



## STUDY ON IMPACT OF ANTITUBERCULAR TREATMENT ON CD4 COUNT IN HIV-TB CO INFECTED PATIENTS.

### General Medicine

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### ABSTRACT

**Background:** There is lack of data comparing the improvement in CD4 count following antitubercular (ATT) and antiretroviral therapy (ART) in patients presenting with Human Immunodeficiency Virus/Tuberculosis (HIV/TB) dual infection.

**Methods:** This Retrospective study was conducted with the access data base available at the ART (Anti retroviral treatment) centre attached to our Medical College. 111 patients who had the dual infection were included for the study. The study design was approved by the Institutional Ethical Committee. The details regarding the duration of HIV and Anti-Retroviral Therapy (ART), types of tuberculosis, pulmonary (PTB) or extra-pulmonary (EPTB), CD4 counts before and after ATD were recorded.

**Objectives:** To find out incidence & distribution of Tubercular infection among different CD4 categories in PLHIV & degree of CD4 cell count increment as a measure of immunological status improvement after completion of antitubercular treatment.

**Results:** The mean age was  $34.27 \pm 7.87$  yr in the study group. Among the study population, 67 (60.36%) of the participants were Pulmonary Tuberculosis and 44 (39.64%) of the participants were Extra pulmonary Tuberculosis cases. The predominant CD4 cell count level observed among pulmonary TB cases were 201-350cells/mm<sup>3</sup> whereas it was between 100-200cells/mm<sup>3</sup> in extra pulmonary TB cases. Among the Pulmonary TB diagnosed patients, the median CD4 after ATD completion was 330 and it was 243 among Extra pulmonary TB diagnosed patients. The difference in CD4 after ATD completion between TB diagnoses was statistically significant. (P value 0.005)

### KEYWORDS

Antiretroviral therapy(ART), Anti tubercular treatment(ATD), Pulmonary tuberculosis, Extra pulmonary tuberculosis.

### INTRODUCTION

Tuberculosis is said to be one of the commonest opportunistic infection in patients with HIV/ AIDS.<sup>1</sup> Of the estimated 21 million people living with HIV in 2020, nearly 30% were estimated to have latent or active TB infection.<sup>2</sup> Conversely, of the 9.4 million cases of incident TB worldwide, an estimated 1.4 million (15%) were co infected with HIV in 2020.<sup>3</sup> India is the third highest HIV burden country in the world, with an adult prevalence of 0.22%.<sup>4</sup> PLHIV (people living with HIV infection) are 21 (16-27) times at higher risk of developing TB. TB-HIV co-infection results in higher mortality rates.<sup>3</sup> Nearly 25% of all deaths among PLHIV are estimated to be due to TB.<sup>4</sup> HIV co-infection rates among incident TB patients are estimated to be 3%. 86,000 HIV associated TB patients are emerging annually.<sup>5</sup> HIV infected patients with TB commonly present with subacute systemic and respiratory symptoms, including fever (88%), weight loss (79%), cough (79%), and diarrhea.<sup>6</sup> Lower CD4 counts are associated with more severe systemic symptoms. At all stages of HIV infection, pulmonary TB is the most common form of TB. In general, HIV-infected patients with high CD4 counts have clinical manifestations of TB similar to those of TB patients without HIV infection.<sup>7</sup> Although pulmonary TB is the most common presentation regardless of the stage of HIV infection, persons with advanced immune suppression are more likely to have extrapulmonary TB than are HIV-infected persons with relatively intact immunity or persons without HIV.<sup>8</sup> So this study was performed to find out incidence & distribution of Tubercular infection among different CD4 categories in PLHIV & the degree of CD4 cell count increment as a measure of immunological status improvement after completion of antitubercular treatment.

### METHODS

This Retrospective study was conducted with the access data base available in the hospital, ART cent Patients who had the dual infection was included for the study. Before the study, the study design was approved by the Institutional Ethical Committee. HIV seropositivity was diagnosed by using NACO (National AIDS Control Organisation) supplied Comb-AIDS, Tridot and Triline test kits and tests interpreted as per manufacturers instruction and diagnosis was done as per national guidelines. CD4 count was performed with FACS (Fluorescent Assisted Cell Sorter) counter, with labelled antibodies. Pulmonary TB was diagnosed when either sputum smear was positive for AFB or when clinical or X-ray findings were strongly suggestive of

TB. Extra-pulmonary TB was defined as the involvement of organs other than lungs like lymph node, pleura, pericardium, meninges, abdomen, bladder, joints and spine. Diagnosis was based on culture, histopathological proof, radiological evidence or strong clinical suspicion. Apart from this dual infection pts with other opportunistic infections were excluded from this study.

### Statistical Analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test. For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). The change in the quantitative parameters, before and after the intervention was assessed by Wilcoxon signed-rank test (In case of two time periods). P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

### RESULTS:

A total of 111 HIV & TB dually infected patients were included in the final analysis. The mean age was  $34.27 \pm 7.87$  yrs in the study population, minimum was 18 years and maximum was 55 years. (95% CI 32.79 to 35.75) Among the study population, 34 (30.63%) of the participants were aged between 18-30 years, 69 (62.16%) of the participants were aged 31-45 years and 8 (7.21%) of the participants were aged 46-60 years. (Figure1)

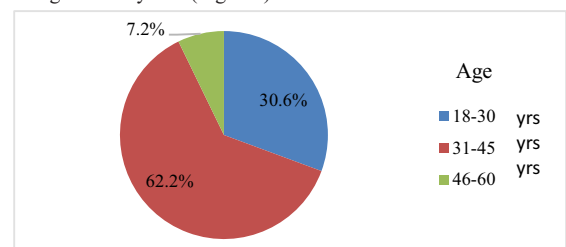
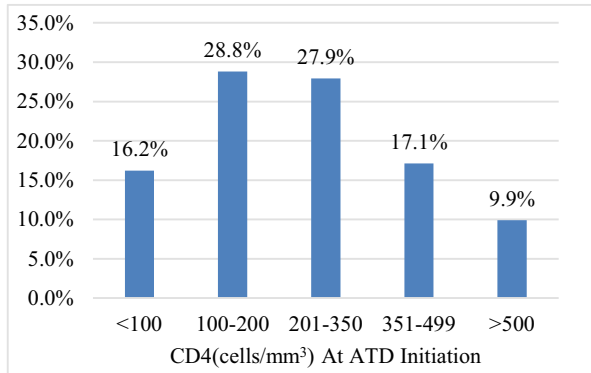


Figure 1: Pie chart of age distribution in the study population (N=111)

Among the study population, 85 (76.58%) participants were males and 26 (23.42%) participants were females. Among the HIV infected study population, 67 (60.36%) participants were Pulmonary TB cases and 44 (39.64%) participants were Extra pulmonary TB cases. Among the study population, 18 (16.22%) of the participants were <100cells/mm<sup>3</sup>, 32 (28.83%) of the participants were 100-200cells/mm<sup>3</sup>, 31 (27.93%) of the participants were 201-350cells/mm<sup>3</sup>, 19 (17.12%) of the participants were 351-499cells/mm<sup>3</sup> and 11 (9.91%) of the participants were >500cells/mm<sup>3</sup>. (Figure2)

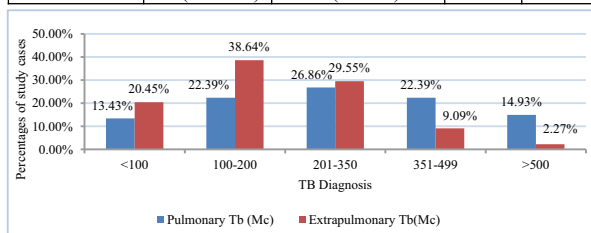


**Figure 2: Baseline CD4 count at the time of Tubercular infection Diagnosis in the study population (N=111)**

HIV infected study population in whom pulmonary tuberculosis diagnosis were made, majority of them had CD4 count in the range of 201-350cells/mm<sup>3</sup> at the time of diagnosis in 18 pts (26.86%) followed by range of 351-499cells/mm<sup>3</sup> in 15pts (22.39%) and least no of pts had CD4count above 500cells/mm<sup>3</sup> that was in 10 pts (14.93%). Conversely, HIV infected study population in whom any form of extra pulmonary tuberculosis diagnosis were made, majority of them had CD4 count in the range of 100-200cells/mm<sup>3</sup> in 17cases (38.64%) and second most commonly found range was between 201-350cells/mm<sup>3</sup> in 13cases (29.55%) followed by 9 pts (20.45%) had <100cells/mm<sup>3</sup> CD4 count at the time of diagnosis. There was statistically significant difference in CD4 count during Pulmonary and Extra Pulmonary Tuberculosis diagnosis (P value 0.035). (Table1, Figure 3)

**Table 1: Comparison between Pulmonary & Extra pulmonary TB cases at different CD4 categories (N=111)**

CD4 At ATD Initiation (cells/mm <sup>3</sup> )	TB Diagnosis Cases		Chi square	P value
	Pulmonary TB (N=67)	Extra Pulmonary TB (N=44)		
<100	9 (13.43%)	9 (20.45%)	10.342	0.035
100-200	15 (22.39%)	17 (38.64%)		
201-350	18 (26.86%)	13 (29.55%)		
351-499	15 (22.39%)	4 (9.09%)		
>500	10 (14.93%)	1 (2.27%)		



**Figure 3: Comparison between Pulmonary & Extra pulmonary TB cases at different CD4 categories (N=111)**

Among the Extra pulmonary TB cases, Pleural effusion was the most common presentation in 23cases(53.4%) followed by TB lymphadenitis in 8 cases(18.6%),Tubercular meningitis in 5 cases(11.6%), Abdominal TB in 4 cases(9.3%).

Among the Pulmonary TB diagnosed patients, the median CD4 at ATD Initiation was 272cells/mm<sup>3</sup> (IQR 168 to 410) and it was 168cells/mm<sup>3</sup> (IQR 112.75 to 220.5) among Extra pulmonary TB diagnosed patients. The difference in CD4 count between pulmonary and extra pulmonary TB cases was statistically significant. (P value 0.002),(Table 2).

**Table 2: Comparison of CD4 level between Pulmonary & Extrapulmonary TB cases before and after ATD therapy. (N=111)**

Parameter	TB Diagnosis Median (IQR)		Mann Whitney U test (P value)
	Pulmonary TB (N=67)	Extra pulmonary TB (N=44)	
Cd4 at ATD Initiation cells/mm <sup>3</sup>	272 (168 to 410)	168 (112.75 to 220.5)	0.002
CD4 after ATD Completion cells/mm <sup>3</sup>	330 (201 to 464)	243 (149.5 to 297.75)	0.005

Among the Pulmonary TB diagnosed patients, the median CD4 at ATD initiation was 272cells/mm<sup>3</sup> (IQR 168 to 410) and it was 330cells/mm<sup>3</sup> (IQR 201 to 464) after ATD completion. The difference between CD4 before and after ATD in Pulmonary TB diagnosed patients was statistically significant.(P value <0.001). Among the Extra pulmonary TB diagnosed patients, the median CD4 at ATD initiation was 168cells/mm<sup>3</sup> (IQR 112.75 to 220.50) and it was 243cells/mm<sup>3</sup> (IQR 149.50 to 297.75) after ATD completion. The difference between CD4 before and after ATD in Extra pulmonary TB diagnosed patients was statistically significant. (P value <0.001)(Table 3)

**Table 3: Comparison of CD4 count at different types of tuberculosis diagnosis and after ATD completion within each intervention group (N=111)**

TB Diagnosis	CD4 Median(IQR)		Wilcoxon sign -ranktest
	CD4 at ATD Initiation (N =111)	CD4 after ATD Completion (N =111)	
Pulmonary TB	272 (168 to 410)	330 (201 to 464)	<0.001
Extra pulmonary TB	168 (112.75 to 220.50)	243 (149.50 to 297.75)	<0.001

ATD=anti tubercular therapy.CD4 cell count expressed as cells/mm<sup>3</sup>.

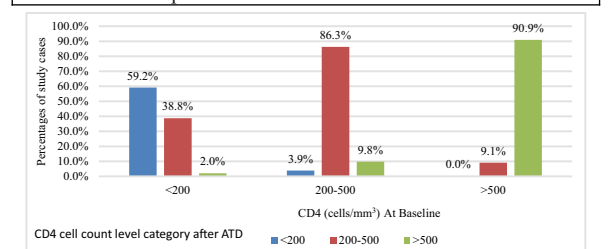
Among the Pulmonary TB diagnosed patients, the median body weight during ATD initiation was 52kgs (IQR 45 to 57) and it was 53kgs (IQR 45 to 59) after ATD completion. The difference between body weight before and after ATD in Pulmonary TB diagnosed patients was statistically significant (P value <0.001). Among the Extra pulmonary TB diagnosed patients, the median body weight at ATD initiation was 46kgs (IQR 40 to 53.75) and it was 47.50kgs (IQR 43 to 55) after ATD completion. The difference between body weight before and after ATD in Extra pulmonary TB diagnosed patients was also statistically significant. (P value <0.001).

Among the patients having <200 cells/mm<sup>3</sup> CD4 at baseline, 29 pts (59.18%) remained same CD4 cell level category after ATD completion, in 19pts (38.78%) count had increased to 200->500 cells/mm<sup>3</sup> category and 1 pt (2.04%) CD4 cell count increased to >500 cells/mm<sup>3</sup> after ATD completion. Among the patients having 200-500 CD4 at baseline, in 2 pts (3.92%) CD4 got reduced to <200 cells/mm<sup>3</sup> after ATD completion and in 44 pts (86.27%) it remained same category level and in 5pts (9.8%) count have increased to >500 cells/mm<sup>3</sup>. Among the patients having >500 cells/mm<sup>3</sup> CD4 at baseline, in 1pt (9.09%) cell count had reduced to 200-500 cells/mm<sup>3</sup> category level and 10 pts (90.91%) remained same cell count level after ATD completion. (Table 4 & Figure 4)

**Table 4: Degree of CD4 level changes after completion of ATD as compared to baseline level. (N=111)**

Cd4 count After ATD Completion	Cd4 count At ATD Initiation(Baseline)		
	<200 (N=49)	200-500 (N=51)	>500 (N=11)
<200	29 (59.18%)	2 (3.92%)	0 (0%)
200-500	19 (38.78%)	44 (86.27%)	1 (9.09%)
>500	1 (2.04%)	5 (9.8%)	10 (90.91%)

CD4 cell count expressed as cells/mm<sup>3</sup>.



**Figure4:CD4 cell count recovery following completion of ATD in comparison to baseline.**

## DISCUSSION

In this retrospective cohort study we compared the change in CD4 count following ATT and ART in HIV/TB co-infected patients. To our knowledge there is no published study analyzing CD4 cell recovery in HIV/TB co-infection patients. CD4 lymphocyte depletion is known to occur in TB patients not infected by HIV<sup>9</sup> and become normalized following ATT.<sup>9</sup> In a series of 85 patients with TB not infected by HIV, 37 showed low CD4 cell count and 48 had normal counts.<sup>10</sup> It has been found in our study that at lower CD4 counts (<200/mm<sup>3</sup>) EPTB cases predominate & at range between 200-350 cells/mm<sup>3</sup> occurring at equal proportion & at higher level (>500 cells/mm<sup>3</sup>) PTB cases predominate. Among EPTB cases Pleural involvement is most common form (53.4%) followed by Lymph node TB (18.6%). The median values of CD4 at the time of diagnosis of PTB & EPTB cases are 272 cells/mm<sup>3</sup> & 168 cells/mm<sup>3</sup> respectively. This difference is statistically significant. (p value 0.002) So, lower CD4 count prompts us for more vigilant search of Extrapulmonary sites. The ATD therapy in HIV-TB dually infected pts brings about significant improvement of immunological status in terms of CD4 count increment. The CD4 count changes after ATD therapy in both PTB & EPTB cases attain statistical significance (0.001). In accordance with our study, study done by Martin DJ et al. CD4 count increased significantly in both cohorts of HIV-TB group and TB group following ATD therapy.<sup>10</sup> Additional increment in CD4 count in patients with co-infection following treatment suggests that CD4 suppression at the onset of TB may be the direct result of mycobacterium growth and inflammation as well as interaction between TB and HIV in addition to the effect of HIV alone. The difference between wt. before & after ATD in PTB & EPTB cases were statistically significant (<0.001). Our study has the limitations of a retrospective study design. We did not have data on viral load in our study group as routine viral load testing was not implemented at that time. A prospective study with three limbs including TB pt alone, HIV infection alone and dual infection can confirm the findings in this study.

## CONCLUSION

Tubercular infection can occur at any CD4 count level in PLHIV and with the lower CD4 count chance of Extra pulmonary TB is more than Pulmonary TB. Tubercular infection in people living with HIV is still highly prevalent occurrence despite isoniazide prophylaxis in HIV infected patients. So, active screening for tubercular infection at every ART centre visit is warranted & should be a mandatory part of ART centre follow up. Baseline CD4 count at the time of diagnosis of tubercular infection can also give us some clue about tubercular focus in the body.

## REFERENCES

- [1] HIV Surveillance among Tuberculosis Patients in the South-East Asia Region World Health Organization Report, New Delhi; 2006. p.11—34.
- [2] Tb India 2011, Revised National Tb Control Programme: Government of India Annual Status Report. Chapter 1: Tuberculosis Burden; 2011.
- [3] Pennap G, Makpa S, Ogbu S. Sero-prevalence of HIV infection among tuberculosis patients in a rural tuberculosis referral clinic in northern Nigeria. *Pan African Medical Journal* 2010;5:22.
- [4] HIV testing and treatment among tuberculosis patients —Kenya, 2006—2009. *Morbidity and Mortality Weekly Report. MMWR* 2010;59(46):1513—7.
- [5] Wang L, Liu W, Wang Lu, Wang Y, Wu Z. HIV prevalence among pulmonary tuberculosis patients in Guangxi, China. *Journal of Acquired Immune Deficiency Syndrome* 2010;53(Suppl. 1):S61.
- [6] Reported HIV Status of Tuberculosis Patients—United States, 1993—2005. *Morbidity and Mortality Weekly Report. MMWR* 2007;56(42):1103—6.
- [7] Thanh DH, Sy DN, Linh ND, Hoan TM, Dien HT, Thuy TB, et al. HIV infection among tuberculosis patients in Vietnam: prevalence and impact on tuberculosis notification rates. *The International Journal of Tuberculosis and Lung Disease* 2010;14
- [8] Giehl C, Roy RB, Knellwolf AL. The situation of HIV/M. tuberculosis co-infection in Europe. *The Open Infectious Disease Journal* 2011;5(Suppl. 1—M3):21—35.
- [9] Swaminathan S, Ramachandran R, Baskaran G, Paramasivan CN, Ramanathan U, Venkatesan P, et al. Risk of development of tuberculosis in HIV-infected patients. *The International Journal of Tuberculosis and Lung Disease* 2000;4(9):839—44.
- [10] Mohanty KC, Basheer PM. Changing trend of HIV infection and tuberculosis in Bombay area since 1988. *Indian Journal of Tuberculosis* 1995;42:117—20.