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# A COMPARATIVE STUDY OF PATIENTS WITH TB AND HIV CO-INFECTION IN REFERENCE TO MEAN CD4 COUNT IN WESTERN INDIA

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## ABSTRACT

**Background:** Individuals with HIV infection are at increased risk for tuberculosis (TB) and other respiratory tract infections. Infection with TB enhances replication of HIV and may accelerate the progression of HIV to AIDS, with rapid fall in CD4 count, as both HIV/TB are individually known to decrease CD4 count. **Aim:** Emphasizing the pivotal role of cART and ATT in TB/HIV patients in maintaining their immune system effective (by maintaining CD4 count) and thus decreasing MDR/XDR, morbidity and mortality among these patients. Calculating average mean CD4 count for Indian scenario in cART era. **Material and methods:** All the 961 HIV infected patients early morning sputa were screened for AFB and few of the samples were even cultured on LJ medium. The samples were also examined for PMNLs in Gram's staining. All patients' CD4 count were also evaluated by flow cytomerty method within one week of sputa collection. Seven other published work of HIV patients were analyzed for TB in relation to CD4 count. Moreover five published research work of CD4 in TB patients but HIV-negative were also discussed in this article. **Results:** Out of 961 patents with RTI, 308(32.06%) found positive for tuberculosis with mean CD4 count found to be 198.5 and 105.9 cells/µl for pulmonary TB and for extra-pulmonary TB respectively in present study. The average mean CD4 count from seven research studies from India were found to be 169.75 and 145.3 cells/µl for pulmonary and extra-pulmonary TB respectively, in TB/HIV co-infected patients on cART. In advanced TB (HIV-negative) patients mean CD4 count found to be 485±321 by other researchers. **Conclusion:** HAART and ATT both are equally important in maintaining immune system(maintaining CD4 count) of TB/HIV co-infected patients. In India, clinician should suspect more for TB at around mean CD4 count of 169.75 even if found negative by AFB staining but should be confirm by culture on LJ medium, PCR or any other advanced techniques for HIV-positive patients.

## INTRODUCTION

The study of Jones et al (1997) demonstrated that the CD4 cell count is depressed in approximately one-half of hospitalized HIV- negative patients with tuberculosis and can be as low as that found in HIV –positive patients. Even, individuals co-infected with HIV and TB are 30 times more likely to develop active TB disease. Infection with TB enhances replication of HIV and may accelerate the progression of HIV to AIDS. Globally a decline in incidence and prevalence of HIV has been observed through implementation of various measures like successful awareness programs and health education system with active participation of governmental and nongovernmental organizations.(Joint United National Programme, 2014). A rise in HIV/AIDS is observed in resource poor countries like India despite successful implementation of control programmes.

However, the rate of mortality still pose a problem to health care system in developing countries like India. Most of these deaths recorded in cases of AIDS are because of opportunistic infections (OI) and other malignancies (Palella FJ et al,2006) The reason may be

attributed to the effective destruction or decrease in CD4 cells which play a pivotal role in immune system. The incidence of HIV associated OI have declined in developed countries by effective implementation of ant-retroviral therapy(ART).

But the relative frequencies of these opportunistic infections, causative agents vary in different countries and even in different places of same country. Respiratory tract infections/TB are among the first of some opportunistic infections to be seen in HIV patients. These OI causes substantial morbidity and hospitalization, economic loss to the society and shorten the survival time of HIV patients. They also affect the quality of life of HIV infected patients by increasing morbidity (Moore RD,1996). All over the world OI has reduced in HIV patients by implementation of ART, which may be due to reduction in the viral load of HIV and hence boosting the immune system. In addition, measures to treat and prevent OI become essential if ART stops working due to poor adherence to the regimen and development of drug resistance if noted.

CD4 count has shown to be an effective predictor in assessing the development of OI in HIV seropositive patients. It is absolutely necessary to have knowledge about the type of OI and the pathogens distributed in the region. Effective management and treatment of these infections not only improves the quality of life but also helps in prevention of transmissible diseases like TB etc.(Smit C, Geskus R et al,2006).

Scientific articles particulates, about 90% of HIV-related morbidity and mortality are caused by OIs compared to 7% due to opportunistic cancers and 3% due to other causes.(Staine JG,et al 2007).The type RTI infections which may be first to be seen and the spectrum of pathogens responsible have been documented in many studies conducted in China, Africa, Korea and Thailand. Studies about the distribution of opportunistic respiratory tract infections among people living with HIV in India have been reported and are limited to place and region. The present comparative study was aimed to emphasis on the pivotal role of HAART to reduce viral load and in turn to maintain mean CD4 count of TB/HIV patients.

## MATERIAL AND METHOD

The present study had been approved by the institutional ethical committee and even got permission of GSACS, Ahmedabad. A predesigned and pretested questionnaires was used to collect data on socio-demographic profile. Blood samples of these subject were tested for HIV. The HIV –infected patients were all diagnosed as HIV reactive as per NACO guidelines. In the patients found HIV sero-positive CD4 count was calculated on FACS count, by flow cytometry method method (Becton Dickinson) method from their blood samples.

Three consecutive early morning sputum samples were collected, they were even concentrated before reporting negative for AFB from 961 HIV infected patients who had complaint of cough and fever for more than one week. The quality of the expectorated sputum was assessed both by macroscopic and microscopic examination. Any sample that was thin, watery and with no purulent matter was considered unsuitable for further processing. Sputa samples were collected in a sterile wide mouth container.

Group T Cases were defined as patients with both HIV sero-positive as well as having complaints of cough and fever for more than one week, one patient was included only once. Patients having history of allergic common cold or allergic respiratory tract infections were excluded from the study.

The most common method of TB detection involved microscopic examination of sputum for acid-fast bacilli. However, to be considered smear positive a specimen needs to contain approximately 105 bacilli per milliliter. The sensitivity of sputum of sputum microscopy in HIV infection ranges from 43 to 51 per cent. Culture of Mycobacterium tuberculosis is much more sensitive than smear microscopy and has been recommended to assist in the diagnosis of TB in HIV patients. But in our study this method was used in vary limited number of patients, which were clinically strongly suggestive of pulmonary TB but negative by ZN staining even after concentration of sputum samples.

### CD4+ cell count

The CD4+ cell count of HIV seropositive persons were estimated within one week of sample collection using FACSCalibur flow cytometer (Becton Dickinson, California, USA). The results of CD4 count was reported as absolute count of CD4 cells/$mm^3$ of blood from the FACSCalibur CD4 counting machine.

## RESULT

**Table: Distribution of TB Patients of T Group to various CD4 Ranges.**

| No | CD4 Ranges | Number of HIV patients in the different CD4 Range | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | TB | PTB | Ext PTB | PTB + ExtPTB | Total Patients | % of TB | % Total |
| 1 | 0-99 | 56 | 85 | 39 | 124 | 180 | **40.25** | 12.90 |
| 2 | 100-199 | 96 | 76 | 22 | 98 | 194 | **31.81** | 10.20 |
| 3 | 200-299 | 131 | 23 | 2 | 25 | 156 | **08.12** | 02.60 |
| 4 | 300-399 | 157 | 19 | 1 | 20 | 177 | **06.49** | 02.08 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 | 400-499 | 66 | 15 | 0 | 15 | 81 | **04.87** | 01.56 |
| 6 | 500-599 | 28 | 11 | 0 | 11 | 39 | **03.57** | 01.14 |
| 7 | 600-699 | 30 | 07 | 0 | 07 | 37 | **02.27** | 00.73 |
| 8 | 700-799 | 13 | 2 | 0 | 2 | 15 | **0.65** | 00.21 |
| 9 | 800-899 | 34 | 1 | 0 | 1 | 35 | **0.32** | 00.10 |
| 10 | 900-999 | 05 | 1 | 0 | 1 | 06 | **0.32** | 00.10 |
| 11 | 1000-1099 | 13 | 1 | 0 | 1 | 14 | **0.32** | 00.10 |
| 12 | 1100-1199 | 03 | 1 | 0 | 1 | 04 | **0.32** | 00.10 |
| 13 | 1200-1299 | 11 | 1 | 0 | 1 | 12 | **0.32** | 00.10 |
| 14 | 1300-1399 | 10 | 1 | 0 | 1 | 11 | **0.32** | 00.10 |
| 15 | **Total** | **653** | **244** | **64** | **208** | **961** | **100** | **32.05** |

## DISCUSSION

TB remains one of the leading causes of death from any infectious disease worldwide (Kochi et al,2001). So severe is the problem that this is the only infectious disease to be declared a "global health emergency" by the World Health Organization (Swaminathan S,2000). Lymphocytes play a central role in human defenses against *Mycobacterium* TB. Of the various subsets of lymphocytes, the importance of $CD4^+$ T cells is clearly brought out in HIV infection, where their depletion renders the patient exquisitely sensitive to TB. $CD8^+$ T cells also play a part in protective immunity against mycobacteria and are seen to accumulate at the site of mycobacterial infections, forming a cuff at the periphery of epithelioid cell granulomas. Despite the pivotal importance of CD4 and CD8 lymphocytes in mycobacterial immunity, very few researchers have studied changes in peripheral blood counts of these cells in the setting of TB and even then with different results.

| **No** | **Author** | **Year** | **Place** | **Mean Cd4 Pul TB** | | **Mean Ex=Pul TB** |
|---|---|---|---|---|---|---|
| | | | | **AFB +ve** | **AFB –ve** | |
| 1 | Neethi Chandra et al | 2017 | Tirupati, AP | 205.6 | | 237.6 |
| 2 | Siddeswari R et al | 2016 | Hyderabad, Telangana | 183 | 175 | 168 |
| 3 | Ajay & Rajeev Raina | 2011 | Shimala | 102 | 175 | 108 |
| 4 | Ackah AN, Coulibaly | 1995 | Abidjan Cote d'Ivoire | 257 | | 198 |
| 5 | Vajpayee M, Kanswal S | 2003 | New Delhi North India | 189 | | |
| 6 | Satyanarayan T.et al | 2018 | Shimoga, Karnataka | 223 | | |
| 7 | Kavya S, Anuradha K | 2014 | Mysore, Karnataka | 184.3 | | 188 |
| 8 | Sarvepalli AK | 2017 | Nellor, AP | 74.5 | | 67.5 |
| | Rajeev Shah | 2013 | Surat, Gujarat | 198.5 | | 104.9 |
| 9 | Average Mean CD4 | 2011-2018 | India | 169.75 | | 145.3 |

Although HIV is the initial causative agent for AIDS, most of the morbidity and mortality seen in immunocompromised patients results from OIs that take advantage of the lowered cellular and humoral defense of the patient. Above table indicate that mean CD4 counts in TB/HIV co-infected patients for extra pulmonary TB were mostly always less than pulmonary TB. But Neethi Chandra et al, (2017) at Tirupati in Andhra Pradesh reported quite opposite scenario, they reported mean CD4 of extra-pulmonary was higher than pulmonary TB, which might be due to geographic and temporal variation.

**Table: Correlation of selected clinical and laboratory variables with the CD4 cell count in 85 HIV-negative patients with tuberculosis. (Brenda et al, 1997).**

| **No** | **Variable** | **Mean (+ SD)** | **P value** |
|---|---|---|---|
| 1 | Extent of pulmonary disease | | |
| | Mild (n=19) | 746 ± 274 | |
| | Moderate (n=22) | 675 + 311 | 0.01 |
| | Advanced (n= 26) | 485 + 321 | |
| 2 | Cavitation | | |
| | Present (n= 20) | 504+283 | 0.07 |
| | Absent (n=64) | 655+324 | |
| 3 | Acid Fast Smear | | |
| | Positive(n=72) | 599 + 320 | 0.21 |
| | Negative (n=13) | 719 + 297 | |
| 4 | Extrapulmonary disease | | |
| | Present (n= 21) | 517+ 271 | |
| | Absent (n=64) | 650 + 327 | |

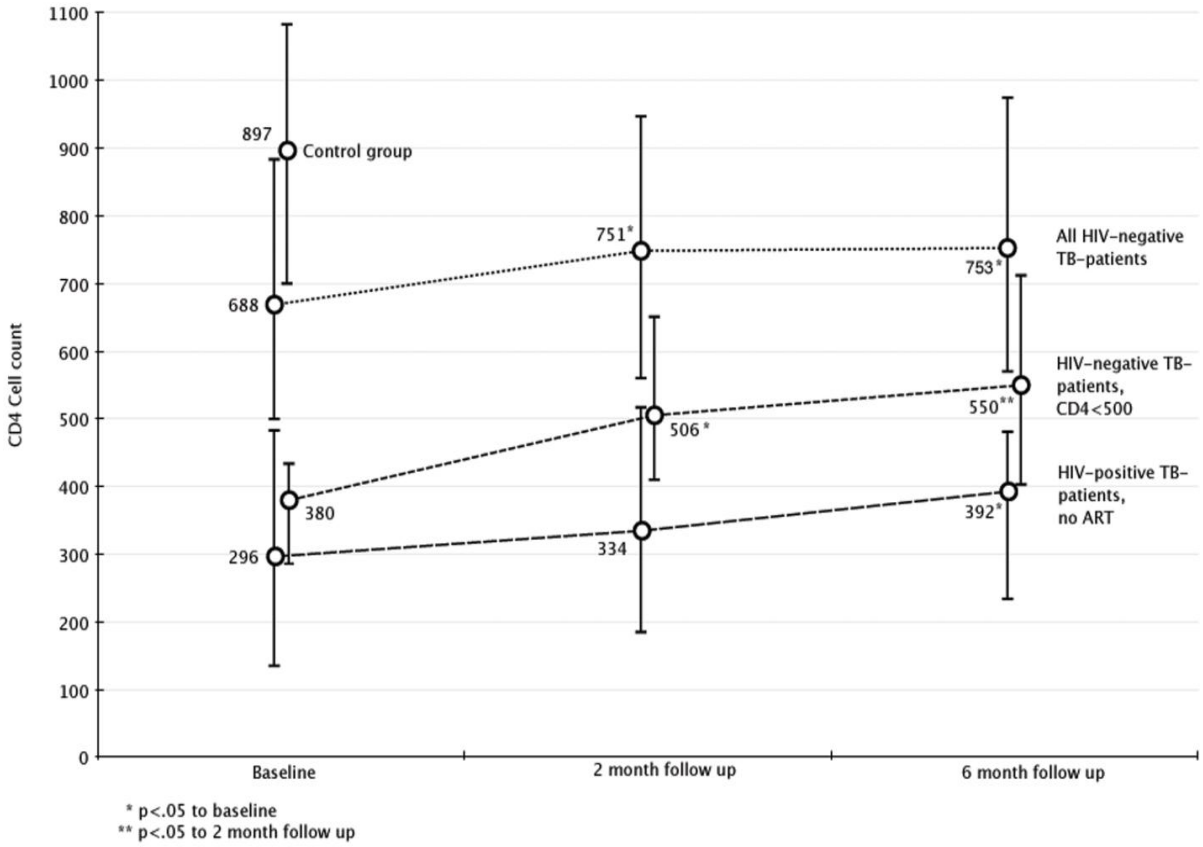
The result of Brenda et al (1997) demonstrated that the Cd4 cell count is depressed in approximately one-half of hospitalized HIV-negative patients with TB and can be as low as that found in HIV –positive patients. However, the CD4:CD8 remains normal in 90% of patients with tuberculosis but it is generally abnormal in HIV- positive patients. In HIV-positive TB patients, there is a strong correlation between the CD4 cell count and the clinical manifestation of TB, as low count are associated with an increased frequency of mediastinal adenopathy, extrapulmonary tuberculosis and mycobacteremia (Jones BE, Young SMM et al, 1993). This has been even confirmed by other previous studies demonstrating that CD4 cell count were seen to be depressed in HIV-negative patients with TB. (Onwubalili JK et al, 1987, Beck JS et al,1985, Turett GS et al,1994 and Bose M et al, 1995).

HIV infection causes a rapid decline of immune responses resulting in multiplication of the mycobacterium with in the granuloma leading to reactivation of the infection. It was also theorized that there will be an increased replication of HIV at the sites of mycobacterium infection by multiplying within the activated CD4+ T cells and the macrophages accumulating at the site of granuloma. The death of CD4 +T cells within the granuloma also causes the reactivation of the infection. Thus HIV infected individuals with lower CD4 counts are more susceptible for attaining TB rather than indivuals with higher CD4 counts(Shankar EM, Vignesh R et al, 2014).

Our data suggest that TB in HIV-infected patients influences the redistribution of lymphocytes during the early phase of immune restoration, and the effects of TB on immune restoration are not overt after the treatment of TB. Generally, in HIV-infected patients, $CD4^+$ T cell recovery in response to cART is thought to be biphasic, with an initial rapid increase during the first 3–6 months after cART initiation, due to the redistribution of cells located within the lymph reticular system. This is followed by a slower recovery, thought to be due to the generation of naive $CD4^+$ T cells through cell division or from the thymus. (Smith CJ. Sabin CA. et al 2003, Staszewski S. Miller V. Sabin C, et al.1999, Pakker NG et al.1998). Further study of the effects of TB on the peripheral redistribution of $CD4^+$ T cells and generation of naive $CD4^+$ T cells through cell division or from the thymus after cART initiation is needed.

Evolution of CD4 cell counts in HIV negative and positive patients with TB during treatment for TB.

The figure shows median CD4 levels and the bars represent IQR. Only patients with follow up CD4 are included in this analysis, and for the control group only baseline CD4 was measured. For HIV+ patients, only patients who did not start ART and had follow up CD4 were included (n = 71). Sten Skogmar et al., 2013.



| | Increase after 6 month (n = 87) | | | Decrease after 6 month (n = 8) | | | No change after 6 month (n = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **2 Month** | **6 month** | **Baseline** | **2 Month** | **6 month** | **Baseline** | **2 Month** | **6 month** |
| Age | 29 | | | 36 | | | 24 | | |
| Male gender, n (%) | 54 (62.1) | | | 7 (87.5) | | | 14 (58.3) | | |
| Smear positive TB, n (%) | 39 (44.8) | | | 3 (37.5) | | | 9 (37.5) | | |
| Smear negative TB, n (%) | 15 (17.2) | | | 3 (37.5) | | | 6 (25) | | |
| Lymph node TB, n (%) | 23 (26.4) | | | 0 | | | 6 (25) | | |
| Other location of TB, n (%) | 10 (11.5) | | | 2 (25) | | | 3 (12.5) | | |
| Median BMI kg/height$^2$ | 18.4 | 19.1 | 19.8 | 17.7 | 19.0 | 18.8 | 17.2 | 18.4 | 18.7 |
| Median MUAC (cm) | 21.5 | 22.0 | 23.0 | 21.0 | 21.8 | 22.0 | 20.0 | 22.0 | 22.5 |
| Median CD4 cells/mm$^3$ | 372 | 557 | 605 | 424.5 | 448 | 342.5 | 400 | 435 | 406 |
| Median Percentage | 29.6 | - | 32.4 | 32.0 | - | 37.0 | 33.5 | - | 30.5 |

*Increase or decrease defined as >50 cells/mm$^3$. Only patients who had follow up CD4 cell counts were included in the analysis
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Sten Skogmar et al., 2013

Although HIV is implicated as the causative agent of AIDS, the mortality and morbidity associated is because of opportunistic infections which occur because of lower humoral and cellular immune mechanisms of the patients. Even most of the deaths reported in AIDS cases are because of opportunistic infections.

The role of CD4 cell count in the care of persons with HIV/AIDS has evolved over the last 30 years. It began as and remains the best way to quantify the degree of immunosupression and associated risk of AIDS illness. The root of using CD4 thresholds for ART initiation lie in the early days of the ART era when drug toxicity, affordability and accessibility is of paramount concern.

**Limitations**

Since the Hospitals where this study was conducted does not routinely perform culture for the diagnosis of TB due to cost factor, this study was limited to identify etiology of most of TB cases. Hence majority of the TB cases were screened clinically and by sputum AFB staining technique which may affect the diagnostic accuracy.

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