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CD 4 Response in HIV Patients on Long Term First Line ART – A Cross Sectional Study from South India

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ABSTRACT
The CD4 count is the most important indicator of immune function in HIV-infected patients. It is also the strongest predictor of subsequent disease progression and survival. We conducted a study to estimate the CD4 count responses in patients who are on long term first line ART, possible predictors of the CD4 count responses & the clinical outcome in relation to their current CD 4 count. We conducted a cross sectional study on patients with HIV infection, on first line anti-retroviral treatment (ART) for at least five years. They were recruited either from medical outpatient department (OPD) /ART centre or admitted in the medical wards of a tertiary care hospital. We included 100 HIV positive patients on first line ART. The mean duration of disease was 7.47 (SD2.78) years. Mean CD4 count pre ART was 169.73 ± 82.78 mm^3, post ART CD 4 count at 1, 5 and 6 years (current) were 371.90 ± 152.94, 506.44 ± 213.75 and 548.48 ± 266.44. There was significant rise in CD4 count from baseline to 1, 5 and 6 years CD 4 counts (p = 0.000). Duration of ART (p=0.01), history of default (p=0.04) and absence of OIs (p=0.03) before ART were significantly associated with immunologic failure. There was a significant decrease in opportunistic infections post ART (P=0). National AIDS control organisation (NACO) recommended first line regimens result in robust immunologic response that is sustained over a mean period of over 6 years in a majority (84%) of the patients & result in significant reductions in opportunistic infections.
Keywords: *HIV, CD4 response, ART, CD4 normalisation.*

INTRODUCTION

Human immunodeficiency virus and acquired immunodeficiency syndrome (HIV AIDS) has become the number one killer infectious disease of mankind within three decades of its discovery. Highly active antiretroviral therapy (HAART) is the cornerstone of management of patients with HIV infection. Widespread use of anti-retroviral therapy (ART) resulted in a marked decline in the incidence of most AIDS defining conditions and mortality, both in the developed and developing world[1]. Suppression of HIV replication & the resultant improvement in CD4 counts prevents HIV associated morbidity and mortality as well as improves the quality of life in patients with HIV infection.

Following the initiation of combination ART and typically within 6 months of adherent therapy,

around 80% of HIV-positive patients have undetectable plasma HIV RNA viral loads (< 50 HIV-1 RNA copies/ml). The suppression of HIV replication facilitates immune reconstitution. The general immunological response to therapy for the majority of patients is characterized by relatively rapid increases in CD4 cell counts during the first 2 years of therapy, followed by smaller but consistent increases through 3–6 years of treatment.[2]

The CD4 count is the most important laboratory indicator of immune function in HIV-infected patients. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies.[3,4] It is the key factor in determining the need to initiate opportunistic infection (OI) prophylaxis[5] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm^3 during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 to 100 cells/mm^3 per year until a steady state level is reached.[5]Patients who initiate therapy with a low CD4 count or at an older age may have a blunted increase in their counts despite virologic suppression.

Older age, male sex, higher baseline viral load, resistance to drugs, poor adherence (non compliance& intolerance), interactions with other medications, co-infections like Hepatitis C, HTLV 1 & 2, anaemia, substance abuse and depression are some of the factors other than the initial low CD4 count which can influence immunological recovery & treatment outcome[6-8].

Clinical trials have established the efficacy of antiretroviral therapy with triple-drug regimens for individuals infected with the human immunodeficiency virus (HIV), but the effectiveness of these regimens in the population of patients enrolled outside clinical trials is unknown.

Therefore, we conducted a study to estimate the CD4 count responses in patients who are on long term (a minimum period of five years) first line ART, possible predictors of the CD4 count responses & the clinical outcome in relation to their current CD 4 count.

MATERIALS AND METHODS

We conducted a cross sectional study on patients with HIV infection, on first line ART for at least five years. They were recruited either from medical outpatient department (OPD) /ART centre or admitted in the medical wards of a tertiary care hospital. The study period was for one year from January 2014 to December 2014. Patients on drugs likely to cause CD4 cytopenia were excluded from the study.

Clinical failure was defined as new or recurrent clinical event indicating severe immunodeficiency [World health organisation (WHO) clinical stage 4 conditions] after 6 months of effective treatment and immunological failure as no increase in CD4 count or a fall in CD4 counts while on ART.[9]

Demographic data, data on duration of HIV, duration of treatment, ART regimens, treatment default, change of ART regimen, opportunistic infections before and after ART, WHO stage before and after ART, reasons for change of ART and serial CD4 counts were collected.

Data were entered & analyzed in the EPI info statistical program. Data are expressed as means and standard deviation (SD) for continuous variables and percentage and frequencies for categorical variables. Student's t test is used for comparing the difference in means for continuous variables and chi square test for comparison of proportions. The co-relation between clinical and immunological response was assessed by Pearson's co-relation co-efficient test. Statistical significance is set at $p<0.05$.

RESULTS

We included 100 HIV positive patients on first line ART for the study. The mean age was 42.75 (SD8.03) years. There were 67 males & 33 females. Majority of the patients included had 6 or more years of HIV. The mean duration of disease

was 7.47 (SD2.78) years. Out of the 100 subjects 87 were symptomatic at the time of detection of the disease. The mean duration of ART in the study subjects was 6.03± 1.64 years.

Initial ART regimes

ZLN (Zidovidine, Lamivudine & Nevirapine) was the most commonly used ART regimen, in 65 patients. Eighteen were on SLN (Stavudine, Lamivudine & Nevirapine), 13 were on ZLE (Zidovidine, Lamivudine &Efavirenz) & 3 were on SLE (Stavudine, Lamivudine & Efavirenz). Only one subject was using TLE (Tenofovir, Lamivudine & Efavirenz).

ART change

Thirty eight subjects out of 100 had changed their ART regimens during the course of treatment. Sixty two had continued to take their initial ART regimens. Out of 38 subjects who changed their ART regimens, the reason for change in 21 subjects was side effects. Sixteen subjects changed their ART regimens because of non-availability and one due to treatment failure.

CD4 responses

There was significant rise in CD4 count after the initiation of ART. The mean CD4 count pre ART was 169.73 ± 82.78 mm^3, post ART CD4 count at 1, 5 and 6 years(current) were 371.90 ± 152.94, 506.44 ± 213.75 and 548.48 ± 266.44 (Fig 1). There was significant rise in CD4 count from baseline to 1, 5 and 6 years CD4 counts (p = 0.000). But in few patients after the initial rise there was drop in CD4 count. In few patients the CD4 count response plateaued and remained same. The mean CD4 counts rose progressively till 5 years of treatment. The mean CD4 was higher at a mean duration of ART of 6.03 ± 1.64 years as compared to the values at 5 years but the maximum CD4 value was higher & the minimum CD4 value was lower, indicating that in some patients the CD4 counts continued to rise even after 5 years & in some patients it had started falling.

Out of 100 subjects 60 attained normalization of CD4 count after the initiation of ART. However CD4 counts of 40 subjects did not reach the normal value after the initiation of ART. Out of the 100 subjects 84 had steady rise in CD4 count after the initiation of ART. Only 15 had a fall in CD4 count after the initial rise. One patient had no significant rise in CD4 counts.

Two parameters were used to evaluate the possible predictors of CD4 response; the normalization of CD4 count & immunological failure (table 1). The following parameters were used to assess normalization of CD4 count & immunological failure: age, gender, duration of disease, mean duration of ART, pre ART symptoms, pre ART OIs, pre ART CD4 count, pre ART WHO stage and treatment default.

A total of 16 patients had immunologic failure (table 2). Patients with immunologic failure had a prevalence of 1.8 ±1.4 OIs as compared to a mean of 0.9 ± 1 OIs without immunologic failure. The difference was statistically significant (p = 0.03).

Immunologic response versus clinical response

An analysis of OIs occurring after 6 months of ART was done to assess the clinical response versus CD4 count at 1 year and 5 years to assess immunological response. There was no correlation between the number of OIs post ART & the CD4 count at 1 year of ART (Correlation coefficient: r = -0.28, r2 = 0.08; 95% confidence limits: -0.34 < r^2 < 0.52) or 5 years of ART (Correlation coefficient: r = -0.47, r^2 = 0.22; 95% confidence limits: -0.15 < r^2 < 0.63). Clinical response in the form of occurrence of OIs and rise in CD4 count post ART showed a significant change as compared to pre ART (table 3).

Eighty four (84%) of patients were in stage 3 and 4 of disease before ART which reduced to 14% after ART.

Figure 1: Serial change in CD4 counts over 6 years

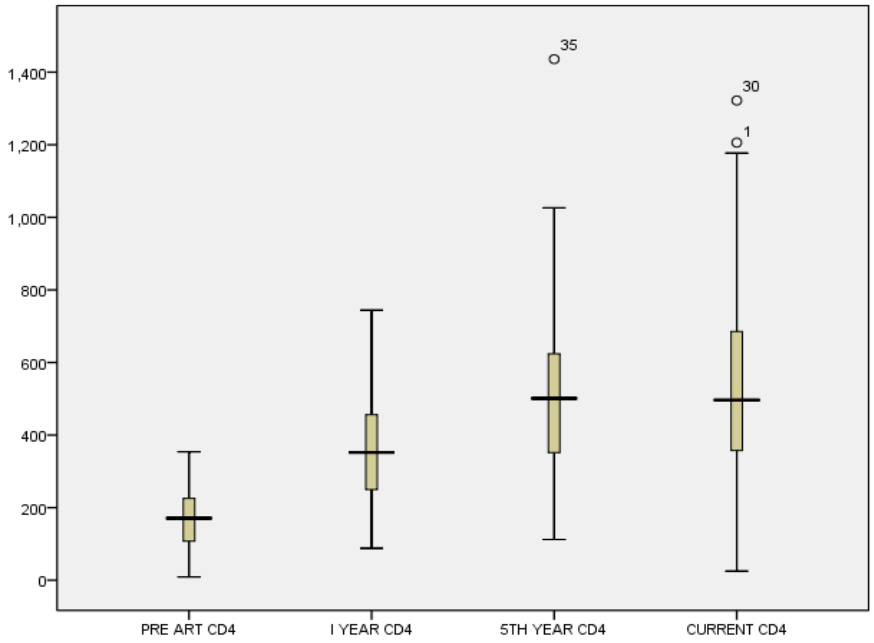

Table 1: Predictors of CD4 normalisation and Immunological failure

Variables	CD4 normalisation Yes	CD4 normalisation No	P value	Immunological failure Yes	Immunological failure No	P value
Age in years (mean)	43.4 ± 7.7	41.8 ± 8.5	0.16	45.2 ±8.4	42.3 ±7.9	0.1
Gender male female	 39(51%) 21(64%)	 28(49%) 12(36%)	 0.27	 13(19%) 3(10%)	 54(81%) 30(90%)	 0.19
Mean duration of disease (years)	7.5 ± 2.9	7.4 ± 2.6	0.88	8.5 ± 3.6	7.3 ± 2.6	0.47
Mean duration of ART	5.9 ± 1.6	6.1 ± 1.7	0.51	6.9 ± 2.3	5.9 ± 1.4	0.01
Pre ART symptoms Present Absent	 49(57%) 11(85%)	 38(443%) 2(15%)	 0.052	 14(16.1%) 2(15.4%)	 73(85.9%) 11(76.4%)	 0.7
Pre ART OI Present Absent	 56(59%) 4(80%)	 39(41%) 1(20%)	 0.35	 13(13.7%) 3(60%)	 82(76.3%) 2(40%)	 0.03
Pre ART WHO stage 1 2 3 4	 0(0%) 12(80%) 33(55%) 15(63%)	 1(100%) 3(20%) 27(45%) 9(37%)	 0.19	 1(100%) 4(26.6%) 9(15%) 2(8.3%)	 0 11(73.4%) 51(85%) 22(91.7%)	 0.054
Mean pre ART CD4 count	177.7 ± 82.78	157. 7 ± 82.36	0.216	204.5 ± 52.1	163.6 ± 85.9	0.08
Treatment default Yes No	 7(30%) 53(69%)	 16(70%) 24(41%)	 0.002	 7(30.4%) 9(11.7%)	 16(69.6%) 68(87.3%)	 0.04

Table 2: Immunological failure and OI numbers

OI number	Immunological failure		TOTAL
	Present	Absent	
0	4(10.8%)	33(89.2%)	37
1	4(10.8%)	33(89.2%)	37
2	2(15.4%)	11(84.6%)	13
3	4(44.4%)	5(66.6%)	9
4	2(50%)	2(50%)	4
TOTAL	16	84	100

Table 3: Clinical response post ART

Variable	Pre ART	Post ART	P value
OI			
Candida	67	28	0.0
CMV	09	06	0.42
Cryptococcus	03	02	0.65
PCP	37	15	0.0
TB (any site)	43	19	0.0
Mean CD4 count (mm^3) at baseline and 5 years	169.72 ± 82.78	506.44 ± 213.75	0.0

OI opportunistic infections, CMV cytomegalovirus,
PCP pneumocystis jiroveci pneumonia, TB tuberculosis WHO World health organisation.

DISCUSSION

Although ART does not cure HIV infection, the decrease in the viral load and the improvement in immunological status brought about by the use of ART drugs have resulted in a marked decrease in the mortality and morbidity associated with the disease[10].

The most common ART regime used in our study were ZLN and SLN. The most common reason for ART change was side effects. Out of 100 patients 87 were symptomatic at the time of detection of disease. In a study done by Chakraborty et al[11]out of 125 patients majority (80%) were symptomatic for HIV infection at the time of detection of disease and others were diagnosed during routine screening.

The mean CD4 count was 169.72 ± 82.78/mm^3& was not significantly different between males & females. In a study done at Pune[12] the median CD4 count was 109/mm^3. In a study done by Rohit Goel et al in eastern UP, the mean CD4 count (mm^3) was107±60[13]. The low CD4 counts at initiation of ART in our study & the first two Indian studies reflect the NACO guidelines at the time these patients were initiated on ART.

There was significant rise in CD4 count after the initiation of ART to 6 years. CD4 response assessed using CD4 normalisation and immunological failure showed that presence of symptoms before the initiation of ART probably has an adverse outcome on the normalization of CD4 counts. However the difference fell short of statistical significance. A history of defaults was associated with a significantly lower CD4 response at 5 years of ART. Duration of ART, history of default and absence of OIs before ART were significantly associated with immunologic failure.

The frequency of different infections in this study is almost similar to other Indian studies[14,15] and data provided by NACO and the most common being candidiasis.[16] The high prevalence of PCP reflects the late presentation of many of our patients & perhaps the fact that in many of these patients the diagnosis of PCP was presumptive. In our study the prevalence of other opportunistic infections were documented in 44%, which included diarrhoea in 20% & respiratory infections in 11%. There was a significant decrease in opportunistic infections (Candida,

PCP and TB) post ART (P=0). The numbers of OIs were significantly lesser in patients with normalization of CD4 counts (0.62 ± 0.72 Vs 1.73 ± 1.3, p = 0.000004). As the CD4 count improved the number of opportunistic infections decreased. There was a mild negative correlation between the number of OIs post ART & the CD4 count at 1 year or 5 years of ART. The numbers are small to confirm this finding.

The patients were grouped into 4 groups according to WHO staging.[9]Sixty patients were found to have WHO stage III before initiation of ART, 24 had stage IV disease, 15 stage II and one had stage I disease. Most of the patients included in the study were on ART from the government ART centre, under the guidance of national AIDS control organisation (NACO). This reflects the criteria for starting ART at the time these patients were initiated on ART. As per 2007 NACO guidelines WHO stage 3 or 4 or a CD4 count below 200/mm^3 for earlier WHO stages (asympto-matic) were the indications for starting ART.

The limitations of the study are small sample size and patients not assessed for virologic failure. Majority of the patients were being followed up in the ART centre & the compliance was very good. The same degree of compliance cannot be expected in clinical settings.

In conclusion, NACO recommended first line regimens result in robust immunologic response that is sustained over a mean period of over 6 years in a majority (84%) of the patients & result in significant reductions in opportunistic infections. Compliance seems to be one of the key factors in ensuring success of an ART regimen.

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