Temporal changes of CD4 Count of HIV infected children using curve fitting models

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Abstract- The CD4 count is a critical measure of immune system and is used as an important biomarker for describing the progress to AIDS in children's and adults. Usually infants will be having better CD4 count with good immune system as age progresses the CD4 count start declining. ˙Present study aims **to** describe the trend of CD4 count with respect to different age group of children's. A prospective and retrospective cohort data was collected from Government ART centers of Bangalore city. Total 100 HIV infected patients alive on HAART were considered from March 2009- 2010. Demographic profile, mode of transmission, age, sex, CD4 count at inception of HAART, follow up CD4 count like 6 months, 12 months and 24 months were recorded..Opportunistic infection, duration of HAART, WHO clinical stage, type of regimen and adherence were documented. Collected data were analyzed by using SPSS-16.50 version software. The mean age of the children was 8.19 ± 3.62 years, CI 95% 7.63-9.08, $P>0.05$. At the time of inception of HAART CD4 count was fewer and negatively correlated ($r= -0.02^{ns}$) with age of the children. the mean CD4 count at the time of 6 month was 573.99 ± 288.73 µ/dL, CI 95% 572.36-576.28, $P<0.05$; CD4 count at 12 months was 654.68 ± 269.09 µ/dl, CI 95% 653.26-655.89, $P<0.05$ and CD4 count at 24 months was 773.20 ± 274 µ/dL. 87, CI 95% 772.64-775.03, $P<0.05$ respectively.Duration of HAART and follow up CD4 count was statistically significant ($p<0.05$) with age of the children .The majority of children's have better CD4 count after inception of HAART .HIV TB confection is the most common in older children(7-15.0years)

Early inception of HAART mainly helps the childrens to maintain better CD4 count with good immune systems and they are less prone to OI's.

Index Terms- CD4, HAART, WHO Stage, HIV

I. INTRODUCTION

AIDS is a scourge, more than 1.30 million children has been affected globally .In India more than a lakh children infected from Mother to child and IUD's. HAART have been initiated during 2004. The CD4 count is a critical measure of immune system and is used as an important biomarker for describing the progress of AIDS in children and adults. Among Infected children over five years of age there is continual loss of CD4-T cells, with a lower CD4 count indicating more sever immune deficiciency and higher risk of developing opportunistic infections (OI's) and AIDS defining illness .The CD4 count is also important biomarker for HIV infected children; however, the CD4 counts vary strongly with different age group of pediatric population. New born infants have substantially

higher cd4 count than older .With increasing age, the CD4 counts in infants decline and begin to approximate those of adults; a decline in children's CD4 count is therefore normal. The rate of CD4 count decline is often much more rapid in infected infants than in infected adults[1]. Many authors have shown that HIV infants have lower CD4 counts than uninfected infants[2].The present study aims to describe the trend of CD4 count with respect to the different age group of children.

II. MATERIALS AND METHODS

A prospective and retrospective cohort data were collected from Government ART centers of Bangalore city. A Total of 100 HIV infected alive and on HAART   patients were considered for study evaluation for the period from March 2009- 2010.Informed consent was obtained from the parents or guardian. Demographic profile, mode of transmission, age, sex, CD4 count at inception of HAART, follow up CD4 count like 6 months, 12 months and 24 months were recorded. Growth parameters; weight, height and BMI was systematically evaluated for each follow up period .Opportunistic infection, duration of HAART, WHO clinical stage, type of regimen and adherence were documented. Collected data were analyzed by using SPSS-16.50 and Minitab 6.50 version software. Exponential model, different polynomial predictive models were used to know the temporal changes of CD4 count over a period of time. Mortality and survivability rate was determined by using Kaplanmeir mortality curve.

III. MODEL FORMULATION

Single exponential smoothing: CD4 count has been changes due to illness and co morbid condition of the patients. The impact of effective comprehensive care support and treatment of antiretroviral treatment, CD4 count can improve and more enable to develop immunity and viralogical suppression in children's. The forecasting is more essential to know the trend and seasonal changes of CD4 count. In this aspect we wish to forecast the predictive value of our time series data. We have assumed that   =observed value at time't '; our forecast was denoted by   ,the predictive error of the model was given by. The method of single exponential forecasting takes the forecast for the previous and adjusts it using the forecasting error .That is, the forecast for the next period was

$$F_{t+1} = F_t + \alpha(Y_t - F_t),$$ Where α is a co

Tab (1): Descriptive statistics of HIV infected children's Demographic profile.

SL.No	Defined variables	Mean±SD	CI-95%	P-Value
I.	Demographic profile			
I(a).	Age(yrs)	**8.19±3.62**	**7.63-9.08**	**P<0.05**
01	2-4 yrs	2.96±**1.22** (05)	2.40-3.05	P>0.05
02	5-7yrs	6.32±**0.98** (12)	5.20-6.89	P<0.05

03	7-9yrs	8.20±**0.30** (15)	7.56-9.08	P<0.05
04	9-12 yrs	10.14±**0.56** (19)	9.22-11.31	P<0.05
05	13-15 yrs	12.55±**0.21** (22)	12.16-16.08	P<0.05
06	16 yrs	14.26±**0.420** (27)	13.05-15.63	P<0.05
II	Gender			
01	Male	65.0%	63.22-66.18	P<0.05
02	Female	35.0%	34.25-36.89	P<0.05
III	Mode of transmission			
01	Parintal transmission	88.90%	87-13-90.16	P<0.05
02	IUD's	6.53%	5.81-7.01	P>0.05
03	Not known	4.57%	4.07-5.2	P>0.05
IV	Parents HIV Status			
01	HIV +Ve			
1(a)	Yes (Both)	79.0%	78.06-80.55	P<0.05
1(b)	Single	15.0%	14.50-16.11	P<0.05
	No	8.0%	7.01-9.50	P<0.05
02	HIV –ve			
2(a)	Yes	90.0%	88.26-91.56	P<0.05
2(b)	Not known	10.0%	8.56-11.56	P<0.05
IV	Mode of transmission in parents			
01	Homosexuality	10.20%	9.04-11.53	P<0.05
02	Heterosexuality	76.33%	74.02-77.30	P<0.05
03	IUD's	7.47%	6.56-8.01	P<0.05
04	Not Known			
V	Economic status			
01	Higher income	14.0%	11.47-13.88	P<0.05
02	Mid income	28.0%	27.02-29.36	P<0.05
03	Low Income	58.0%	57.52-59.01	P<0.05

*Significant p<0.05

The mean age of the children's was 8.19±3.62years, CI 95% 7.63-9.08, P>0.05. Male and female comprises 65.0% and 35.0%.The mean of age of the different age groups of children was 2-4years 05(,2.96±**1.22,** CI 95 % 2.40-3.05**) ,** P>0.05; 5-7yrs 12(6.32±**0.98,** CI 95% 5.20-6.89**),p<0.05;** 7-9yrs 15 (8.20±**0.30,** 7.56-9.08**),** P<0.05; 9-12 yrs 19 (10.14±**0.56,** 9.22-11.31**),** P<0.05 13-15 yrs was

22 (12.55±**0.21,** CI 95% 12.16-16.08**),** P<0.05; 16 yrs 27 (14.26±**0.420,** CI 95% 13.05-15.63),p<0.05.HIV mode of transmission were recorded and Parintal transmission (89.0%), IUD's (7.0%) and not known (4.0%).Both parents were get infected (79.0%),single parents(15.0%), and not infected (8.0%).Parents mode of transmission were obtained from white cards, Homosexuality (10.0%), Heterosexuality(77.0%),IUD's (8.0%) and Not Known (3.0%) ; High income (14.0%) , mid income(28.0%) and low income status (58.0%).

Tab (2): Mean CD4 count and other defined variables of Infected children (N=100).

SL.No	CD4 Count	Mean±SD	CI 95%	P-Value
01.	**Age**	**8.19±3.62**	**7.63-9.08**	**P<0.05**
02.	**CD4 count at base line**	**293.71±74.40[a]**	**291.99-295.63**	**p>0.05**
03.	**CD4 count at six month**	**573.99±288.73[b]**	**572.36-576.28**	**P<0.05**
04.	**CD4 count at 12months**	**654.68±269.09[ab]**	**653.26-655.89**	**P<0.05**
05.	**CD4 count at 24 months**	**773.20±274.87[b]**	**772.64-775.03**	**P<0.05**
06.	**Mean HAART duration**	**542.79±224.79[b]**	**540.89-226.03**	**P<0.05**
VIII	Co morbid condition			
	Yes	**12.00%**	**10.99-13.58**	**P>0.05**
	No	**88.00%**	**87.63-90.21**	**P<0.05**
	Death	**8.00%**	**7.08-9.15**	**P<0.05**
	LFU	**4.0%**	**3.50-4.23**	**P>0.05**
	Survivar	**88.0%**	**87.85-90.52**	**P<0.05**
XI	HIV TB co infection			
	Yes	**18.0%**	**17.53-19.08**	**P>0.05**
	No	**82.0%**	**81.55-83.89**	**P<0.05**
X	Mean Duration of HAART	**598.01±9.80**	**596.33-601.56**	**P<0.05**
XI	WHO clinical stage			
	Stage I	3.0**%**	2.56-3.06	**P>0.05**
	Stage II	18.0**%**	17.35-19.22	**P>0.05**
	Stage III	45.0**%**	44.56-46.21	**P<0.05**
	Stage IV	65.0**%**	64.36-66.05	**P<0.05**

Superscript a, b significant mean differences, DMRT test.

At the time of inception of HAART CD4 count was fewer and negatively correlated (r= -0.02) with age of the children. HAART should improve the CD4 count and it was found to be 573.99±288.73 μ/dL at the time of six month, CI 95% 572.36-576.28, P<0.05; CD4 count at 12 months was 654.68±269.09 μ/dl, CI 95% 653.26-655.89, P<0.05 and   CD4 count at 24 months was 773.20±274 μ/dL. 87, CI 95% 772.64-775.03, P<0.05respectively.The Mean duration of HAART was 542.79±224.79days, CI 95% 540.89-226.03,p<0.05.Duration of HAART and follow up CD4 count was statistically significant (p<0.05) presented in Tab(2)
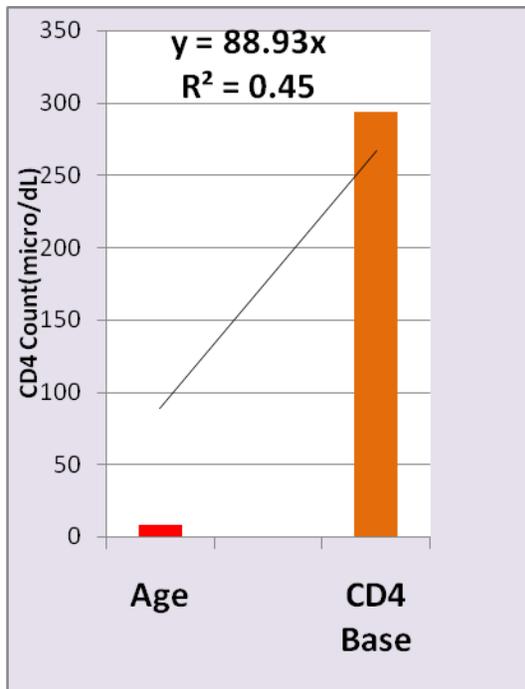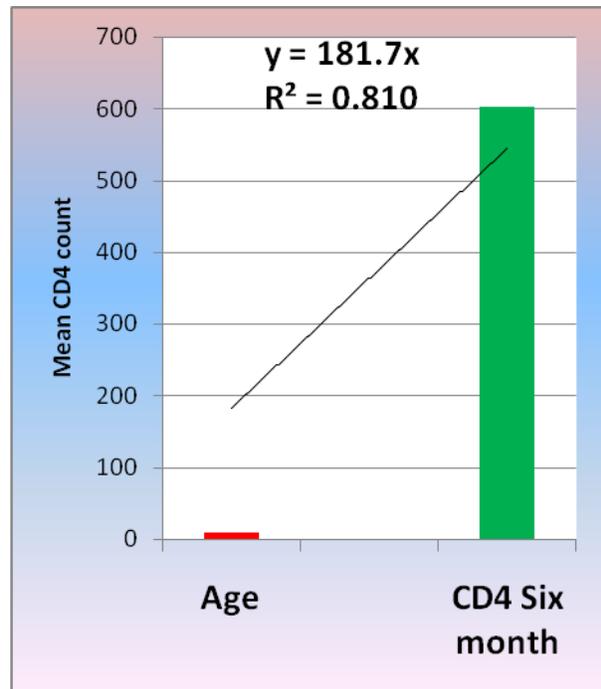
Fig 1(a): Trend of CD4 at base line

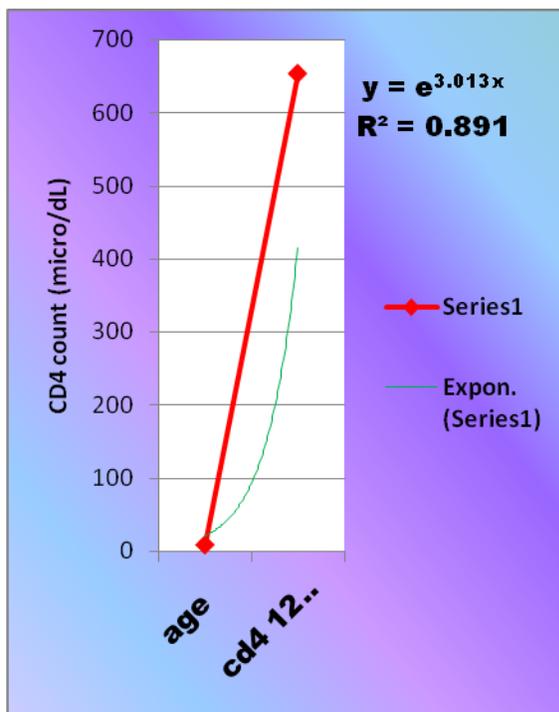Fig 1(b): Trend of CD4 count at after six months

Fig 1(c): Trend of CD4 count at 12 months
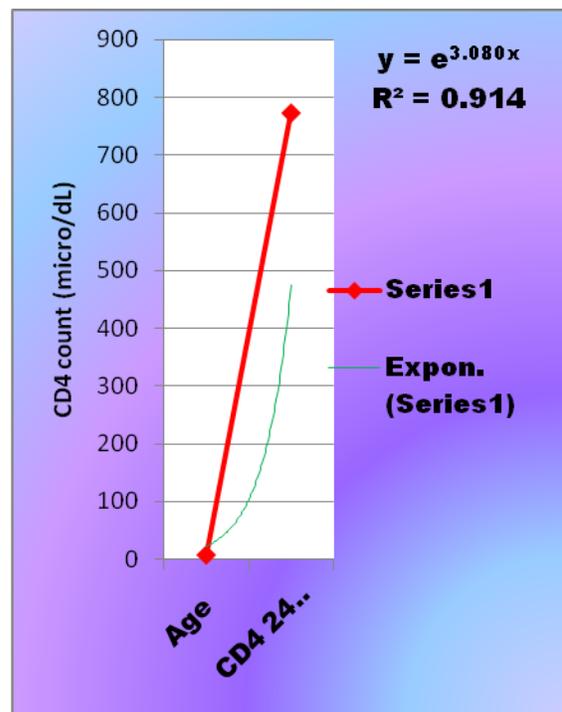

Fig1(d):Trend of CD4 count at 24 months

The trend of CD4 count was observed by different curve fitting methods.asper the model the mean predicted CD4 count at inception

of HAART was 89.93µ/dL with co- efficient of determination was R^2 =0.45 presented in Fig 1(a),Age and CD4 count was not

statistically significant (p> 0.05) at the time of HAART initiation. It was explained that R² 45.0% variation was observed from both

the variables. Fitted linear trend equation was 88.93 xs. After effective comprehensive treatment, palliative support, good adherence

and WHO clinical stage can improve the CD4 count and it was observed in Figures 1(b), 1(c) and 1(d). The Exponential model was

fitted to explain the variations among CD4 count changes in mean age at different follow up period.Asper the predicted model

smoothing was positively associated with age of the children and follow up CD4 count .The predicted equation was found to be y =

181.7x, CD4 count at six months; 12 months was $y = e^{3.013x}$ R² = 0.891 and 24 months was $y = e^{3.080x}$ R² = 0.914 respectively.

Tab (3): KPM –Model for estimation of mean survival of HAART duration censored by mortality

SL.No	[a] Mean				[a] Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
01	572.810	23.086	527.562	618.058	547.000	45.965	456.909	637.091

a. Estimation is limited to the largest survival time if it is censored.
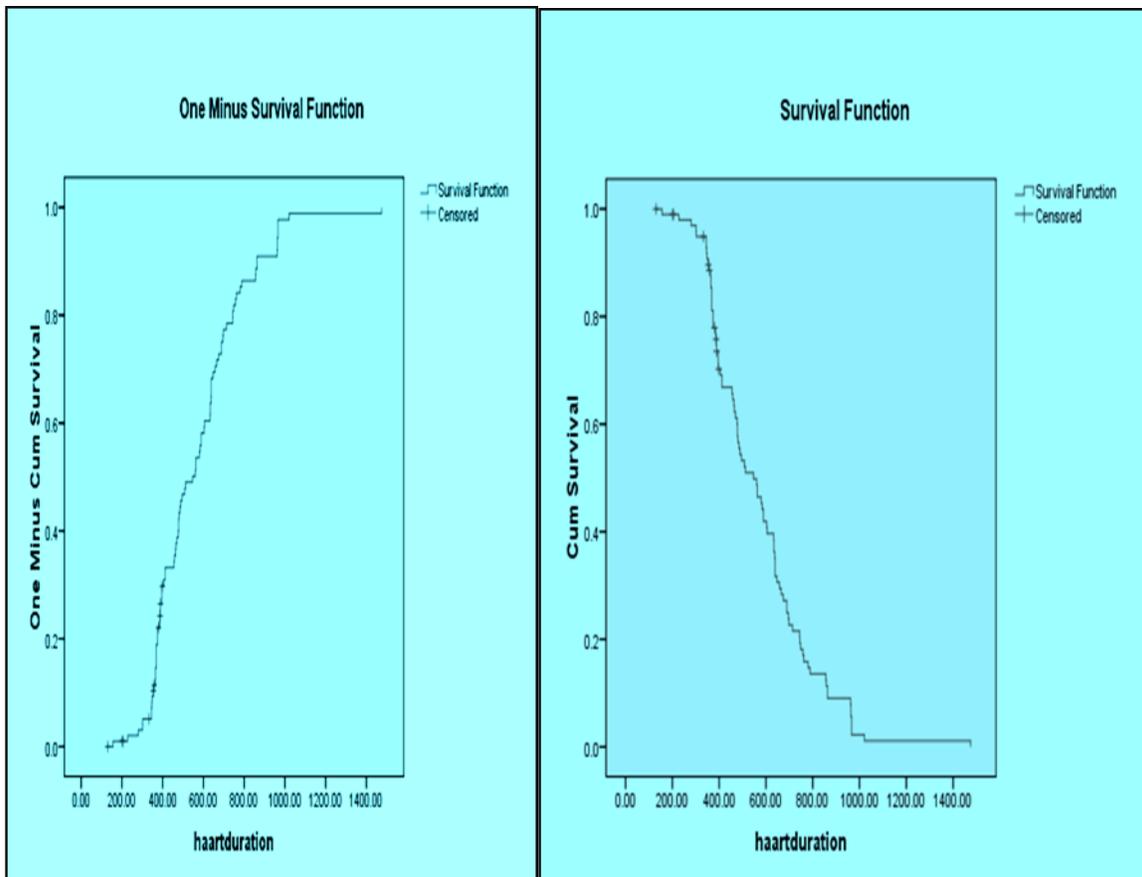
Fig 2(a): 1-Survival of Children's   Fig2(b): Survival of children's

Over a period of time Mean HAART duration was 572.810±23.08 days with CI 95% 527.562-618.058 and median was 547.000±45.965 days with CI 95%456.909-637.091 days. The KPM –model was clearly showed that ,reduced mortality (7.98%) p=0.001, low risk , good prognosis , adherence, familial support, lower stigma ,effective strategic and comprehensive treatment would increase the survivability of the children.Psychosoial support and level of literacy were predictors of the survivability and it was documented as a indicator variables Tab(3)

Tab (4): Relation between OI's and age of the children's.

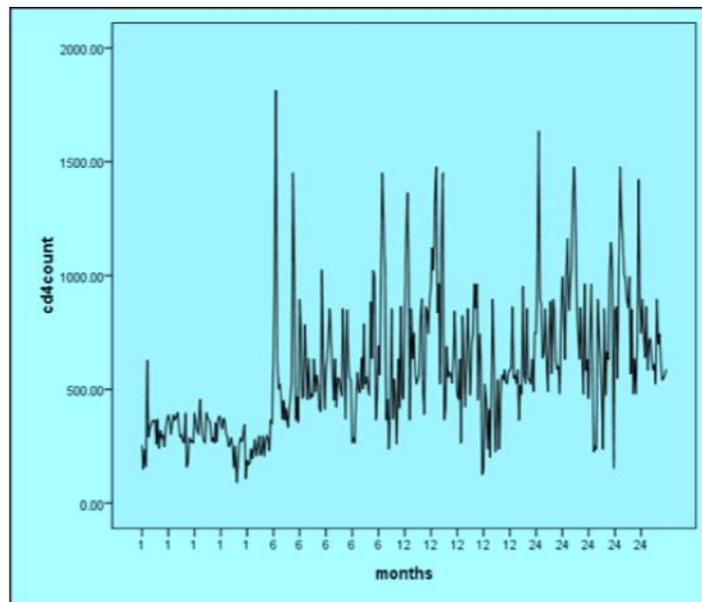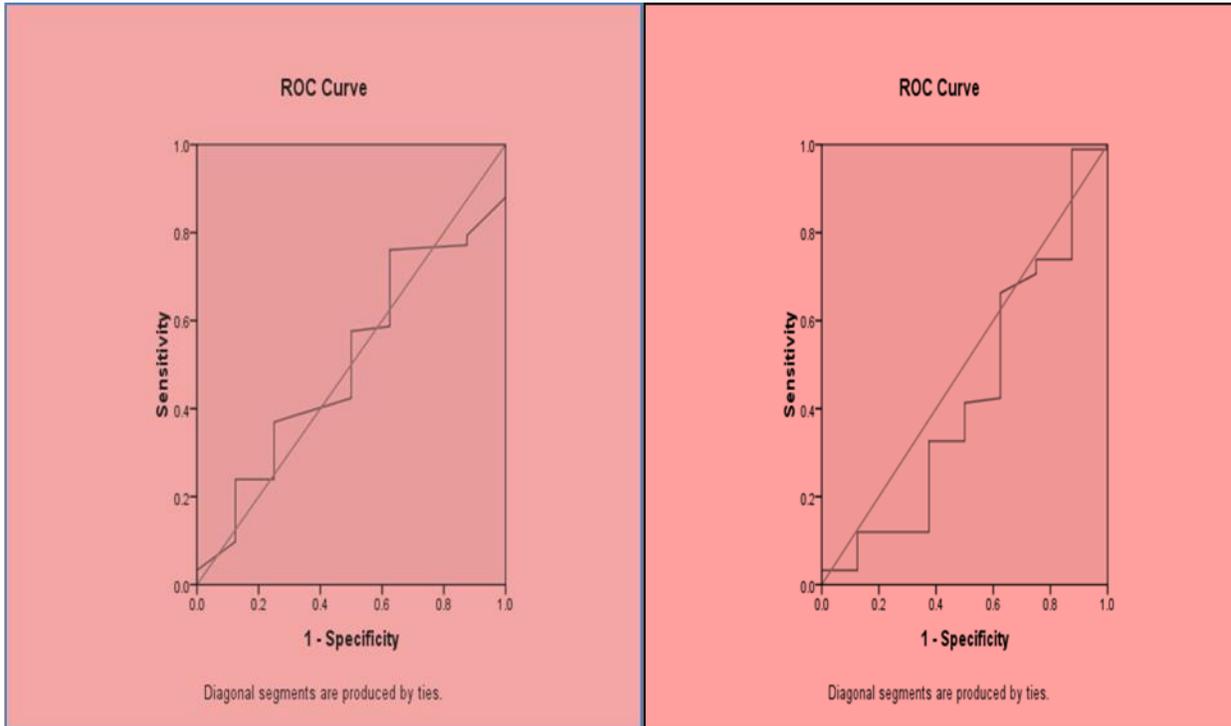| SL.No	Variables	B	S.E.	Wald	Sig.	Exp(B)
01	Age (Years)	.007	.112	.003[ns]	.953	1.007
	Base line CD4 count(μ/dl) At the time of inception of HAART	.001	.006	.037[ns]	.848	1.001
02	CD4 at Six month (μ/dl)	-.001	.002	.648*	.421	.999
03	CD4 at 12 month (μ/dl)	-.002	.002	.988*	.320	.998
04	CD4 at 24 month (μ/dl)	.001	.002	.869*	.351	1.001
05	WHO clinical stage	6.399	4.721	1.837*	.175	601.007
06	Duration of HAART	-.003	.002	1.880*	.170	.997
07	Opportunistic infection	-3.697	3.598	1.055*	.304	.025

*2 Log likelihood-49.18, Cox & Snell R Square-0.064, Nagelkerke R Square-0.149

Inception of HAART at lower CD4 count (<100μ/dl) is more eager to acquainted with Oi's .The relation was expressed by using logistic regression. Different types of TB were found with different episode. Many studies showed that spectrum of TB was associated with baseline CD4 count(<100μ/Dl), advanced WHO clinical stage(Stage IV) ; lower body weight, low BMI and adolescent were influenced factors of TB . The Present study correlates with the age group and OI's. Age and base line CD4 count was not statistically significant (p>0.05). CD4 at Six month.648*(p=0.05) , CD4 at 12 month.(988*,p=0.05) , CD4 at 24 month .869*(p<0.05) , Duration of HAART 1.880* p<0.05 ,WHO clinical stage 1.837,p=0.05 were statistically significant and -2 Log likelihood-49.18, Cox & Snell R Square-0.064, Nagelkerke R Square-0.149.The co efficient were presented in Tab (4).

Tab (5): AUC-for age and base line CD 4 count of the children's

SL	variables	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
					Lower	Upper

					Bound	Bound
01	Age	.506	.098	.954	.313	.699
02	Base line CD4 count (µ/Dl)	.429	.118	.505	.198	.659

Fig(1):Changes of CD4 count over a period of base line HAART to after 24 months of treatment

Tab (6): Specificity and sensitivity of OI's with respect to different age groups and baseline CD4 count

	Age (years)			Base line CD4 count(µ/dl)		
	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
01.	1.0	1.000	1.00	1012.22	1.000	1.00
02.	2.50	.989	1.00	1986.23	.989	1.00
03.	3.150	.913	1.00	1136.12	.989	.875
04.	3.40	.902	1.00	1052.08	.978	.875
05.	3.50	.891	1.00	157206	.967	.875
06.	3.82	.880	1.00	1636.90	.946	.875
07.	4.25	.793	.875	1681.21	.935	.875
08.	4.65	.783	.875	1711.50	.924	.875
09.	4.90	.772	.875	1761.00	.913	.875
10.	5.25	.761	.625	1832.50	.902	.875
11.	5.55	.739	.625	1922.50	.891	.875
12.	5.70	.728	.625	2000.00	.880	.875
13.	5.90	.717	.625	2041.50	.870	.875
14.	6.10	.609	.625	2071.50	.859	.875
15.	6.55	.598	.625	1152.00	.848	.875
16.	6.95	.587	.625	1252.00	.837	.875
17.	7.15	.576	.500	333.00	.826	.875
18.	7.45	.565	.500	372.00	.804	.875
19.	7.74	.554	.500	239.00	.793	.875
20.	7.94	.543	.500	243.50	.783	.875
21.	8.45	.446	.500	248.50	.739	.875
22.	8.95	.424	.500	253.00	.739	.750
23.	9.30	.370	.250	257.00	.717	.750
24.	9.70	.348	.250	260.50	.707	.750
25.	9.86	.337	.250	265.50	.663	.625
26.	9.96	.326	.250	268.50	.652	.625
27.	10.50	.283	.250	271.50	.620	.625
28.	11.10	.239	.250	276.00	.587	.625
29.	11.60	.239	.125	279.00	.576	.625
30.	12.50	.174	.125	282.00	.565	.625
31.	13.50	.098	.125	285.50	.554	.625

32.	14.50	.033	.000	288.00	.543	.625
33.	15.50	.011	.000	292.50	.467	.625

Receiver operating characteristic analysis (ROC) was used to compare with age and CD4 count in respect to OI's .Study showed that AUC for age was 0.506 ±0.098 (CI 95% 0.313-0.699) ;AUC for base line CD4 count was 0.429±0.118 (CI 95% 0.198-0.659) Tab (). The matrix of analysis were clearly pointed out 50.60 % of children's with higher age (between 7-15 years) suffered HIV TB co infection .In case of younger age group, with good CD4 count were not susceptible to HIV TB co infection.Asper the ROC model Tab () age group between 1 to 6.95 years have better CD4 count with better sensitivity and specificity 98.90%,87.50% to 83.75% , 87.50% respectively. In case of Older age group between 7-15 years had lesser CD4 count and very much susceptible to HIV TB co infection. The specificity and sensitivity was 46.70%, 62.50% respectively Tab (6)

IV.   DISCUSSION

The relevance of this finding is yet to be clarified, but suggests more effective immune reconstitution in children treated early in their course. Fitted models allow us to predict long-term CD4 count based on age and different clinical parameters. Curve fitting models were used to account for inter-individual variability and examine effects of HAART with respect to different age groups, sex, WHO staging and HIV TB co infections. Early inception of HAART mainly helps the childrens to maintain better CD4 count with good immune systems and they are less prone to OI's and it also reduces the progression of disease, mortality and RNA plasma viral load. The children with Low CD4 count at Pre-ART level initiated with HAART are more proned to OI's , AIDS defining illness like malignancies, low BMI, decreasing Body weight ,advanced clinical stage, poor phenotypic appearance , growth retardation and lipoatrophy and dystrophy.

However, we observed that improvement in CD4 count was better among children with higher baseline CD4 count i.e. lesser degree of immunosupression. Similar observations have been reported in adults by Lawn, *et al*. [11], but seldom reported in children. This could be attributed to overwhelming opportunistic infections observed with higher degrees of immunosupression. Hence earlier detection and higher baseline CD4 count might improve the outcome of antiretroviral treatment.

V.   CONCLUSION

The majority of children have better CD4 count after inception of HAART and that the slope of rise was greater in older children in the first six months of therapy. Present study shows that children with older age are more prone to HIV TB confection (7-15 years).

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