ORIGINAL ARTICLE
pISSN 0976 3325 | eISSN 2229 6816
Open Access Article
www.njcmindia.org

CORRELATES OF CHANGE IN CD4 COUNT AMONG THE HIV PATIENTS AT ANTIRETROVIRAL TREATMENT CENTRES IN INDIA: CROSS SECTIONAL ANALYSIS OF SECONDARY DATA

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Financial Support: None declared
Conflict of interest: None declared

How to cite this article:
Bajpai RC, Chaturvedi HK, Bhatnagar N, Jha UM. Correlates of Change in CD4 Count among the HIV Patients at Antiretroviral Treatment Centres in India: Cross Sectional Analysis of Secondary Data. Ntl J Community Med 2016; 7(2):71-77.

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Date of Submission: 16-09-15
Date of Acceptance: 18-02-16
Date of Publication: 29-02-16

ABSTRACT

Introduction: The CD4 count supervision is an important part of the HIV-care programme worldwide. The monitoring of CD4 counts over time could provide insight into the way patient's respond to the treatment with effectiveness over time.

Methodology: Information on demographic and programme variables was extracted from 114210 patients across the country registered during 2007 with initial CD4 counts and longitudinally reassessed in 2012. The logistic regression method was used to find the factors associated with CD4 change either positive or negative.

Results: The CD4 counts increased significantly over time in different subcategories of age, sex, ART status and time to ART initiation. 50.7% of total registered HIV-patients exhibits any change in their CD4 from initial measurement. The regression analysis showed any change in CD4 was associated with age, TS/TG group, on ART patients and ART initiation after 1 year. Further, 75% of these patients were displayed increase in CD4 counts. The likelihood of increase in CD4 was statistically associated with higher chances within the subgroup of factors as age <15 years, TS/TG group and on ART patients.

Conclusion: Strategic interventions to increase early diagnosis of HIV infection, linkage to HIV-care and rapid access to ART must be implemented at country level, especially among the key population with poor access to HIV services.

Key words: CD4 count, HIV/AIDS, ART, Secondary data, Regression analysis, India

INTRODUCTION

Around four decades ago, it was widely believed that infectious diseases were no longer threat in the developed world. That confidence was shattered in the early 1980's by the advent of HIV infection. At the end of 2011, approximately 34 million people (31.6-35.2 million) were living with HIV worldwide that increased 17% from 2001[1]. National adult HIV prevalence was estimated as 0.31% (0.25-0.39%) in 2009 with persons living with HIV/AIDS were 2.40 million (1.93-3.04 million)[2]. As in the absence of HIV-cure, antiretroviral treatment (ART) has effectively and consistently reduced HIV-related morbidity and mortality around the world since its inception[1,3,4]. The ART program in India was launched in 2004 to prolong survival and free services are being provided at more than 250 ART centers across the country[5]. Early start of ART with

higher CD4 counts is one of the predictors of virological success after treatment that prevents disease progression and transmission[6,7]. An uninfected individual has nearly 1100 CD4 cells per milliliter of blood[8]. This CD4 count decreases in numbers with time due to the HIV virus, so it can be used to monitor the progression of the disease [9].

The European AIDS Clinical Society guidelines have recommended ART initiation for patients with CD4 counts ≤350[3,10]. However, the International Antiviral Society guidelines and the Department of Health and Human Services guidelines recommend ART initiation in all HIV-positive patients regardless of CD4 count[11]. Guidelines for resource-limited countries have been revised and CD4 count threshold increased from 200 to 350 or 500[3,12,13]. According to the Joint United Nations Programme on HIV/AIDS, approximately eight million people were receiving ART in low and middle-income countries, which was only 54% of those eligible for ART at the end of 2011[1].The CD4 cell count has huge predictive and therapeutic implications and forms the foundation for most HIV-treatment decisions[14-17]. Once a patient enrolls at HIV-care, the CD4 count is examined routinely to check any increase in it to a relatively normal-level (>500) or otherwise[13].

Several studies have looked at change from the cross sectional point of view rather than considering the pattern of change over time in CD4 counts [18, 19]. Luguterah and Adams (2013) however used a longitudinal approach and suggested that the pattern of growth in CD4 cell was not linear[14]. There is a little evidence on studies on CD4 count variations among HIV-infected individuals in India by large due to the lack of prospective studies. This study therefore took into consideration, the changes in the CD4 count over the period of study.

METHODS

The study population included in this secondary data analysis consisted of patients from Indian PLHA database which is routinely collected for HIV control programme since 2004. Currently, more than 250 ART centres throughout country provide free ART services and collect data on monthly reporting basis. The initial information on demographic variables includes age (in complete years), sex and vulnerability indicators: ART status, initial CD4 cell count and time to ART initiation were extracted from the PLHA database who registered during 2007. Since the ART treatment criteria and management were widely revised in 2007 therefore, the data prior to 2007 left with the quality issue. Further, for this cohort the current CD4 cell counts were extracted from PLHA database in 2012 to see the changes in CD4 counts. A total records of 114,210 HIV-positive patient's ware found without missing information on CD4 cell counts and registered at different ART centers during 2007. Out of this, 65,980 (57.7%) were male, followed by female (48,046; 42.1%) and remaining 184 (0.2%) were registered as TS/TG cases.

These demographic and vulnerability indicators were categorised to assess any association with the survival probability. Age was categorised into four groups as <15, 15-35, 36-50 and ≥50 years. Sex was divided into male, female and TS/TG. The ART status was categorised as on ART and not on ART. Time to ART initiation was sub-grouped into within month, 1-6 months, 6-12 months and >12 months. The initial and current CD4 cell counts were categorised as ≤50, 51-100, 101-200, 201-300 and ≥300. The difference between current and initial CD4 cell count was calculated and considered as a response variable for regression analysis.

Permission to use ART programme data for this study has been obtained from National AIDS Control Organization (NACO), Department of AIDS Control, Ministry of Health and Family Welfare, Government of India, New Delhi.

Statistical analysis: The descriptive statistics is presented using mean (with SD) or median (with IQR) for quantitative variables and categorical variables were presented in frequencies along with respective percentages. A comparative line diagrams were made for comparing different subgroups of initial and current CD4 cell counts. The Z-test for two independent proportions was used to compare different categories of CD4 cell counts between initial and current CD4 cell measurements. Nonparametric ANOVA (or Krushkal-Walli's 'H') test was used for statistical differences between mean age of male, female and TS/TG and Chi-squared test for categorical variables. The mean differences from initial to current CD4 counts were calculated in different age categories, sex, ART status and time to ART initiation with 95% confidence interval and also compared using Wilcoxon nonparametric test for two dependent variables. The Spearman's rank correlation was applied for estimating correlations between initial CD4 counts and age, time to ART initiation.

The widely accepted univariate and multivariable binary logistic regression model were applied to identify the associated factors with 95% C.I.'s responsible for any change in CD4 count[20]. Further the response variable i.e., any change in CD4 cell count was categorized into no change, positive change and negative change. The multinomial logistic regression was used to estimate the adjusted risk ratios with 95% confidence intervals for associated factors with reference to no change in CD4 cell count. The no change is defined as <20 counts in

CD4 cells. The Akakike information criteria (AIC), Bayesian information criteria (BIC) and -2log likelihoods were calculated for goodness of fit for multinomial regression model. The data were analyzed using IBM SPSS statistics for windows version 21.0 (Armonk, NY, USA). The two tailed 'p' value less than 0.05 was considered as statistical significance.

RESULTS

The general profile of the respondents including demographic and programme variables are presented in table 1. The median age (IQR) at registration of PLHIV was recorded as 34 (28-40) years among males and 29 (24-35) years among females which was statistically significant ($p < 0.01$). The median age of TS/TG was found to 33 (26-39) years with no association with male or female ($p > 0.05$) at the time of ART registration. More than 90% of HIV patients were acquired infection at their younger age (up to 50 years), 57.7% were male, 85.7% on ART, 60.6% reported as below 200 initial CD4 cell count and 66.7% of these HIV-patients were started antiretroviral treatment (ART) within month of HIV detection (table 1). The median initial and current CD4 were statistically significant ($p<0.05$) among all subcategories of demographic and programme variables except those who not on ART, CD4 more than 200 and ART initiation at more than 12 months ($p>0.05$) (table 1).

Initially the CD4 count of HIV-patients was distributed as 13.7% below or equal to 50, 15.9% between 51-100, 31.0% between 101-200, 17.1% between 201-300 and 22.3% were more than or equal 300 and it was increased consistently during current measurement of CD4 count as depicted in figure 1. The overall initial and current CD4 cell counts in various subcategories of CD4 counts were found statistically significant ($p<0.05$).

The significant improvement in CD4 counts showed in all categories of different predictor variables except to those who not on ART and time to ART initiation were more than 12 months (table 2). The maximum change in CD4 was observed in below 15 years of age, TS/TG group, on ART patients and those who started ART within month of HIV detection.

Univariate and multivariate logistic regression analysis were used to examine the association between different background variables and chances of any change either positive or negative in CD4 counts. 50.7% of total registered HIV-patients showed any change in their CD4 count from initial measurement and these changes were statistically significant within the subgroup of demographic and programme variables as presented in table 3.

Table 1: Distribution of CD4 cell counts according to background characteristics

Background characteristics	Patients	CD4 cell count	
		Initial	Current
	N (%)	Median (IQR)	Median (IQR)
Total number of PLHA	**114210 (100.0)**		
Age group at registration (years)			
<15	10297 (9.0)	316 (141-636)	485 (205-872)
15-35	66426 (58.2)	169 (89-275)	242 (125-454)
36-50	32982 (28.9)	142 (74-224)	209 (104-394)
>=51	4505 (3.9)	147 (78-231)	202 (106-360)
Median (IQR)	32 (26-38)	165 (86-276)	241 (120-461)
Sex			
Male	65980 (57.7)	148 (76-244)	214 (104-409)
Female	48046 (42.1)	190 (104-329)	286 (150-526)
TS/TG	184 (0.2)	177 (93-300)	282 (144-523)
ART Status			
On ART	97847 (85.7)	148 (78-227)	217 (111-423)
Not on ART	16363 (14.3)	425 (262-638)	410 (255-611)
CD4 category			
<=50	15691 (13.7)	28 (15-40)	41 (19-241)
51-100	18151 (15.9)	75 (63-88)	90 (69-278)
101-200	35370 (31.0)	149 (125-175)	183 (138-384)
201-300	19586 (17.1)	238 (217-264)	266 (223-445)
>=300	25412 (22.3)	473 (368-652)	471 (337-689)
Time to ART initiation			
Within month	76149 (66.7)	133 (69-205)	204 (100-420)
1-6 months	12776 (11.2)	216 (114-405)	311 (158-535)
6-12 months	8270 (7.2)	251 (140-448)	320 (174-553)
>12 months	17015 (14.9)	316 (207-483)	311 (203-504)

PLHA: people living with HIV/AIDS; IQR: inter quartile range;

Table 2: Univariate and multivariate binary logistic regression analysis with 95% C.I.'s of background variables

Background variables	N	Any change in CD4 count (%)	URR (95% C.I.)	MRR (95% C.I.)	df	P value
Age group at registration (years)						
<15	10297	5608 (54.5)a	1.3** (1.2-1.5)	1.5** (1.3-1.6)	3	*<0.001*
15-35	66426	33695 (50.7)b	1.2** (1.1-1.4)	1.1* (1.0-1.3)		
36-50	32982	16516 (50.1)b	1.1* (1.1-2.0)	1.1* (1.0-1.3)		
>=51	4505	2119 (47.0)c	1 (Ref.)	1 (Ref.)		
Sex						
Male	65980	32280 (48.9)a	1 (Ref.)	1 (Ref.)	2	*<0.01*
Female	48046	25556 (53.2)b	1.3** (1.1-1.7)	1.2* (1.1-1.3)		
TS/TG	184	102 (55.4)ab	1.3 (0.9-1.7)	1.5** (1.1-2.0)		
ART status						
On ART	97847	52789 (54.0)a	2.6** (2.5-3.2)	3.7** (3.5-3.9)	1	*<0.001*
Not on ART	16363	5149 (31.5)b	1 (Ref.)	1 (Ref.)		
Time to ART Initiation						
<1 month	76149	37709 (49.5)a	1 (Ref.)	1 (Ref.)	3	*<0.001*
1-6 months	12776	5848 (45.8)b	2.8** (2.1-3.9)	1.3* (1.2-1.5)		
6-12 months	8270	3896 (47.1)b	3.1** (2.3-4.7)	1.5** (1.4-1.7)		
>12 months	17015	10485 (61.6)c	4.5** (2.4-6.9)	2.3** (2.2-2.5)		
Total	114210	57938 (50.7)				

URR=univariate rate ratio; MRR= multivariate rate ratio; *p<0.05; **p<0.01; a,b,c = letters in same script show no significance

Table 3: Multinomial logistic regression analysis of changes in CD4 cell counts according to background variables with model fitting information

Background Variables	Any change in CD4 count	Negative change		Positive change	
		n (%)	MRR (95% CI)	n (%)	MRR (95% CI)
Age group at registration (years)					
<15	5608	1808 (32.2)	1.6**(1.4-1.8)	3800 (67.8)	1.4**(1.3-1.5)
15-35	33695	8415 (25.0)	1.1 (1.0-1.2)	25280 (75.0)	1.1**(1.2-1.4)
36-50	16516	3407 (20.6)	1.0 (0.9-1.2)	13109 (79.4)	1.1**(1.1-1.5)
>=51	2119	462 (21.8)	1 (Ref.)	1657 (78.2)	1 (Ref.)
Sex					
Male	32280	7400 (22.9)	1 (Ref.)	24880 (77.1)	1 (Ref.)
Female	25556	6676 (26.1)	0.9 (0.5-1.6)	18880 (73.9)	1.3**(1.2-1.5)
TS/TG	102	16 (15.7)	1.2*(1.1-1.7)	86 (84.3)	1.7**(1.2-2.3)
ART status					
On ART	52789	10957 (20.8)	1.9**(1.8-2.0)	41832 (79.2)	6.5**(6.1-6.8)
Not on ART	5149	3135 (60.9)	1 (Ref.)	2014 (39.1)	1 (Ref.)
Time to ART Initiation					
<1 month	37709	5600 (14.9)	1 (Ref.)	32109 (85.1)	1 (Ref.)
1-6 months	5848	1680 (28.7)	2.1**(2.0-2.3)	4168 (71.3)	1.3**(1.2-1.4)
6-12 months	3896	1342 (34.4)	2.7**(2.5-2.9)	2554 (65.6)	1.3**(1.2-1.4)
>12 months	10485	5470 (52.2)	6.8**(6.4-7.1)	5015 (47.8)	1.4**(1.3-1.5)
Total	56272	14092 (25.0)		43346 (75.0)	
Model fitting information					
Akaike information criteria (AIC)			2301.6		
Bayesian information criteria (BIC)			2494.6		
-2Log likelihood criteria			2261.6		

URR=univariate rate ratio; MRR= multivariate rate ratio; *p<0.05; **p<0.01

The univariate regression analysis demonstrated age, gender, ART status and time to ART initiation were associated with the chance of any change in CD4 count of a patient. Further, all these variables were used in multivariate regression analysis to estimate the chance of any change in CD4. Multivariate rate ratio (MRR) was significantly higher in paediatric age group (1.5; p<0.01 for below 15 years) and similar in 15-50 years of age (1.1; p<0.05 for both 15-35 and 36-50 years) with reference to the ≥51 years. MRR was also higher in the TS/TG group (1.5; p<0.01) followed by females (1.2; p<05) as compared with males and those who are on ART have MRR 3.7 (p<0.01) as compared with no on ART. The adjusted rate ratio was significantly higher as time to ART initiation increased (1.3 for 1-6 months, 1.5

for 6-12 months and 2.3 for ≥12 months) with respect to within month of initiation.

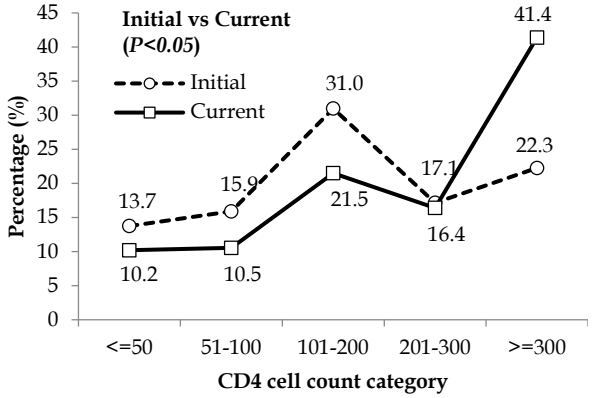

Figure 1: Comparison of proportions between initial and current CD4 cell counts in different categories.

Any change in CD4 category was further divided into no change, negative change and positive change to see insight of it by taking no change as reference category by using multinomial logistic regression analysis shown in table 4. The proportion of increase in CD4 counts was increased over time in higher age up to 50 year (<15: 67.8%; 15-35: 75.0%; 36-50: 79.4), TS/TG (84.3%) followed by male (77.1%) and female (73.9%), among on ART patients (79.2%) and those who started ART within month (85.1%). The multivariate regression model exhibits the significantly associated factors to the positive increase in CD4 were lower age (≤50 years), among females and TS/TG, on ART and one month or later starting of ART treatment. However, decline in CD4 count was statistically associated with age less than 15 years (1.6), TS/TG (1.2), on ART (1.9) and initiation to ART one month or later. Akaike information criteria (AIC), Bayesian information criteria (BIC) and -2log likelihood were used to diagnose robustness of the model. All the measurements produced similar results that imply goodness of fit for the multinomial regression model and these results were valid and reliable.

DISCUSSION

The initial CD4 cell counts were negatively correlated with age (r=-0.28; p<0.001) and time to ART initiation (r=-0.23; p<0.01). The probable explanation is due to immunity decreases as age and time to ART initiation increased. These negative correlations exhibit by this analysis corroborates the findings from several other studies[21-23] however not in agreement with Wright et al[24]. This empirical research showed gain in current CD4 cell count from initial counts in each category of CD4 count as presented in figure 1. The overall initial median CD4 count was 165 cells/mm^3 that significantly increased to 241 cells/mm^3. The gain in current CD4 count from the initial measurements was also observed in each subcategory of age group, sex, ART status, CD4 at registration and time to ART initiation (table 1). These changes could be due to revision in ART treatment threshold as recommended by WHO and expansion in HIV control programme throughout country. Similar researches conducted in other parts of the world were also supported our hypothesis[1,3,7]. The majority of the registered patients were young males (15-50 years) that represents the most vulnerable group for HIV transmission. The proportion of HIV-patients with late ART initiation had significantly decreased over time. Other studies conducted by Kiertiburanakul et al.[6] at 22 sites from 13 Asian countries and Lahuerta et al.[25] in Mozambique reported similar results. In our study, the mean differences in CD4 from baseline observation in different categories of predictor variables were positive except to those who not on ART and initiated ART after 12 months (p>0.05) (table 2). These insignificant results could be explained as if the individual's CD4 count is higher and consistent then does not require initiating the ART treatment[24]. In addition, 50.7% of the total registered HIV-patients displayed any change from the first time recorded CD4 count at ART centre after HIV detection. The univariate and multivariate regression analysis showed the predictors associated with any change in CD4 count (table 3). The chances of change in CD4 were high in below 15 years of age (1.5; C.I.:1.3-1.6), TS/TG gender (1.5; C.I.: 1.1-2.0), patients on ART (3.7; C.I.: 3.5-3.9) and those who started ART after one year (2.3; C.I.: 2.2-2.5). As previously reported, the ART treatment affects rapidly these factors therefore lower age (below 15), TS/TG group, on ART patients and late initiation to treatment have tendency to influence CD4 count directly as emphasis in other studies[6,7,22-24].

Further, those patients who showed any change in CD4 counts from initial measurement were subcategorised into negative and positive changes. 75.0% of these patients were displayed increase and 25.0% reported decrease in CD4 counts (table 4). Our study clearly showed significant increase in proportions of CD4 counts in younger age (below 50 years). It could be explained as the younger persons have higher immunity level to the older one[22]. In our cohort 84.4% TS/TG demonstrated improvement in CD4 counts that could be due to greater awareness about HIV infection and increased coverage of HIV control programme. However, both male and female have shown lower than TS/TG but similar proportions in this regard. The effectiveness of ART treatment proved by on ART patients as they reflect to 79.2% of any change in CD4 were increased their CD4 counts. Time to ART initiation was defined as

the duration from HIV detection to eligibility for ART treatment that depends on individual's immunity against retrovirus. We found that ART initiation time was responsible for positive increase in CD4 counts. As far as you delay the ART treatment, the chances of improvement in CD4 were reduced. This trend is probably explained as the resistance against HIV infection is inversely related to ART initiation time. Such finding were also reported elsewhere[6,22]. The factors related to either decrease or increase in CD4 was extracted by multinomial logistic regression analysis with respect to no change in CD4 counts. The likelihood of increase in CD4 counts was statistically associated with higher chances within the subgroup of factors as age less than 15 years (1.4; C.I.: 1.3-1.5), TS/TG group (1.7; C.I.: 1.2-2.3), on ART patients (6.5; C.I.: 6.1-6.8) and among who started ART after one year (1.4; C.I.: 1.3-1.5). On the other hand, the decrease in CD4 counts was found to be in age below 15 years (1.6 times; C.I.: 1.4-1.8), TS/TG sex (1.2 times; C.I.: 1.1-1.7), on ART patients (1.9 times; C.I.: 1.8-2.0) and gradually delay in ART initiation (2.1times for 1-6 months; 2.7 times for 6-12 months and 6.8 times for after one year). The multivariate rate ratios (MRR) in time to ART initiation reflect that the delay in the start of ART increases the chances of negative change in CD4 counts[6].

There are limitations such as without a healthy HIV-negative control group we were unable to compare the effect of HIV in declination of CD4 counts. To our knowledge there are no published population based comparable longitudinal data for long-term CD4 cell count trend. This analysis is based on the secondary data that excludes the samples with missing initial CD4 counts. Therefore, we could not predict about those whose first measurement on CD4 was unavailable with the system. The information on other potential factors responsible for change in CD4 counts such as viral load, co-infections, HBV and HCV status were not available.

CONCLUSIONS

In summary, the median CD4 cell count at ART registration was low, however did increase over time. The change in CD4 was correlated with initial CD4 measurement. ART treatment does impact on change in CD4 count. Late ART initiation increases the risk of decline in CD4 whereas the patients on ART have likelihood to improve their CD4 cell count. Earlier ART initiation at higher CD4 cell counts remains a challenge. Strategic interventions to increase earlier diagnosis of HIV infection, linkage to HIV care and rapid access to ART must be implemented at country level, especially among the high risk population with poor access to HIV services.

ACKNOWLEDGEMENTS

This paper was written as a part of PhD research, under GGS Indraprastha University, New Delhi. The views expressed herein are those of the authors and do not necessarily reflect the official policy of AIDS control programme. Authors are thankful to National AIDS Control Organisation, Department of AIDS Control, Ministry of Health & Family Welfare for providing individual level ART data.

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