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ORIGINAL RESEARCH

Evaluation of the effect of ART on CD4 counts and other laboratory parameters in the HIV infected people with different CD4 counts at the time of ART initiation

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ABSTRACT

Background: The benefits of Highly Active Anti-Retroviral Therapy (HAART) on mortality and morbidity in HIV-positive persons are well documented. The guidelines on When to start ART have evolved over the years towards earlier initiation of ART & present study was aimed to compare early versus late initiation of ART in PLHIV, in terms of effect on the CD4 counts and other laboratory parameters.

Material and Methods: Present study was prospective, observational study, conducted in patients ≥18 years, of either gender, recently diagnosed with HIV-1 infection or PLHIV, with CD4 count ~ 500cells/cu.mm & patients with CD4 count~350 cells/cu.mm.

Results: Enrolment of newly diagnosed clients for ART rose from 2.34 % in the L.I. group to 3.58% in the E.I. group & correlation was found to be statistically significant. In E.I group, median increase in CD4 count from baseline to 6 months was 119 cells/mm^3 and from 6 months to 12 months was 57 cells/cu.mm. At 12 months of ART initiation, statistically significant deranged LFT, increased anemia was noted in the L.I group, as compared to E.I group. No statistically significant change in RFT, WBC count was noted.

Conclusion: Early initiation of ART was instrumental in a significant improvement as compared to Late Initiation of ART with regards to rise in CD4 counts at 6 & 12 months, improvement in LFTs, rise in Haemoglobin levels.

Keywords: PLHIV, HAART, CD4 counts, Liver Function Tests (LFT), Haemoglobin,

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INTRODUCTION

Ever since the first case of HIV was detected in the state of Tamil Nadu in 1986, the spread of HIV / AIDS across the nation has been relentless.[1] However, with the advent of Anti-Retroviral Therapy (ART), it is now possible to control HIV.[2] The benefits of Highly Active Anti-Retroviral Therapy (HAART) on mortality and morbidity in HIV-positive persons are well documented.[3]

While monitoring response to ART, a decreasing frequency of opportunistic infections is an important sign of good clinical response. HIV viral load measurement, which may detect

treatment failure earlier than immunological and clinical assessment, is currently not available in most resource-limited settings.[4] It is known that HAART results in an improvement in immunological status, one feature of which is an increase in the CD4 cell count.[3]

The guidelines on When to start ART have evolved over the years towards earlier initiation of ART; CD4 count cut-off point for ART initiation moving from less than 200 cells/cu.mm in 2004 to less than 350 cells/cu.mm in 2010. However as per the recent guidelines by the National AIDS Control Organization (since June 2016), the threshold CD4 level for ART initiation has been brought up to 500 cells/cu.mm from the earlier threshold of 350 cells/cu.mm.[5] Present study was aimed to compare early versus late initiation of ART in PLHIV, in terms of effect on the CD4 counts and other laboratory parameters.

MATERIAL AND METHODS

Present study was prospective, observational study, conducted in Department of Microbiology , LTMMC & LTMGH , Sion , Mumbai, India. Study period was of 1 year. The study was initiated after obtaining approval from the institutional ethics committee.

Inclusion criteria

- Adult patients [≥18 years] of either gender, recently diagnosed with HIV-1 infection or living with HIV-1 infection.
- Patients with CD4 count ~ 500cells/cu.mm (450-500) & patients with CD4 count~350 cells/cu.mm (300-350).
- Patients without any prior exposure to ART.

Exclusion criteria

- Patients below 18 years of age.
- Patients with CD4 count >500 cells/cu.mm.
- Patients with CD4 count between 350-450 cells/cu.mm.
- Patients with CD4 count <300 cells/cu.mm.
- Patients with any prior exposure to ART.

Total 82 patients were selected, out of which 40 patients were enrolled retrospectively in late initiation group (L.I), who were started on ART at CD4 count~350 cells/mm^3 during march to august 2016. 42 patients were enrolled in early initiation group (E.I), who were started on ART at CD4 count~500 cells/cu.mm during march to august 2017.

The demographics, clinical data & laboratory data were recorded in the case record form after taking consent. All these patients were asked to report to follow up after at least 6 months gap and then after 12 months of ART initiation. At baseline and on each follow up at 6 month and at 12 month, patient's detailed clinical history was taken and tested for CD4 counts, laboratory parameters such as CBC (Haemoglobin, WBC count), LFT (SGOT, SGPT, total bilirubin), RFT(serum creatinine and BUN) results were noted from patient's case records.

History of symptoms for TB/OIs was elicited. Screening & Diagnosis for the same was done using standard Microbiological techniques.

In case of Serodiscordant couples, serostatus of spouse was noted at baseline. In case the status of spouse was negative or unknown, they were asked to follow up at 6 month and 12 month and tested for HIV antibody test according to the NACO guidelines for testing at F-ICTC.

Estimation of CD4 count was done with BD FACSCount^{TM} CD4 instrument (Becton, Dickinson and Company BD Biosciences), which is based on principle of flow cytometry. Total WBC count and Hemoglobin estimation was done using Sysmex XP-300^{TM} Automated Hematology Analyzer in the Department of pathology of the institute. AST (SGOT) and ALT (SGPT) enzymes values were measured by AU 680 Chemistry Analyser by Beckman

Coulter. Total Bilirubin estimation, creatinine estimation was done with Beckman Coulter AU System.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In the present study- during March to August 2016, as per the prevailing NACO guidelines for ART initiation, 2.34% (40) clients were newly initiated on ART, at CD4 counts of ~350 cells / cu. mm in Late initiation group-L.I {60% (24) patients were male and 40% (16) were female}. While, during March to August 2017, 3.58% (42) clients were newly enrolled on ART, at CD4 counts of ~500 cells/mm^3 {50% (21) patients were male and 50% (21) patients were female}. So the enrolment of newly diagnosed clients for ART rose from 2.34%in the L.I. group to 3.58% in the E.I. group & correlation was found to be statistically significant (p value = 0.025).

Table 1: Total clients enrolled[10,11]

	Late initiation group-L.I	**Early initiation group-E.I**
Total clients	8536	7759
No. of clients tested for baseline CD4 counts	550 (6.40%)	520 (7%)
No .of clients tested for follow up CD4 counts	1158 (13.6%)	653 (8%)
No. Of clients on ART & tested for CD4 counts	6828 (80%)	6586 (85%)
ART started- at CD4 count	300-350	450-500
Patients started on ART	6828(85.5%)	6586(91%)
Total patients followed up for CD4 count testing	7986	7239

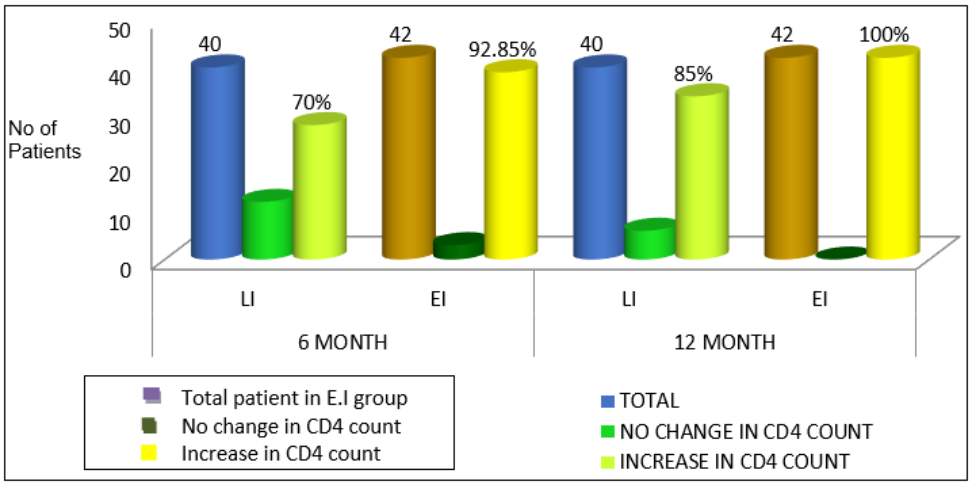

Figure 1: Effect of ART on CD4 counts in L.I group and E.I group

Out of the 40 patients, who had received late initiation of ART, 70% (28) achieved a rise (at least 50 cells/mm^3) in CD 4 count within 6 months and 85% (34) within 12 months. 15% (6) patients no rise in CD 4 count even after 12 months. However, of the 42 patients, having early initiation of ART, 92.85% (39) patients achieved a rise (at least 50 cells/ mm^3) in CD4

count within 6 months and all 100% within 12 months & this correlation was found to be statistically significant.

In present study, in L.I group , median increase in CD4 count from baseline to 6 months was 130cells/cu.mm and from 6 months to 12 months was 105 cells/cu.mm.

In E.I group, median increase in CD4 count from baseline to 6 months was 119cells/cu.mm and from 6 months to 12 months was 57 cells/cu.mm.

Table 2: Effect of ART on CD4 counts in L.I group and E.I group[14]

	At 6 months			**At 12 months**		
CD4 Count	L.I Group	E.I Group	Total	L.I Group	E.I Group	Total
No change	12	3	15	6	0	6
Increase of at least 50 cells/mm^3	28 (70%)	39 (92.85%)	67	34 (85%)	42 (100%)	76
Total	40	42	82	40	42	82
	p value=0.004, Chi square value- 7.16			p value= 0.005, Chi square value- 6.80		

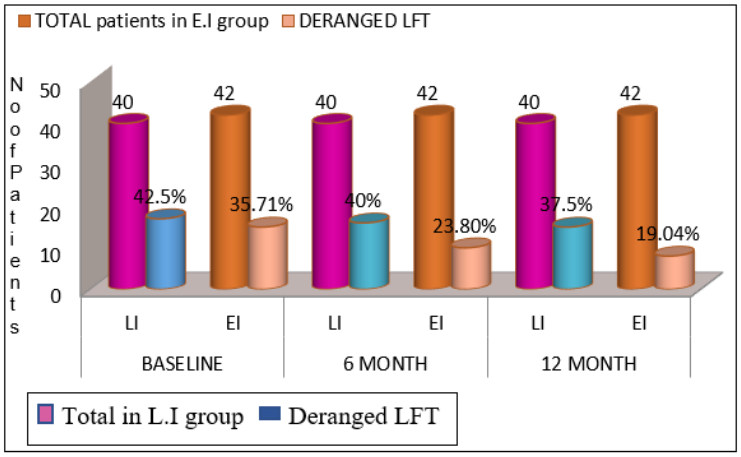

Figure 2: Effect of early versus late initiation of ART on LFT

At the time of enrollment, in the L.I group, out of 40 patients ,42.5% (17) patients had deranged LFT while In the E.I group, 35.71% (15) patients had deranged LFT.

At 6 months of ART initiation, in the L.I group, 40% (16) patients had deranged LFT as compared to 23.80% (10) patients had in the E.I group & difference was not statistically significant (p value-0.09). At 12 months of ART initiation, in the L.I group, 37.5% (15) patients had deranged LFT as compared to 19.04% (8) patients in the E.I group & difference was statistically significant (p value-0.05).

In the L.I group, 57.5% (23) patients had anaemia as compared to 52.38% (22) patients in the E.I group. At 6 months of ART initiation, in the L.I group 42.5% (17) patients were anaemic, as compared to 30.95% (13) patients in the E.I group & difference was not statistically significant (p value-0.28). At 12 months of ART initiation, in the L.I group 32.5% (13) patients were anaemic, as compared to only 9.52% (4) patients in the E.I group & difference was statistically significant (p value-0.01).

At the time of enrollment, in the L.I group, 22.5% (9) patients had deranged RFT while In the E.I group, 16.66% (7) patients had deranged LFT. At 6 months of ART initiation, in the L.I group, 30% (12) patients had deranged RFT as compared to 14.28% (6) patients had in the E.I group & difference was not statistically significant (p value-0.09). At 12 months of ART

initiation, in the L.I group, 17.5% (7) patients had deranged RFT as compared to 9.52% (4) patients in the E.I group & difference was not statistically significant (p value-0.29).
In the L.I group, 5% (2) patients had decreased WBC count at the time of enrolment but none of the patients (0%) had leucopenia at 6 months and at 12 months. In the E.I group, 4.76% (2) patients had decreased WBC count at the time of enrolment, but none of the patients (0%) had leucopenia at 6 months and at 12 months.

Table 3: Effect of early versus late initiation of ART on LFT, RFT, hemoglobin & WBCs[12,16,17]

	L.I GROUP			**E.I GROUP**		
	AT Baseline	**At 6 months**	**At 12 months**	**AT Baseline**	**At 6 months**	**At 12 months**
LFT (SGPT + bilirubin)						
Deranged LFT	17(42.5%)	16(40%)	15(37.5%)	15(35.71%)	10(23.80%)	8(19.04%)
Normal	23	24	25	27	32	34
Hemoglobin						
Anaemia <12 gm%	23 (57.5%)	17(42.5%)	13(32.5%)	22(52.38%)	13(30.95%)	4(9.52%)
Normal ≥ 12 gm%	17	23	27	20	29	38
RFT (creat.+BUN , creat/BUN)						
Abnormal	9(22.5%)	12(30%)	7(17.5%)	7(16.66%)	6(14.28%)	4(9.52%)
Normal	31	28	33	35	36	38
WBC						
Abnormal <4000cells/mm^3	2(5%)	0	0	2(4.76%)	0	0
Normal 4000-11000 cells/mm^3	38	40	40	40	42	42

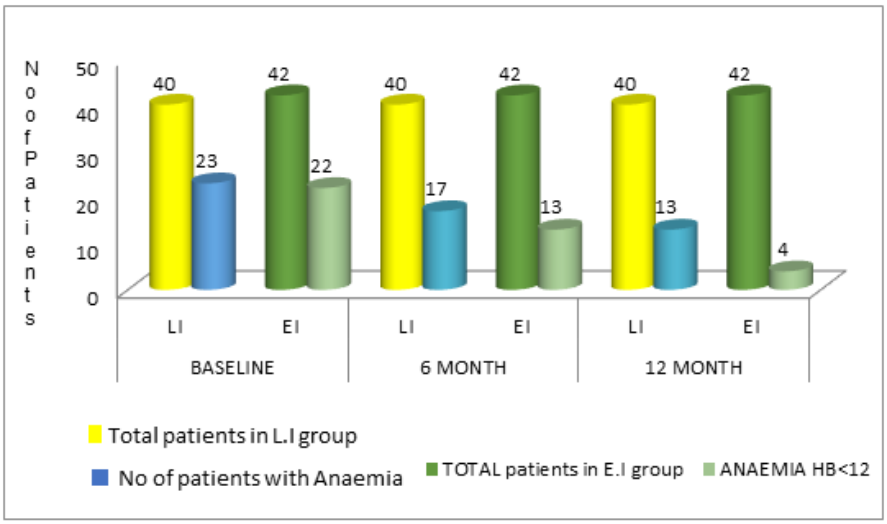

Figure 3: Effect of early versus late initiation of ART on Hemoglobin in PLHIV

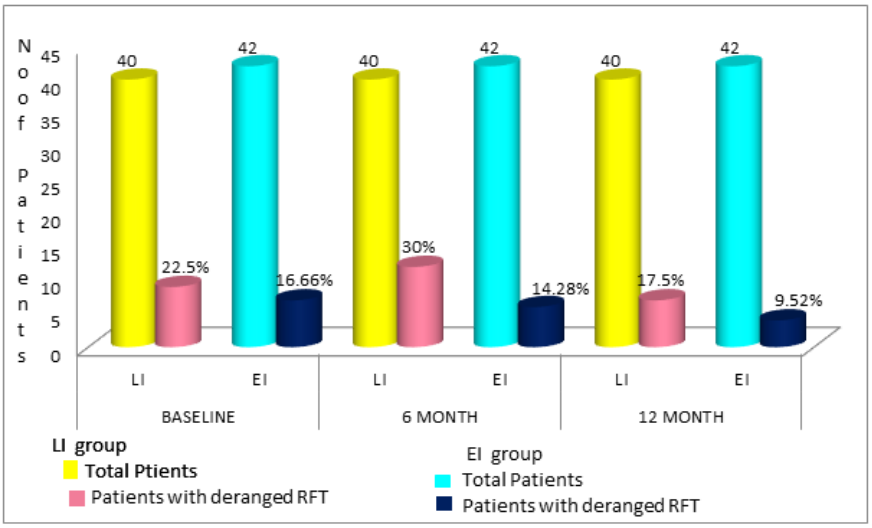

Figure 4: Effect of early versus late initiation of ART on RFT profie in PLHIV

DISCUSSION

With millions of people infected with HIV, it was once thought to result in "medical apocalypse". However, with the advent of antiretroviral therapy (ART), it is now possible to control HIV.[2] CD4 cells serve as important immunologic markers of HIV disease progression that facilitate both clinical decision- making about when to initiate Anti-Retroviral Therapy and clinical monitoring of treatment effectiveness and drug resistance. Use of HAART has been associated with improved clinical outcomes. [6]

Lot of new evidence from resource rich environments has accumulated showing that starting ART at higher CD4 counts is associated with better treatment outcomes.[4] The early initiation of ART before substantial decrease in CD4 counts significantly improves survival, as compared with deferred therapy.[7] Also, initiation of ART before severe immunosuppression results in long-term maintenance of normal CD4 cell counts and percentages.[8]

Taking ART is a lifelong commitment and the first six months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART. When ART is initiated; CD4 cell counts rise by 40- 60 cells per year and immune recovery starts. In most adults and children generally, this increase occurs during the first year of treatment, achieves a plateau and then continues to rise further during the second year.[9]

H Gautam, et al.,[10] studied, 43 drug naive HIV patients & found that 84% cases showed an increase of > 50 cells/µL following HAART, after a minimum period of 1-2 months. Babu SK et al.,[11] studied 139 subjects, receiving ART for 2 years. They found that at baseline, 19.4% subjects were in Stage-3 with moderate clinical symptoms and CD4 counts of 200–500 cells/mm^3. After a follow up of 6 months 90.6% patients showed increase in CD4 counts from baseline.

In present study, in the L.I group, median increase in CD4 count from baseline to 6 month was 130cells/cu.mm and from 6 month to 12 month was 105 cells/cu.mm. In E.I group, median increase in CD4 count from baseline to 6 month was 119cells/cu.mm and from 6 month to 12 month is 57 cells/cu.mm.

This rapid increases in CD4 cell count during the first few weeks after starting HAART are believed to be mainly a result of redistribution of cells stored in the lymphoreticular system. It is followed by a prolonged period of less-rapid increase, which is thought to be, due to the generation of naive CD4 cells through cell division or from the thymus.[3]

It has been estimated that approximately 15% of the deaths of patients with HIV infection are related to liver disease.[12] Many of the drugs used to treat HIV infection are metabolized by

the liver and can cause liver injury. Fatal hepatic reactions have been reported with a wide array of antiretroviral drugs including nucleoside analogues, nonnucleoside analogues, and protease inhibitors.[13]

Subir kumar Dey et al.,[14] in their study found that there was a significant increase in the activities of the serum enzymes like AST and ALT in all the cases of HIV as compared to the control group. Similarly in our study deranged LFT at enrollment was seen in 42.5% patients in the L.I group and 35.71% in the E.I group. Similarly in our study in the L.I group, 40% patients had deranged LFT at 6 month which decreased to 37.5% at 12 months. Also in the E.I group, 23.8% patients had deranged LFT at 6 months and only 19 % at 12 months.

Anaemia has been recognized as an important clinical problem in HIV-infected patients with an estimated prevalence ranging from 10% in asymptomatic HIV-infected patients to 92% in patients with AIDS.[15] Among the specific reversible causes of anemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections.[12]

In a study done on 905 patients by Richard D.Moore et al.,[16] they noted that 21% had a hemoglobin count >14g/dl at baseline. After 1 year of HAART hemoglobin levels>14g/dl was seen in 42% of patients. Similar findings were noted in present study. So we can interpret that initiation of ART has a definite role in raising the haemoglobin level of patients. However, when the ART is started at an earlier stage of the infection, the improvement is much better.

HIV infection and HIV-induced inflammation can cause chronic kidney disease (CKD), which is associated with increased morbidity & mortality. The occurrence of renal dysfunction in the HIV-infected population may be further increased by drug-induced renal toxicity, opportunistic infections, and comorbid diseases including hypertension, diabetes, and Hepatitis C. Diseases of the kidney or genitourinary tract may be a direct consequence of HIV infection, due to an opportunistic infection or neoplasm, or related to drug toxicity.[12]

Mpondo C. T B et al.,[17] in their study on 238 HIV infected patients, reported the effect of ART and outcome of baseline renal dysfunction in HIV infected adults. They found that Renal dysfunction decreased from 76.6% at ART initiation to 29.2% after 2 years of follow-up. Moderate dysfunction decreased from 21.1% at ART initiation to 1.1% at 2 years of ART. Similar findings were noted in present study.

Disorders of the hematopoietic system including lymphadenopathy, anemia, leukopenia, and or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy.[12]

Tamirat Edie ET al.,[18] in their study on 231 HIV positive, ART naïve patients and 130 patients on HAART reported leucopenia in 13% of the participants. Leucopenia was found to the extent of 3.9%, 5.9% &13.6% in patients with CD4 count> 500 cells/µl, 350-500 cells/µl and 200-349 cells/µl respectively. These figures were similar to those of our study. However they found no difference in the prevalence of leucopenia with relation to WHO clinical stages ART status or ART regimen.

CONCLUSION

Early initiation of ART was instrumental in a significant improvement as compared to Late Initiation of ART with regards to rise in CD4 counts at 6 months as well as at 12 months, improvement in Liver Function Tests (LFT) after 12 months of ART, rise in Haemoglobin levels after 12 months of ART during the course of ART. However, there was no significant improvement in Renal Function Tests.

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