	Variables used for TB diagnosis	(%)	Sensitivity (%)	Specificity (%)	PPV (%)
1.	History of chronic cough >1 month.	10	44.40	92.50	21.10
2.	Positive history of contact (TB)	39	55.6	80.10	11.10
3.	+Ve Chest X-ray (TB)	3.00	11.1	82.6	2.10
4.	History of ingestion of unpasteurised cow milk	5.00	12.2	98.50	40.0
5.	Monteux test >5mm in diameter	0	0	0	0
6.	Gastric lavage for AFB	4	0	0	0
7.	Sputum for AFB	5	0	0	0
8.	Wt loss(>10kgs)	29	100	80.0	18.40

Tab (5): Association between presence and absence of Opportunistic infection, categorical variables and HIV –CD4 count marker.

SL.	Variables	β	SE	Wald	df	Sig	Exp(β)	CI-95% for Exp(β)
01	**Base line CD4 Count**	**-0.02**	**0.01**	**3.91**	**1**	**0.048**	**0.998**	**1.00**
02	**CD4 count after one year HAART**	**0.00**	**0.02**	**0.072**	**1**	**0.788**	**6.00**	**1.003**
03	**Age**	**0.071**	**0.104**	**0.464**	**1**	**0.469**	**1.073**	**1.315**
04	**Sex**	**-0.414**	**0.668**	**0.385**	**1**	**0.535**	**0.661**	**2.446**
05	**Opportunistic infection**	**0.794**	**1.37**	**0.335**	**1**	**0.563**	**2.221**	

-2log likelihood function -60.57, Coxsnell R square =0.140, Negelkereke R square=0.203,P≤0.05

THEOREM AND PROOF:

Logistic regression method Used to relate linear functions of explanatory variables to the probability of ("Diseases presence1=yes, 0=no".). We had adjusted for the confounding effect of CD4 count and age. The effect of relationship

$$\log\left(\frac{p}{1-p}\right) = \alpha + \beta X$$

The function log [p/ (1-p)] is called the "logit".ODD of CD4 count with respect to OI's were 6.00 times greater than ODD for those with non TB presented in Tab (5).Younger Age groups were highly associated with exposure of TB ,1.07 times greater risk of co infection. Tab (4) depicts that, identification of AFB in sputum specimens, and radiological diagnosis was used as standards for diagnosis in this review. The sensitivity, specificity and PPV of the common clinical presentations, signs, and radiological/laboratory investigations were tabulated. The variables tested were, history of chronic cough for >1 month, severe weight loss, history of contact with adults with chronic cough (TB), Mantoux test with in duration of >5 mm, chest x-ray, and non response to conventional antibiotics. All showed low to moderate sensitivity and specificity with the exception of severe weight loss of >-3SD which showed sensitivity/specificity of 88.9%, 88.6% respectively. The outcome showed that two patients (3.33%) died from disseminated TB; and also had developed IRIS. All patients received ATT, and all were started on HAART.The Serial CD4 count after start of HAART had significantly improved .Logistic regression were employed to draw the risk factors of TB HIV Co infection TB is a communicable disease ,spread primarily through droplets expelled by someone who has infectious pulmonary or laryngeal TB when they cough or sneeze, (14).It can occasionally be contracted by ingestion of contaminated unpasteurized cow's milk. The number/concentration of the organism expelled into the air during coughing or sneezing, the duration of exposure to infected persons, and the condition of the immune system of the host are the major factors that predict the transmission of TB to another person.(14) . Close contacts are at highest risk, and children acquire this from infected adults. TB is equally a disease of poverty and easily acquired in overcrowded environment with low standard of living. This is the true picture in most under developed/Developing countries in the sub Saharan region,(19). Some studies among HIV patients have shown great association between low CD4 cell counts and susceptibility to TB especially extra-pulmonary forms. (3) .In the present study, all the TB co-infected children were in WHO stages 3 and 4 disease with severe imunosuppression and very low CD4 Count, at the time of initiation of HAART. Some authors have reported association between low CD4 cell count and TB in HIV patients. [22][25] Cohen and co-workers [10] however made no such observation. They however attributed such observation to the small number of their study population. HIV is notoriously known to cause depletion and dysfunction of CD_4 cells. (5) (8) other immunological defects caused by this virus include lymphoid tissue destruction, CD_8 cell and thymic cell dysfunction, B cell abnormalities and auto-immune abnormalities. The degree of depletion of CD_4 cell determines the degree of immune suppression. The two infections by having the capability of depleting the CD_4 cell count could explain the reason why the majority of patients in the present study had low CD_4 cell count. Diagnosis of TB in HIV children has been very challenging especially in India and as poor resource settings, because of non-availability of newer modern methods of diagnosis, and overlap of TB and HIV symptoms and signs. In this present study, culture proven methods and newer techniques were not available. Diagnosis was mainly based on combinations of older methods. These include history of contact with adult with chronic cough (80.10%), history of cough of greater than 1 month duration (82.60%), chest x-ray suggestive of pulmonary TB (95.1%), Monteux test of indurations

(8.60%). The main aim of this study was to provide information that will guide healthcare providers in these areas with limited facilities to predict HIV infected children for risk of co-infection with TB. Severe weight loss of greater than (> 3SD) below the mean weight for age was found to have greater sensitivity and specificity, though with lower predictive value, and can be used to predict HIV infected children for the risk of co-infection with TB, Many cases of IRIS associated with TB in adult HIV patients occurs on commencement of HAART, and several have been reported in India. [11][12] Little information is available on Peadiatric patients. Immune reconstitution syndrome, defined as paradoxical clinical deterioration after starting HAART CD4 accounted at the time of IRIS was (1256±85.60µ/Dl) and median duration was IQR (4-6) weeks, resulting from improving immune system interaction with organisms that have colonised the body during early stages of HIV infection.

CONCLUSION

TB co-infection with HIV in children is common. Severe weight loss and cough can be used as a clinical guide to identify HIV-infected children at risk of co-infection with TB who will require careful observation, further evaluationandintervention.

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