Original Article

Trends of CD4 count after initiation of antiretroviral therapy and the predictors of immunological non response in HIV infected patients in a tertiary care centre of Southern Bengal

Kripasindhu Gantait[1], Atanu Chandra[2], Puspendu Biswas[3], Indranil Sen[4], Rajat Goswami[5]

This retrospective cross sectional study was done by reviewing the records of 422 patients of HIV (who received ART from the ART clinic of Midnapore Medical College) to assess the trends in CD4 cell recovery among HIV patients after initiation of ART, the effect of different baseline characteristics on CD4 cell count response & to find out predictors of immunological non response (Rise of CD4 counts of <50 cells/µl after first 12 months of ART). Relationship of different variables like baseline CD4 counts, age etc with immunological non response were also assessed. The overall median change from baseline to the 48 months CD4 count was +359 cells/µl. The median changes at 48 months were +216 cells/µl,+35cells/µl & +59 cells/µl in the strata of baseline CD4 of >350, 201-350 & <200 cells/µl respectively. CD4 counts almost returned to normal at the end of 48 months in those with initial CD4 counts of >350 cells/µl. The patients with a lower baseline CD4 had lower peak CD4 counts. Patients with lower CD4 counts at the beginning had subsequent poor CD4 recovery & higher chances of immunological non response as well. Female patients & patients of WHO clinical stage 4 was also found to be at significantly higher risk of immunological non response. Our findings suggest that HAART should be initiated early for better immune recovery & female patients should be given more consideration regarding adherence to the therapy.

[*J Indian Med Assoc* 2019; **117:** 12-5]

Key words **: CD4 counts, ART, HAART, HIV.**

Infection with HIV is a common public health problem all over the world, especially in developing countries like India.Vital cells in the human immune system such as helper T cells (mainly CD4+ T cells), macrophages, and dendritic cells are primarily infected by HIV[1]. This gradual decline of CD4 T cells leads to general decline in immune functioning and is the primary determining factor in the clinical course of the HIV infected individual. The CD4+ T-cell count is the single best laboratory determinant of clinical outcomes[2]. The Antiretroviral Therapy (ART), results in reduction of plasma HIV-RNA that in turn allows increase in the CD4 cell count. In India, the availability of measurement of viral load is limited & CD4 cell counts is a very important marker of starting and monitoring of highly active antiretroviral therapy (HAART)[3]. Sustained increase in the CD4 cell response to HAART and suppression of HIV load were both associated with greater increases in CD4 cell counts[4]. Previous recommendation by the World Health Organization (WHO) was to start ART in patients with CD4 cell count <350 cells/µl[5]. But the current WHO recommendation is to initiate ART in everyone living with HIV at any CD4 cell count. This is based on evidence from clinical trials and observational studies released since 2013 showing that earlier use of ART results in better clinical outcomes for people living with HIV compared with delayed treatment[6].

The relationship between the recovery of CD4 counts with ART & baseline CD4 counts is still a matter of debate. The objective of the present study was to determine trends in CD4 cell recovery among HIV patients after initiation of ART and the effect of different baseline characteristics on CD4 cell count response in a sample of Indian patients. We also studied to find out predictors of immunological non response (increase of CD4 cell count <50 cells/µl from baseline after 12 months of therapy). To the best of our knowledge, there are no such studies before from the area on this topic.

Department of Medicine, Midnapore Medical College & Hospital, Paschim Medinipur 721101

[1]MD (Med), Associate Professor

[2]MD (Med), DNB (Med), RMO *cum* Clinical Tutor and Corresponding author

[3]MBBS, Junior Resident, Department of Community Medicine, Burdwan Medical College, Burdwan 713104

[4]MD (Med), DNB (Med), RMO *cum* Clinical Tutor, Department of Medicine, Calcutta National Medical College & Hospital, Kolkata 700014

[5]MD (Med), Senior Consultant Physician, SD Hospital, Uluberia

Material and Method

Midnapore Medical College & Hospital is one of the largest tertiary care centre in southern region of West Bengal, India. This retrospective cross sectional study was conducted by reviewing the medical records of HIV infected patients aged 16 years or more who received antiretroviral treatment at the ART Clinic of Midnapore Medical College & Hospital during the period of 2006 to 2013. Seriously ill patients & those who did not complete 4 years of antiretroviral treatment either due to death, transfer out or lost follow up were excluded from our study.

For the purpose of this study, a baseline and 6-monthly CD4 cell count(by flow cytometry) upto 48 months and basic information such as patients' sex, age, weight, presence of TB co infection, anemia and WHO clinical stage were collected from medical records.

Our study was approved by Institutional Ethics committee for human research, Midnapore Medical College & Hospital.

Sample size, sampling technique & Statistical analysis : 422 sample size. Formula Z^2pq/L^2.

Z=1.96, on 95% confidence interval, p= 50%, q=(1-p), L=absolute error of 5%. 422 records were evaluated at ART clinic from 2006-2013 those who completed 4 years ART.

Data were being entered and analyzed by using SPSS for Windows, version 20.0. The median (IQR) in the absolute CD4 cell count at baseline and every six months thereafter was determined. Changes in CD4 cell count every six months were also examined and stratified on the basis of baseline CD4 cell count (<200, 201–350, and >350cells/µl). Categorical variables were summarized as frequencies and percentages while numerical variables with non-normal distribution were summarized as median and IQR. To assess the factors associated with the risks of immunological non response, logistic regression analysis was applied. All tests of significance were two-sided, with $p<0.05$ indicating statistical significance.

Observations

Baseline characteristics of the patients :

A total of 422 medical records of the ART Clinic of Midnapore Medical College & Hospital were reviewed. Baseline characteristics of the patients are depicted in Table 1.

Trend of CD4 count after comencement of ART :

The changes in the median CD4 cell count at 6 months interval after the commencement of ART is plotted in Fig 1. The overall median CD4 Count & median CD4 count in different strata are depicted in Table 2. CD4 count Median IQR at 0 m was 132 (93-168), 265 (230-301), 380 (364-397) and at 48 m 191 (188-203), 300 (274-324), 596 (488-698) cells/µl of CD4 <201, 201-350, >350 cells/µl respectively (Table 2, Fig 1).

Table 1 — *Baseline characteristics of the patients (n=422)*

Baseline variables	Frequency	Percentage
Gender :		
Male	198	46.9
Female	224	53.1
Age (years) :		
<45	369	87.4
≥45	53	12.6
Mean±SD	34.05±8.459	
WHO clinical stage :		
1	95	22.5
2	146	34.6
3	139	32.9
4	42	10.0
Baseline CD4 count :		
≤200	191	45.3
201-350	204	48.3
>350	27	6.4
Weight (kg) :		
<40	77	18.3
40-60	323	76.5
>60	22	5.2
TB co-infection :		
Yes	117	27.7
No	305	72.3
Anemia :		
<12	354	83.9
≥12	68	16.1

Baseline CD4 cell count was evaluated whether it was a risk factor associated with immunological non-response. The percentages of immunological non-response was 17.5% (74 out of 422 patients). The proportions of patients who had immunological non responses were 31% (23 out of 74), 46% (34 out of 74) and 23% (17 out of 74) among patients with baseline CD4 <200, 201–350 and >350 cells/µl respectively. Results of logistic regression analysis of baseline characteristics associated with the risk of immunological non-response are depicted in Table 3.

Discussion

The overall median CD4 cell count had improved among HIV-infected patients over the period of 48 months in our study. It was also seen that the CD4 counts almost returned to normal at the end of 48 months in those with initial CD4 counts of >350 cells/µl. The patients with a baseline CD4 cell count <200 cells/µl had the lowest peak CD4 counts. So a lower CD4 cell count at the start of antiretroviral therapy was related to a lower plateau CD4 cell count. These findings are in accordance to the literature[7,8,12-15].

A study by Moore RD et al showed that, only patients with baseline CD4 cell counts >350 cells/µl returned to nearly normal CD4 cell counts after 6 years of follow-

Table 2 — *Distribution of CD4 median values among categories of CD4 count (n=422)*

	All	CD4≤200	CD4 201-350	CD4 >350
0m	219	132	265	380
6m	322	160	291	415
12m	365	181	301	453.5
18m	405	158.50	301	462
24m	449.50	168	286	490
30m	473.50	186	282	502
36m	501	146	287	544
42m	545	198	298	578
48m	578	191	300	596

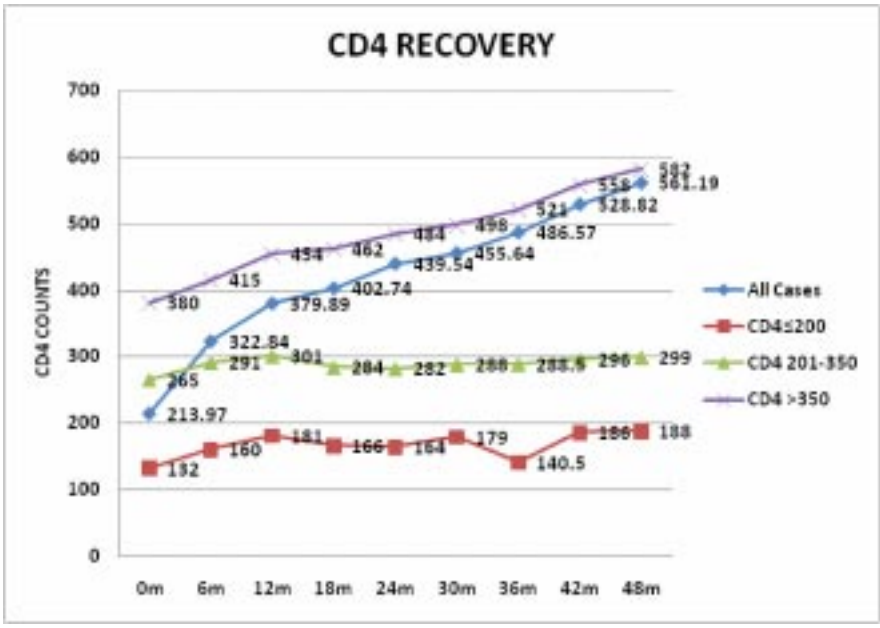

Fig 1 — Changes in the median CD4 cell count at 6 months interval

up[11]. Another study by Kelley CF *et al* revealed that a substantial proportion of patients who delay therapy until their CD4 cell count decrease to <200 cells/mm do not achieve a normal CD4cell count, even after a decade of otherwise effective antiretroviral therapy[7]. Palella FJ Jr *et al* found that survival rates in HIV-infected patients has been significantly improved by ART through its ability to increase the CD4 lymphocyte count in peripheral blood as well as reducing HIV load to undetectable levels[12]. In most of the studies it is seen that there is increase in CD4 counts for initial few years followed by a less pronounced increase or decline thereafter. A study by Kaufmann GR et al showed that the recovery of CD4 T lymphocytes occurs mainly in the first 2 years after the initiation of ART, and is associated with age and the pre-existing degree of HIV-1-related immunodeficiency, suggesting that the long-term exposure to HIV-1 infection has caused damage to the immune system that is difficult to correct[13]. Another study by Hunt DW *et al* showed that most patients who achieve and maintain viral suppression on HAART continue to experience CD4 T-cell gains through 4 years of therapy. The immune system's capacity for CD4 T lymphocyte restoration is not limited by low pre-therapy CD4 counts[8]. A longitudinal study was conducted in northern Ethiopia where the median CD4 lymphocyte count had improved over the five year period except at the 54th and 60th months where the median CD4 cell count showed a slight decline[14].

Table 3 — *Results of logistic regression analysis of baseline characteristics associated with the risk of immunological non-response (increase of < 50 cells/microlitre)*

Charecteristics	Risk of immunological non-response at 12 months	
	OR (95% CI)	P value
Gender :		
Male	1	
Female	1.901 (1.038, 3.481)	0.038
Age (years) :		
<45	1	
≥45	0.466 (0.203-1.072)	0.073
WHO clinical stage :		
1	1	
2	1.825 (0.873, 3.814)	0.110
3	2.094 (0.902, 4.865)	0.086
4	6.287 (1.352, 29.228)	0.019
Baseline CD4 count :		
≤200	1	
201-350	0.739 (0.389, 1.404)	0.355
>350	0.068 (0.025, 0.189)	0.000
Weight (kg) :		
<40	1	
40-60	1.403 (0.661, 2.978)	0.378
>60	2.818 (0.606, 13.113)	0.187
TB Co infection :		
Yes	0.592 (0.286, 1.226)	0.158
No	1	
Anemia :		
<12	1	
≥12	1.713 (0.758, 3.870)	0.196

Among the different predictors, immunological non-response was significantly observed among female patients. Patients of WHO Clinical stage 4 was associated with higher risk of immunological non response, whereas patients with baseline CD4 cell counts of >350 cells/µl was at significantly lower risk of it.

In most of the studies, male patients are seen at increased risk of immunological non-response. Higher rate of subsequent CD4 cell recovery was observed among female patients than males was also seen in those studies[15,16]. A study by Addisu A *et al* described that better immunological response in female could reflect the feminization of the HIV epidemic, better health seeking behavior of women and possibly the linkage of treatment sites with the antenatal clinics and the prevention-of-mother-to-child HIV programs resulting in better immune recovery & unimproved outcomes among male patients were because of poor health seeking behavior of men, lower rates of HIV testing, lower rates of repeat-testing and lower acceptance of linkage to HIV-care after a positive result[14]. Some other studies showed that gender was not related to initial &

subsequent CD4 responses[4].

The poor initial CD4 recovery (immunological non response) among females in our study may be due to the fact that most of the patients belonged to lower socio economic & male dominated societies. As a result, females were much neglected, they had poorer adherence to the health seeking behavior & poorer general condition. We found in our studies that, patients with baseline CD4 cell counts of >350cells/µl had significantly lesser chances of immunological non response compared to those with lower baseline CD4 cell counts. These findings are in accordance to the previous studies.

A study by Florence E et all showed that a lower CD4 cell count was associated with a lower rate of CD4 cell recovery at 12 months of HAART[17]. In contrast, a study by Lawn SD *et al* showed that patients with baseline CD4 cell counts < 50 cells/µl have equivalent or greater capacity for immunological recovery compared to those with higher baseline CD4 cell counts[10]. Another retrospective study in Thailand reported that the outcomes of HIV patients did not differ by baseline CD4 cell count[18].

Therefore, our study findings suggest that HAART should be initiated early for better immune recovery & female patients should be given more consideration regarding adherence to the therapy.

References

1 Fauci AS, Pantaleo G, Stanley S, Weissman D — Immunopathogenic mechanisms of HIV infection. *Ann Intern Med* 1996; **124:** 654-63.

2 Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, *et al* — Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *The Lancet* 2002; **360:** 119-29.

3 Gottlieb GS, Sow PS, Hawes SE, Ndoye I, Redman M, Coll Seck AM, *et al* — Equal plasma viral loads predict a similar rate of CD4+T cell decline in human immunodeficiency virus (HIV) type 1- and HIV-2-infected individuals from Senegal, West Africa. *J Infect Dis* 2002; **185:** 905-14.

4 Smith CJ, Sabin CA, Youle MS, Kinloch-de Loes S, Lampe FC, *et al* — Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. *J Infect Dis* 2004; **190:** 1860-8.

5 WHO — Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva. 2010.

6 WHO —Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. September 2015.

7 Kelley CF, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, Crane HM, *et al* — Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis* 2009; **48:** 787-94.

8 Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI, *et al* — Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. *AIDS* 2003; **17:** 1907-15.

9 Kilaru KR, Kumar A, Sippy N, Carter AO, Roach TC — Immunological and virological responses to highly active antiretroviral therapy in a non-clinical trial setting in a developing Caribbean country. *HIV Med* 2006; **7:** 99-104.

10 LLawn SD, Myer L, Bekker LG, Wood R — CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infect Dis* 2006; **6:** 59.

11 Moore RD, Keruly JC — CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis* 2007; **44:** 441-6.

12 Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, *et al* — Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338:** 853-60.

13 Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D, Cooper DA — The extent of HIV-1-related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. *AIDS* 2002; **16:** 359-67.

14 Addisu A, Dagim A, Tadele E, Adissu A, Mussie A, Filmon K — CD4 Cell Count Trends after Commencement of Antiretroviral Therapy among HIV-Infected Patients in Tigray, Northern Ethiopia: A Retrospective Cross-Sectional Study. PLoS ONE 10(3): e0122583.

15 Malaza A, Mossong J, Ba¨rnighausen T, Viljoen J, Newell M-L — Population-Based CD4 Counts in a Rural Area in South Africa with High HIV Prevalence and High Antiretroviral Treatment Coverage. *PLoS ONE* 2013; **8:** e70126.

16 Shastri S, Boregowda PH, Rewari BB, Tanwar S, Shet A, Kumar AMV— Scaling Up Antiretroviral Treatment Services in Karnataka, India: Impact on CD4 Counts of HIV-Infected People. *PLoS ONE* 2013; **8:** e72188.

17 Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult A, *et al* — Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. *HIV Med* 2003; **4:** 255-62.

18 Kyaw NL, Thanachartwet V, Kiertiburanakul S, Desakorn V, Chamnanchanunt S, ChierakulW, *et al* — Baseline CD4 cell counts and outcomes among adult treatment naïve HIV patients after taking fixed dose combination GPO-VIR-S and GPO-VIR-Z in Thailand. *Southeast Asian J Trop Med Public Health* 2013; **44:** 232-43.