

## Tuberculosis-HIV Coinfection: The Relationship Between Manifestation Of Tuberculosis And The Degree Of Immunosuppression (CD4 Counts)

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**Abstract:** The incidence of tuberculosis (TB) is currently increasing. HIV induced immuno-suppression modifies the clinical presentation of TB. Our aim is to determine the differences in clinical presentation of HIV-TB co-infection based on their CD4 counts. This retrospective study looked at cases of adult active TB and HIV-1 co-infection treated in Penang Hospital from January 2004 to December 2005. Of the 820 patients treated for active TB, HIV-1 seropositivity rate was 12.6% (103 patients). Majority of HIV-1 co-infected patients presented with prolonged insidious and non-specific symptoms like weight loss, fever and night sweats. The clinical presentation of TB depended on the stage of HIV-1 infection and associated degree of immunodeficiency. Compared to the less immuno-compromised HIV-1 and TB co-infected population (CD4 > 200/mm<sup>3</sup>), patients with CD4 counts ≤ 200 are more likely to have atypical chest radiographs (P = 0.009). During active TB, the Mantoux test was positive in 12 (14.5%) HIV-1 infected patients with a CD4 counts ≤ 200/mm<sup>3</sup> and in 16 (80%) of those with CD4 counts > 200/mm<sup>3</sup> (P = 0.0001). In our series, the AFB smear / AFB culture and type of TB did not show obvious correlation with CD4 counts. Therefore to diagnose TB in severely immuno-compromised HIV patients, we need to have a high index of suspicion.

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*Key Words:* CD4 Counts; HIV-1; HIV-TB Co-infection; Mantoux test; Tuberculosis.

### Introduction

The incidence of tuberculosis (TB) is currently increasing in HIV-1 infected patients in many parts of the world. Though tuberculosis has been present since time immemorial and has always been endemic in certain parts of the world, renewed interest has been generated due to its rising incidence, especially in the developed world. This is probably also due to the fact that tuberculosis is one of the commonest opportunistic infections encountered in patients with HIV-1 infection.

The risk of developing TB after an infectious contact has been estimated to be 5 – 15%/year in HIV-1 infected patients (compared to 5 – 10% during life time of non HIV-1 infected patients).<sup>1</sup> HIV induced immuno-suppression modifies the clinical presentation of TB. In the early stages of immune-suppression, most tuberculous patients with HIV-1 infection present in the same fashion as others with tuberculosis which are not infected with HIV-1. As immune-suppression progresses, however disseminated and extra-pulmonary forms of tuberculosis become more frequent. The treatment of tuberculosis is also becoming increasingly more complex and difficult in HIV-1 infected patients due to the rising incidence of MDR-TB.<sup>9</sup>

The objective of this study is to determine the difference in clinical presentation of tuberculous and HIV-1 co-infected patients based on their CD4 counts, on a local population of Malaysian patients.

### Methodology

The Penang General Hospital is a tertiary center and teaching hospital in the state of Penang, Malaysia. It is a 1090 bedded hospital that serves a population of 47% Chinese, 40% Malay, 10% Indian and others. This retrospective study looked at cases of adult active TB in adult treated in the Respiratory Unit, Penang General Hospital from January 2004 to December 2005. The information was obtained from patients' medical reports, TB booklets, HIV clinic records and in-patient records (if they were admitted before). Demographic characteristics, clinical presentation, method of diagnosis, CD4 counts and HIV-1 status were recorded and analyzed.

Diagnosis of TB is based on clinical impression and relevant investigations including a chest radiograph, sputum examination, tissue/blood culture for Mycobacterium Tuberculosis and biopsy when deemed necessary by the physician. HIV serological testing is performed using ELISA method and confirmed by Western Blot. Absolute CD4 lymphocyte counts are quantified. Severe immuno-suppression is defined as CD4 counts ≤ 200 cell/mm<sup>3</sup>. HIV serological testing is

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done routinely for all newly diagnosed adult TB cases, as required by the Ministry of Health, Malaysia and vice versa.

Included were adult TB patients (>12 years old) diagnosed according to the WHO criteria and the Malaysian practice guideline for the control and management of TB with confirmed positive HIV status. Excluded were patients with other concomitant non-TB active infections such as fungal or protozoal infection.

All analyses were performed using Statistical Package for Social Sciences (SPSS version 13.0) by using Chi-square test with 95% confidence level. Values of  $P \leq 0.05$  were considered to be statistically significant.

## Results

### *Demographic characteristics*

Of a total of 820 patients treated for TB, 103 patients were HIV-1 co-infected (HIV-1 seropositivity rate of 12.6% in new TB cases). There were 13 females and 90 males (57 Chinese, 27 Malays; 14 Indians and 5 foreigners). Majority of patients were of the age 35 – 59 (71, 68.9%). Mean CD4 counts were 63.69 (for those with CD4 counts  $\leq 200$ ) and 295.35 (for those with CD4 counts of  $> 200$ ) respectively. Demographic characteristics of patients are shown in table 1. It is common for patients to be diagnosed HIV-1 positive after developing TB (as shown in our study, 63.1% of patients confirmed their HIV-1 status after TB was diagnosed). Refer table 1.

### *Clinical presentation*

The occurrence of TB does not correlate with CD4 counts, although TB is more commonly seen in severely immuno-compromised patients. In our series, patients usually presented to us late and had low CD4 counts during the time of diagnosis. Only 19.4% of them had CD4 counts  $> 200$  cells/mm<sup>3</sup>. This late presentation makes the treatment of TB more complicated. Refer table 1.

Table 2 summarized the common clinical presentation observed in the study population. Majority of HIV-1 co-infected patients presented with prolonged, insidious and non specific symptoms like weight loss, fever and night sweats.

Compared to the less immuno-compromised HIV-1 and TB co-infected population (CD4  $> 200$ /mm<sup>3</sup>), patients with CD4 counts  $\leq 200$  are more likely to have atypical chest radiographs. Cavitating lesions are less commonly seen ( $P = 0.017$ ); upper lobe involvement is also less ( $P = 0.003$ ). Pleural effusions are found in 7.7% of cases. During active TB infection, the Mantoux test was positive in 12 (14.5%) of the HIV-1 infected patients with a CD4 counts  $\leq 200$ /mm<sup>3</sup> and in 16 (80%) of those with CD4 counts  $> 200$ /mm<sup>3</sup>. In our series, we did not see any statistically significant differences between AFB smear / AFB culture and type of TB. Refer table 3, 4 & 5. We also noted that in those with CD4 counts of  $\leq 200$ , there were 6.0% of patients with drug resistance TB.

## Discussion

Tuberculosis has become of interest due to increased prevalence in many countries. The HIV pandemic has changed TB, from an endemic disease to a worldwide epidemic. The risk of developing TB after an infectious contact has been estimated to be 5 – 15%/year in HIV-1 infected patients compared to 5 – 10% during the lifetime of non HIV-1 infected patients.<sup>1</sup> Our HIV-1 seropositivity rate for newly diagnosed TB cases is 12.6%, almost similar to our neighbouring country, Thailand (15.8% in 1998).<sup>2</sup>

The clinical presentation of TB depended on the stage of HIV-1 infection and associated degree of immunodeficiency.<sup>3</sup> In early HIV-1 infection, the features are characteristic for post primary TB and resemble those seen in the pre-HIV era. More advanced immunodeficiency is usually associated with an increased frequency of disease resembling primary pulmonary TB and extra-pulmonary disease.<sup>4-6</sup>

The clinical and radiographic presentation of HIV-1 associated TB may be atypical. Compared to the immuno-competent population, HIV-1 associated TB is more likely to have normal chest radiograph or be smear negative but culture positive.<sup>4,7</sup>

Prolonged insidious symptoms found in majority of patients consisting of weight loss, prolonged low grade fever and nocturnal sweat may delay the diagnosis. The classical picture of pulmonary TB is seen mainly in less immuno-compromised patients (CD4 counts > 200 cells/mm<sup>3</sup>).<sup>6</sup>

Atypical features like lower lobe involvement with diffuse infection are more commonly seen than cavitation. Cavitating lesions are rarely seen in patients with a CD4 counts < 200/mm<sup>3</sup>.<sup>8,10</sup> Radiographic findings observed in our cohort include pulmonary basal involvement, tuberculous pneumonia, hilar or mediastinal lymphadenopathy and military TB. These are seen more frequently in severely immunocompromised HIV-1 infected patients. Similar findings were also noted by other researchers.<sup>8,10,11</sup> Chest radiograph is normal in 8 – 20% despite the presence of smear positive sputum.<sup>8</sup> In our series, we observed that chest radiograph is normal in 2% despite the presence of smear positive sputum.

All varieties of extra-pulmonary TB have been described in HIV-1 infected patients. Isolated extra-pulmonary localizations are described in 53 – 63% of HIV-1 associated TB cases in various studies. It is more frequently seen in severely immuno-compromised HIV-1 patients than in non HIV-1 infected individuals.<sup>4,5</sup> In our series, we could not observe any statistically significant differences between the type of TB and the CD4 counts. It may be due to the small sample size. But if looking at the number of patients with isolated extra-pulmonary TB, (19 patients), 15 of them (78.9%) belonged to the group with CD4 counts ≤ 200. Extra-pulmonary manifestations of TB observed in our cohort include lymphadenitis, bacteraemia, meningitis, military TB and gut TB.

The contribution of skin test / Mantoux test for TB diagnosis depends on the immune status. During active TB, the Mantoux test is positive in 30% of HIV-1 infected patients with a CD4 counts < 200/mm<sup>3</sup> and in 50% of those with CD4 counts > 200/mm<sup>3</sup>.<sup>4</sup> (In our series, it is 14.5% and 80.0% respectively).

The risk of drug resistant TB is higher among HIV-1 infected persons. TB drug resistance is usually related to non adherence to therapy, severe immunodeficiency, concurrent anti-fungal therapy and diarrhea. MDR TB (defined as combined resistance to at least Isoniazid and Rifampicin) is more common in HIV-TB co-infected population.<sup>9</sup> Multi-resistance is a poor outcome predictor.<sup>9</sup>

There are a few limitations to be considered in relation to the findings in our study. The sample size is small and there is limited prospective follow up. Statistical analyses therefore have limited power, and hence our simple models may not be optimally representing the HIV sub-population.

In conclusion, worldwide incidence of TB is increasing, particularly in areas where HIV-1 is prevalent. The CD4 count does not predict the occurrence of TB. Majority of HIV-1 co-infected patients presented with prolonged, insidious and non specific symptoms like weight loss, fever and night sweats. HIV-1 and TB co-infected patients with CD4 counts ≤ 200 are more likely to have atypical chest radiographs. Mantoux test is not helpful to diagnose TB in those with late HIV disease. Therefore to diagnose TB in severely immuno-compromised HIV-1 patients, we need to have high index of suspicion especially in countries with high tuberculosis rate.

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Table 1: Characteristics of HIV-TB co-infected patients in Respiratory Unit, Penang Hospital 2004 – 2005

	N	%
<b>TOTAL HIV-TB CO-INFECTION</b>	103	12.6
<b>SEX</b>		
Male	90	87.4
Female	13	12.6
<b>AGE</b>		
13 – 34 yrs	26	25.2
35 – 59 yrs	71	68.9
> 60 yrs	6	5.9
<b>ETHNIC</b>		
Malay	27	26.2
Chinese	57	55.3
Indian	14	13.6
Others	5	4.9
<b>HIV STATUS</b>		
Known Case	38	36.9
Newly Diagnosed	65	63.1
<b>MODE OF TRANSMISSION</b>		
Sexual	68	66.0
IDU	34	33.0
Blood Transfusion	1	1.0
<b>TYPE OF TB</b>		
PTB	49	47.6
Extra-TB	19	18.4
Combination	35	34.0

	N	%
<b>METHOD OF DIAGNOSIS</b>		
Clinical	17	16.4
AFB Culture	26	25.2
AFB Smear	66	64.1
Tissue HPE	25	24.3
<b>CD4 COUNTS (CELL/MM<sup>3</sup>) AT PRESENTATION</b>		
> 500	2	1.9
201 – 500	18	17.5
≤ 200	83	80.6

IDU = Intravenous Drug User

Table 2: Common clinical presentation observed in HIV-TB co-infection

CLINICAL PRESENTATION	DEGREE OF IMMUNODEFICIENCY (CD4 COUNTS – CELL/MM <sup>3</sup> )		
	≤ 200	201 – 500	> 500
Weight Loss	81	17	2
Prolonged Fever	73	18	1
Night Sweat	78	10	2
Cough	60	12	1
Lymph Node Enlargement	33	2	0
Dyspnoea	27	3	1
Hemoptysis	13	1	0
Meningism	3	0	0
Diarrhoea	3	1	0
Others	6	3	1

Table 3: Type of TB observed in HIV-TB co-infection as a function of immune status

TYPE OF TB	CD4 COUNTS > 200	CD4 COUNTS ≤ 200	P VALUE
Pulmonary TB	12 (24.5%)	37 (75.5%)	0.842
Extrapulmonary TB	4 (21.1%)	15 (78.9%)	0.215
Pulmonary + Extrapulmonary TB	4 (11.4%)	31 (88.6%)	0.141

Table 4: Chest radiographic finding observed in HIV-TB co-infection as a function of immune status

CHEST RADIOGRAPH	CD4 COUNTS > 200	CD4 COUNTS ≤ 200	P VALUE
<b>NORMAL</b>	0 (0 %)	2 (2.4%)	0.483
<b>Abnormal</b>	17 (85.0%)	74 (89.2%)	
• Cavitating lesion	3 (15.0%)	8 (9.6%)	0.017
• Site			
• UL	13 (76.5%)	26 (35.1%)	0.003
• ML + LL	4 (23.5%)	48 (64.9%)	0.009

UL = Upper Lobe; ML = Middle Lobe; LL = Lower Lobe

Table 5: Bacteriological results observed in HIV-TB co-infection as a function of immune status

	CD4 COUNTS > 200	CD4 COUNTS ≤ 200	P VALUE
<b>Mantoux Test</b>			
• Positive (>10 mm)	16 (80.0%)	12 (14.5%)	0.0001
• Negative (<10 mm)	4 (20.0%)	71 (85.5%)	
<b>AFB Smear</b>	15 (75.0%)	51 (61.4%)	0.257
<b>AFB Culture</b>	3 (15.0%)	21 (25.3%)	0.240
• Sensitive	3 (15.0%)	16 (19.3%)	
• Drug resistance	0 (0.0%)	5 (6.0%)	
• MDR	0 (0.0%)	0 (0.0%)	

AFB = Acid Fast Bacilli; MDR = Multi Drug Resistant