

## Antiretroviral therapy- Changing patterns of CD4 levels in HIV positive individuals: An over view

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### Abstract

**Introduction:** The major brunt of the HIV epidemic has been in South and South-east Asia—predominantly in India and Thailand. Infection with HIV leads to a progressive impairment of cellular immune function. Current CD4 count is a strong predictor of the immediate risk of acquired immunodeficiency syndrome (AIDS) CD4 cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy (ART).

**Aims and Objectives:** 1. To know the changing patterns of CD4 levels in HIV infected persons on ART. 2. To evaluate the response to ART after 6 months & 12 months on therapy.

**Methods:** Retrospective cross sectional study was conducted on 250 HIV positive individuals taking antiretroviral treatment at ART centre. Their personal information, opportunistic infection if any, along with CD4 levels before starting ART and 6 months & 12 months after ART were collected.

**Results:** The mean CD4 level was more in females (343.06 cell/ cumm) than males (289.17 cell/cumm). Age group of 11- 20 yrs had more mean CD4 level (438 cell/cumm). The median CD4 level was high in females in all times i.e. before and during ART.

**Discussion:** As per NACO guidelines, currently in India, absolute CD4 cell count is being used as the basis for initiation of ART. International and national guidelines advocate the use of CD4 count for treatment decisions, as a predictor of disease progression, a criterion for treatment initiation, and as a marker of treatment outcome in both adults and children. All the studies including present study showed that there is a clear rise in CD4 levels with ART.

**Keywords:** HIV, ART, CD4 levels

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### Introduction

The HIV/AIDS pandemic has become one of the most important public health problems in recent times and it is having a profound impact on the lives of infected people and their families.<sup>[1]</sup> The major brunt of the HIV epidemic has been in South and South-east Asia—predominantly in India and Thailand.<sup>[2]</sup> India has the 3rd highest number of estimated people living with HIV/AIDS (PLHA) in the world.<sup>[3]</sup> More people than ever are living with HIV, largely due to greater access to treatment. Andhra Pradesh has been identified as one of the six high HIV- prevalence states of India. It accounts for an estimated 10 percent of the HIV cases in India.<sup>[4,5]</sup> Infection with HIV leads to a progressive impairment of cellular immune function, characterized by a gradual decline in peripheral CD4+ T-Lymphocyte levels which result in an increasing susceptibility to wide variety of opportunistic viral, bacterial, protozoal and fungal infections and to certain malignancies

also.<sup>[6,7]</sup> As a priority, ART should be initiated among all adults and adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/mm<sup>3</sup> (strong recommendation, moderate-quality evidence).<sup>[8]</sup> A predominant source of morbidity and mortality among HIV positive individuals in late stages of HIV infection and low CD4 count below 500/cumm, is opportunistic infection caused by agents that rarely infect immuno competent individuals.<sup>[9]</sup> Current CD4 count is a strong predictor of the immediate risk of acquired immunodeficiency syndrome (AIDS) or death than HIV RNA level.<sup>[10]</sup> For more than two decades, CD4 cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy (ART).<sup>[11]</sup> The current study was done to evaluate changing patterns of CD4 levels in HIV infected individuals on Antiretroviral therapy.

### Aims and Objectives

1. To know the base line levels of CD4 cells for initiation of ART
2. To know the changing patterns of CD4 levels in HIV infected persons on ART
3. To evaluate the response to ART after 6 months & 12 months on therapy
4. To know common opportunistic infection in HIV infected individuals

## Material and Methods

Retrospective cross sectional study was conducted on 250 HIV positive individuals taking antiretroviral treatment at ART centre were included. Their personal information, opportunistic infection if any along with CD4 levels before starting ART and 6 months & 12 months after ART were collected both from the ART data base and patients' cards. The data was analyzed statistically in Microsoft excel.

## Results

In the present study 177HIV positive individuals on ART had CD4 counts of below 350 cells/cumm(70.8%). CD4 counts of most of the HIV positive individuals was between 201 -350cells/cumm (103/250; 41.2%) followed by 101-200 in 50 individuals (20%). The most common age group was 31- 40 years (38%), followed by 21- 30 yrs (33.2%) as shown in Table 1. The mean CD4 level was more in females (343.06 cell/ cumm) than in males (289.17 cells/cumm). Individuals in the age group of 11- 20 yrs had more mean CD4 level (438 cell/cumm) when compared to other age groups as shown in Table 2. The mean rise of CD4 levels of individuals on ART in subsequent visits after 6 months and 12 months was

high in less than 10 yrs age group, followed by 11-20 and 21-30 yrs age groups as shown in Table 3. The median age was 37 years in males and 30 years in females. The median CD4 level was high in females in all times i.e. before and during ART as shown in Table 4. Standard deviation in CD4 levels was less in below 10 yrs (19.0918 cells/ cumm) and high in age group of 11- 20 years (262.1339 cells/ cumm) as shown in Table 5. After 6 months of ART, 102 individuals showed increase in CD4 levels of > 200 cells/cumm from their base level counts. 191 individuals showed increased CD4 counts after 6 months (76.4%) but only 136 cases showed increased counts after 12 months of ART (54.4%). 27.2% of individuals showed decreased CD4 levels after 12 months of ART and it was only 11.6% after 6 months. 12% and 18.4% of cases exhibited no change in their CD4 levels in 6 months & 12 months of ART respectively as shown in Table 6. The most common opportunistic infection was tuberculosis followed by candidiasis in the study group. Opportunistic infections were common in individuals with CD4 levels of less than 350 cells/cumm as shown in Table 7. Only 4 individuals had not developed any opportunistic infections.

**Table 1: CD4 levels at the time of ART in relation to age and gender**

Age	<100		101-200		201-350		351-500		501-700		701-1000		>1000		Total		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
<10			-	-	2	-	-	-	-	-	-	-	-	-	2	-	2(0.8%)	
11-20		1	-	1	1	1	-	3	-	2	1	1	-	-	2	9	11(4.4%)	
21-30	4	1	8	10	12	19	3	10	2	4	2	5	-	3	31	52	83(33.2%)	
31- 40	5	5	11	6	27	20	12	1	4	1	2	-	-	1	61	34	95(38%)	
41- 50	6		8	2	10	7	6	1	-	1	-	-	1	-	31	11	42(16.8%)	
51- 60	2		1	1	1	-	-	4	1	-	2	-	-	-	7	5	12(4.8%)	
>60			1	1	3	-	-	-	-	-	-	-	-	-	4	1	5(2%)	
Total	17	7	29	21	56	47	21	19	7	8	7	6	1	4	138	112	250	
	24(9.6%)		50(20%)		103(41.2%)		40(16%)		15(6%)		13(5.2%)		5(2%)		55.2%		44.8%	250

**Table 2: Showing Gender wise Mean CD4 levels in various age groups**

Age group	No. of cases			Mean CD4		
	Male	Female	Total	Males	Females	Total
<10	2	0	2	253.5	00	253.5
11-20	2	9	11	526.5	418.33	438
21-30	31	52	83	284.1	391.07	354.06
31-40	61	34	95	298.18	266.91	286.87
41-50	31	11	42	252.4	298	265.42
51-60	7	5	12	358.85	340.8	351.33
>60	4	1	5	245	114	218.8
Total	138	112	250	289.17	343.06	313.96

**Table 3: Age wise distribution of Mean CD4 levels at different visits**

Age group	I visit	II visit	III visit
<10	253.5	1305.5	1179.5
11-20	438	639.45	769.64
21-30	354.06	519.17	572.46
31-40	286.87	484.99	544.60
41-50	265.42	433.17	471.28
51-60	351.33	412.44	511.4
>60	218.8	398.20	389.40
	313.96	496.26	552.176

**Table 4: Showing median levels of age and CD4 levels**

Median	Males	Females	Total
Age in years	37	30	35
CD4 on I visit	269	307	282
CD4 on II visit	407	476	440
CD4 on III visit	496	535	508

**Table 5: Showing mean CD4 levels and standard deviation in different age groups**

Age group	No. of cases	Mean CD4 levels	Standard deviation
<10	02	253.5	19.0918
11-20	11	438	262.1339
21-30	83	354.06	245.3685
31-40	95	286.87	169.6673
41-50	42	265.42	176.5645
51-60	12	351.33	232.7462
>60	5	218.8	74.3552

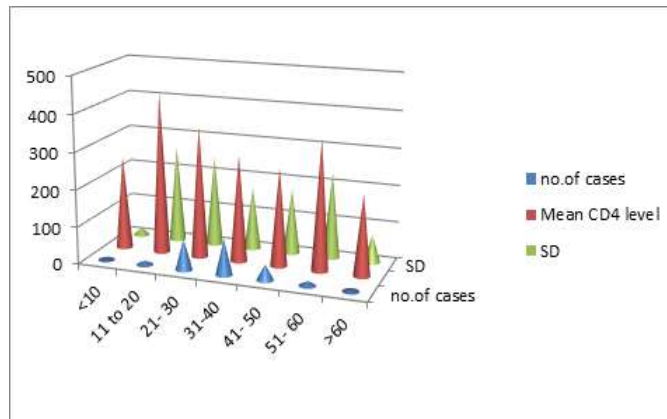
**Table 6: Showing the changing pattern of CD4 levels in individuals on ART after 6 months and 12 months**

Cd4 count on I visit	No. of cases	II Visit															III Visit													
		increase						decrease						No change			increase						decrease						No change	
		<100		100- 200		>200		<100		100- 200		>200		No change		<100		100- 200		>200		<100		100- 200		>200		No change		
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
<100	24	3	1	6	1	6	4	-	1	-	-	-	-	2	-	3	1	5	1	3	1	2	1				1	3	2	
101- 200	50	4	2	7	2	15	14	2	-	-	-	-	-	1	3	10	5	3	2	9	7	1	3	1	-	1	1	4	2	
201- 350	103	14	9	6	6	25	24	-	5	1	1	-	-	10	2	15	12	10	4	8	2	7	7	2	2	6	9	9	9	
351- 500	40	3	4	2	5	6	2	5	2	1	-	1	1	2	5	7	3	3	3	4	6	4	2	1	-	1	1	3	3	
501- 700	15	3	4	1	1	1	2	-	-	-	1	1	-	1	0	-	-	1	1	1	1-	3	-	1	-	3	1	2	3	
701- 1000	13	1	1	1	1	2	1	-	-	-	-	2	2	1	1	-	1	-	1	2	1	1	-	-	-	1	1	3	2	
>1000	05	-	1	-	-	-	-	1	1	-	-	1	-	-	1	-	-	-	-	-	-	2	1	-	-	-	1	-	1	
Total	250	28	22	23	16	55	47	8	9	2	2	5	3	18	12	35	22	22	12	27	18	20	14	5	2	12	15	24	22	
		50		39		102		17		04		08		30		57		34		45		34		07		27		46		
		191(76.4%)						29(11.6%)						12%			136(54.4%)						68(27.2%)						18.4%	

**Table 7: Showing opportunistic infections at the time of starting ART in relation to CD4 count**

Name of OI	<100		101-200		201-350		351-500		501-700		701-1000		>1000		Total		Grand Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Pul. TB	8	3	11	8	17	17	4	6	4	4	2	-	1	2	48	40	88
Extra Pul TB	-	1	2	1	7	4	3	-	-	1	-	-	-	-	12	7	19
Diarrhea	2	1	2	-	4	9	3	2	-	-	2	-	-	-	13	12	25
Candidiasis	6		9	6	11	10	8	4	2	1	2	2	-	-	38	23	61
Genital Herpes	-	1	-	1	6	2	1	3	-	-	-	-	-	-	7	7	14
Herpes zoster	-	1	2	-	-	1	1	1	-	-	-	-	-	-	3	3	6
Recurrent ARTI*	-	-	2	1	-	-	-	-	2	-	-	-	-	-	4	1	5
Skin rash	1	-	3	2	7	3	-	2	-	-	-	-	-	-	11	7	18
Fever	-	-	1	2	2	1	1	-	-	1	-	-	-	-	4	4	8
Toxoplasmosis	-	-	-	-	-	-	-	1	-	-	-	-	-	-	0	1	1
Pencilliosis	-	-	-	-	-	-	-	1	-	-	-	-	-	-	0	1	1
Total	17	7	32	21	54	47	21	20	8	7	6	2	1	2	140	106	246

\*ARTI =Acute respiratory tract infection



**Fig. 1: Showing the mean CD4 levels and standard deviation of CD4 levels in various age groups**

## Discussion

The emergence and pandemic spread of the acquired immunodeficiency syndrome (AIDS) has posed the greatest challenge to public health in modern times. Steps at immunorestorative therapy such as administration of interleukin-2, thymic factors, leucocyte transfusion and bone marrow transplantation have not been very helpful. Specific treatment with antiretroviral drugs is the main stay in the management of HIV infection.<sup>[12]</sup>

Government of India launched the free ART programme on 1st April 2004, starting with eight tertiary-level government hospitals in the six high-prevalence states of Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur, and Nagaland. *The Clinical goals of ART are:* To improve quality of life, To reduce HIV-related morbidity and mortality, To provide maximal and durable suppression of viral load and, To restore and/or preserve immune function.<sup>[13]</sup> As per NACO guidelines, currently in India, absolute CD4 cell count is being used as the basis for initiation of ART(5). ART (antiretroviral therapy) refers to the use of a combination of three or more ARV drugs for treating HIV infection and involves lifelong treatment.<sup>[8]</sup> International and national guidelines advocate the use of CD4 count for treatment decisions, as a predictor of disease progression, a criterion for treatment initiation, and as a marker of treatment outcome in both adults and children. Therefore it is recommended at multiple instances in the course of patient care.<sup>[14]</sup> Baseline CD4 cell count was evaluated whether it was a risk factor associated with immunological non-response (defined as a CD4 cell increase of <50 cells/cumm at 12 months).<sup>[15]</sup>

Patients showing decrease in CD4 count should be investigated for viral load and drug resistance studies. Reasons for lowering count may be non-adherence, lack of support from families, shortage of drugs and toxicity of drugs.<sup>[10]</sup> CD4 cell counts will continue to play an important part in initial decisions about ART initiation and clinical management, particularly for patients presenting late to care, and for treatment monitoring

where viral load monitoring is restricted.<sup>[11]</sup> Badri *et al.* have reported that the negative CD4 count slope in patients on ART was associated with virological failure.<sup>[16]</sup> Present study showed that the most common affected age group was between 31-40 years followed by 21-30 years and mean age for initiation of ART was 35 years (SD 10.53 yrs) which was almost near to the studies of Kumarswamy *et al.* (32yrs) and Duga *et al.* (31.89 yrs; SD 8.29 yrs).<sup>[7,17]</sup> As a priority, ART should be initiated among all adults and adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/mm<sup>3</sup> (strong recommendation, moderate-quality evidence). The mean CD4 level for initiation of ART in our study was 313.96 cells/cumm but it was less in the studies by Kumarswamy *et al.* (216 cells/cumm) and Duga *et al.* (146.84 cells/cumm).<sup>[7,17]</sup> This variation would be due to conducting studies before 2013 where ART was initiated when CD4 count less than 200cells/ $\mu$ l). There was an increased CD4 level in 191 of 250 cases (76.4%) in our study that was similar to the study by Mrudula *et al.* (77.19%). The present study showed not only increase in CD4 levels but also there were cases that showed decrease (29/250, 11.6%) and no change (30/250, 12%). But it varied in the study of Mrudula *et al.* in which the values were 21.05%(12/250) and 1.75%(1/57) for decreased and no change in CD4 levels respectively.<sup>[10]</sup> The mean CD4 levels after 6 months of ART was 496.27cells/ $\mu$ l in our study and in Duga *et al.* study it was 302.36 cells/ $\mu$ l.<sup>[17]</sup> The mean difference of 172.30cells/ $\mu$ l was in present study but it was 139 cells/ $\mu$ l in the study by Mrudula *et al.* and 155.52 in Duga *et al.* study.<sup>[10,17]</sup>

In most patients, the CD4 cell count rises with the initiation of ART and immune recovery. However, this may be blunted if the baseline CD4 count is low. In general, the lower the baseline CD4 count is at the start of ART, the longer it will take for the count to increase with time.<sup>[13]</sup> According to WHO Guidelines ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count. As a priority, ART should be initiated among all

adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/cumm.<sup>[8]</sup> New data analysis demonstrates that for every 10% increase in treatment coverage there is a 1% decline in the percentage of new infections among people living with HIV. The report highlights that efforts to increase access to ART are working.<sup>[18]</sup>

All the studies including present study showed that there is a clear rise in CD4 levels with ART. But there were certain cases where there was no change or further fall of CD4 levels. For that many host factors like patient compliance, nutritional status, immune reconstitution & socioeconomic status and agent factors like drug resistance are to be evaluated. The mortality in HIV positive persons mostly depends upon the occurrence of OIs. Tuberculosis-related deaths in people living with HIV have fallen by 33% since 2004. But still Tuberculosis remains the leading cause of death among people living with HIV.<sup>[19]</sup> The most common OI in the present study was tuberculosis (107/250) of both pulmonary (88/250) and extra pulmonary (19/250). In some HIV positive individuals ART was started because of tuberculosis as OI, even though their CD4 count was more than 350cells/cumm.

It would be more beneficial to the HIV positive persons if ART is started soon after diagnosis irrespective of CD4 count and measures were taken for prevention and treatment of OIs. At the level of tertiary care hospitals, to monitor the efficacy of ART, the available method is CD4 level estimation. If facilities for viral load are available, it would be more helpful to the unresponsive cases, which can be identified early to start/change ART. These measures will definitely improve the life span and quality of life of PLHAs.

The UNAIDS strategy is a roadmap for the Joint Programme with concrete goals marking milestones on the path to achieving UNAIDS' vision of "Zero new HIV infections. Zero discrimination. Zero AIDS-related deaths."<sup>[20]</sup> This could be achieved persons if ART is started soon after diagnosis irrespective of CD4 count and measures were taken for prevention and treatment of OIs and facilities for viral load estimation are available.

### Conclusions

1. ART was started in 70.8% of HIV positive persons (177/260) when their CD4 count was less than 350/cumm. In the rest of the persons it was due to the development of OIs.
2. Common age group in this study was 31-40 years followed by 21-30 years.
3. The mean CD4 level was more in females (343.06 cell/ cumm) than in males (289.17 cell/cumm).
4. 191 individuals showed increased CD4 counts after 6 months (76.4%) and 136 cases showed increased counts after 12 months of ART (54.4%). 11.6% of individuals showed decreased CD4 levels after 6 months of ART and 27.2% after 12 months. 12%

and 18.4% of cases exhibited no change in their CD4 levels in 6 months & 12 months of ART respectively.

5. The most common OI to start ART when CD4 count was more than 350/cumm was tuberculosis (107/250) of both pulmonary (88/250) and extra pulmonary (19/250) type.

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