



## **Pulmonary Tuberculosis in Patients with HIV/AIDS in Iran**

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### **Abstract**

**Background:** Pulmonary tuberculosis is still the most common form of tuberculosis in HIV infected patients having different presentations according to the degree of immunosuppression. This study appraised the impact of HIV infection on clinical, laboratory and radiological presentations of tuberculosis.

**Methods:** The clinical, laboratory and radiological presentations of pulmonary TB in 56 HIV-infected patients were compared with 56 individually sex and age matched HIV-seronegative ones, admitted to Imam Hospital in Tehran (1999-2006) using paired *t*-test in a case control study.

**Results:** All cases and the controls were male. Fever was found in 83.9% of the HIV positive patients compared to 80% of the HIV negative ones. Cough was the most common clinical finding in the HIV negative group (89.3% vs. 82.1% in HIV positive group). Among radiological features, cavitory lesions, upper lobe and bilateral pulmonary involvement were observed significantly less often in the HIV-infected group. On the contrary, lymphadenopathy was just present in the HIV positive group in this series of patients (12%) and primary pattern tuberculosis was more common, as well (71% vs. 39%, *P*= 0.02). The Tuberculin test was reactive in 29% of the HIV/TB patients.

**Conclusion:** The coexistence of both infections alters the picture of tuberculosis in many aspects and should be taken into account when considering a diagnosis of HIV infection and its potential for TB co-infection, and vice-versa.

**Keywords:** *Pulmonary Tuberculosis, HIV, TB and HIV, Iran*

### **Introduction**

“It is estimated that approximately one third of the 40 million people living with Human Immunodeficiency Virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS) worldwide are co infected with TB” (1). The highest global rates of TB/HIV co-infection are reported from sub-Saharan Africa, Asia, and Latin America (More than 95%) (2). HIV infection increases the risk of developing active TB, either by the reactivation of a latent infection or the rapid progression of a newly acquired infection; co-infection can enhance HIV replication, thereby shortening survival and potentially enhancing HIV transmission (3). The risk of the progression of infection into

active tuberculosis is 5-15% per year or 30% during the lifetime period of the HIV positive patients compared to 5-10% lifetime risk in an immunocompetent host (4, 5). Available data shows growing epidemics in several countries such as Iran; the estimated number of people living with HIV in Iran increased from 46000 in 2001 to 86000 in 2007 (6). In other words, tuberculosis, with an annual incidence of 27/100,000 population in 2004 is an endemic disease in Iran. It is also estimated that HIV co-infection comprises 0.8% of all TB cases in our country (7).

However, HIV-positive patients especially those who are severely immunosuppressed are more likely to have atypical and unique clinical and radio-

graphic features (3). Considering the increased number of HIV/TB cases in the developing countries and the potential atypical presentations of this group, special care, and attention should be provided for the timely diagnosis of TB in HIV positive patients.

The purpose of this study was to assess the differences existent between HIV seropositive and seronegative TB patients with regard to clinical and laboratory features and radiographic appearance.

### Materials and Methods

Imam hospital is the main referral teaching hospital for HIV/AIDS patients in Iran. The records of all patients with TB/HIV co-infection admitted to the Infectious Disease Department of the hospital from 1999 through 2006 were evaluated (n=56). In this period, about 550 definite cases of pulmonary TB without HIV infection were admitted to the same department. From the admitted cases, 56 were selected as pair-matched controls. The matching factors were sex and age ( $\pm 3$  yr). Pulmonary tuberculosis was defined in both groups according to the WHO criteria; the definitions include one of the followings: a) two positive sputum smears for acid-fast bacilli, b) one positive sputum smear plus a positive sputum culture for *Mycobacterium tuberculosis*, c) one positive sputum culture plus radiological findings suggestive for tuberculosis (8). The HIV seropositivity was confirmed by at least two positive ELISA tests followed by a positive western blot test as confirmations. In HIV positive patients, tuberculin skin test  $\geq 5$  mm and in HIV negative patients, tuberculin skin test  $\geq 10$  mm were considered as positive. The clinical presentations extracted from the records were the presence of fever, weight loss, sweating, fatigue, chronic cough, sputum and respiratory distress. The laboratory findings including the results of tuberculin skin test, Erythrocyte Sedimentation Rate (ESR), hemoglobin level, leukocyte, lymphocyte and CD4 cell count (if available) were also reviewed. All chest X-rays (CXR) were reviewed by one radiologist for infiltration, cavity formation, miliary pattern, fibrosis,

pleural effusion and hilar and/or mediastinal lymphadenopathy. The primary TB pattern was defined as the presence of one of the following presentations: pleural effusion, lymphadenopathy, lower and middle lobe infiltration and miliary pattern. Likewise, pulmonary fibrosis, cavity and apical involvement were the indicators of secondary patterns.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

### Statistics

The disease presentations were compared between the pair-matches using paired *t*-test and Mantel-Haenszel test for matched-pair strata; the odds ratios (OR) and their 95% confidence interval (CI) were calculated using this method. Unpaired comparisons were made using chi-squared test and the independent sample Student's *t*-test. The statistical analyses were performed using the SPSS software version 16 (SPSS Inc., Chicago, IL).

### Results

In the present study, all cases were male. The mean age of the patients in the HIV/TB group was  $35.1 \pm 9.9$  (range: 16-74) yr compared to  $35.8 \pm 10.2$  in the matched control group.

The most common clinical findings in the HIV+ group were fever and chronic cough (83.9% and 82.1%, respectively), while the most common symptoms in the HIV negative group were chronic cough (89.3%), weight loss (80.4%) and fever (80%). Weight loss and sweating were more frequently reported in the HIV negative group with a statistically significant difference (80% vs. 50%,  $P=0.001$  and 73% vs. 45%,  $P=0.01$ , respectively). Other clinical manifestations did not show any significant differences between the two groups (Table 1). Among all the radiological patterns reviewed in CXR, cavitation, upper lobe and bilateral involvements were found to be significantly more common in the HIV negative patients (34% vs. 9%; 59% vs. 21% and 42% vs. 21%, respectively). In contrast, lymphadenopathy was only revealed in the HIV positive group (12%); also, tuberculosis with the

primary pattern was also reported to be more common in the same group (71% vs. 39%). Although some other features such as normal CXR and pleural effusion were more frequent in the HIV positive patients, the differences were not statistically significant (Table 2).

Moreover, important laboratory findings were studied in the two groups; 29% of the HIV positive patients and 42% of the HIV negative ones had positive tuberculin skin test (OR= 0.56; 95%CI= 0.2-1.3;  $P= 0.23$ ). The mean hemoglobin level (11.6±2.5 g/dl vs. 12.3±2.1;  $P= 0.001$ ) and the mean WBC count (6113±3463/mm<sup>3</sup> vs. 8094±4244;  $P= 0.001$ ) were significantly lower in the HIV positive patients. On the contrary, erythrocyte sedimentation rate (ESR) was higher in HIV/TB

co-infected patients (78±31 mm/h) compared to 63±37 mm/h in the HIV negative ( $P= 0.02$ ). Total lymphocyte count (TLC), used in order to determine the stage of HIV was less than 1200/mm<sup>3</sup> in 46.6% of the cases; this finding indicates symptomatic patients in advanced stages. CD4 count was available for 28 patients with the median (interquartile range) of 181 (74.5–318.0) /mm<sup>3</sup>, among which, 14 (50%) had CD4 count < 200 /mm<sup>3</sup>. As shown in table 3, there was no statistically significant difference in the association between the radiological features and patient category of CD4 count (CD4 count < 200 /mm<sup>3</sup> vs. ≥ 200 /mm<sup>3</sup>) except the bilateral lesions which were more frequent among patients with CD4 count < 200/mm<sup>3</sup>.

**Table 1:** Clinical manifestations tuberculosis with and without HIV co-infection

Clinical Signs	HIV+ n (%)	HIV- n (%)	OR (95%CI)	P-value*
Fever	47 (83.9)	44 (80.0)	1.60 (0.5-4.9)	0.58
Weight loss	28 (50.0)	45 (80.4)	0.19 (0.06-0.5)	0.001
Sweating	25 (44.6)	41 (73.2)	0.38 (0.18-0.80)	0.012
Fatigue	30 (53.6)	38 (67.9)	0.56 (0.26-1.20)	0.18
Chronic cough	46 (82.1)	50 (89.3)	0.56 (0.19-1.66)	0.42
Sputum	40 (71.4)	41 (73.2)	0.90 (0.37-2.21)	1.00
Respiratory Distress	24 (42.9)	25 (47.2)	0.86 (0.40-1.85)	0.84

\* Calculated by Mantel Haenszel test for matched – pair strata.

**Table 2:** Radiological manifestations tuberculosis with and without HIV co-infection in our study and other studies

Clinical Signs	HIV+ n (%)	HIV- n (%)	OR (95%CI)	P-value *	Other studies (% in HIV+)	
					Hong <sup>5</sup> Kong (n=47)	Brazil <sup>20</sup> (n=60)
					38	-
Cavitation	5 (8.9)	18 (33.8)	0.19 (0.05-0.64)	0.006	-	-
Pleural Effusion	13 (23.2)	10 (18.2)	1.37 (0.55-3.40)	0.64	11	6
Normal CXR	10 (17.9)	4 (7.1)	2.50 (0.78-7.97)	0.18	8	-
Infiltration	25 (44.6)	30 (56.6)	0.61 (0.29-1.29)	0.26	-	-
Miliary pattern	5 (8.9)	7 (12.7)	0.50 (0.12-2.00)	0.50	15	39
Lymphadenopathy	7 (12.5)	0 (0.0)	-	0.023	-	-
Fibrosis	1 (1.8)	6 (11.1)	0.17 (0.02-1.38)	0.13	-	-
Upper lobe	12 (21.4)	32 (59.3)	0.20 (0.07-0.52)	0.001	36	-
Middle or lower lobe	16 (28.6)	12 (22.6)	1.33 (.56-3.16)	0.66	21	-
Bilateral	12 (21.4)	23 (41.8)	0.45 (0.20-0.99)	0.063	-	-

\* Calculated by Mantel Haenszel test for matched-pair strata.

**Table 3:** Radiological manifestations of patients of tuberculosis/HIV co-infection with CD4 count < 200/mm<sup>3</sup> vs. ≥ 200 /mm

Clinical Signs	CD4 count< 200 /mm <sup>3</sup> n (%)	CD4 count≥ 200 /mm <sup>3</sup> n (%)	P-value
<b>Predominant radiological lesion</b>			
Cavitary lesions	0	3 (21.4)	0.222
Pleural Effusion	3 (21.4)	3 (21.4)	1.0
Normal CXR	2 (14.3)	4 (28.6)	0.648
Infiltration	6 (42.9)	3 (21.4)	0.42
Miliary pattern	4 (28.6)	1 (7.1)	0.326
Mediastinal lymphadenopathy	2 (14.3)	3 (21.4)	1.0
Fibrosis	1 (7.1)	0	1.0
<b>Zone involvement</b>			
Upper lobe	2 (14.3)	3 (21.4)	1.0
Middle or lower lobe	4 (18.0)	1 (7.1)	0.326
Bilateral	5 (35.7)	0	0.04

## Discussion

Based on the global data, it is estimated that one out of three HIV/TB co-infected patients die of tuberculosis (5, 10). However, most of these fatalities are due to the progression of HIV disease in the course of tuberculosis rather than tuberculosis alone (10). That is why tuberculosis should always be a differential diagnosis in the HIV patients with pulmonary symptoms.

All the HIV/TB patients observed in our department during the study were male, which was quite predictable due to the male dominance of HIV infection in our country. This phenomenon could be explained by the fact that drug injection, which is more prevalent among males, is the most common route of HIV infection in our society (7). The mean age of the HIV group was 35 yr, which was compatible with other studies and the age distribution of the HIV patients in our country (5, 7, 11-14).

The clinical presentation of TB in an HIV-infected person may differ from that of persons with relatively normal cellular immunity that develops TB reactivation. In our patients, the clinical picture was different in HIV positive and negative patients, but only night sweating and weight loss were significantly more prevalent in HIV negative patients. On the other hand, chronic cough was the most common symptom (89%) in the

HIV- patients, though 82% of the HIV+ patients had chronic cough. The most common manifestation in the HIV/TB group was fever (89%); considering the wide range of diseases causing fever, the diagnosis of tuberculosis would be problematic due to the confusion with other opportunistic infections and other HIV related diseases. The decreased frequency of cough in the HIV positive patients in comparison to the HIV negatives can be due to the different patterns of pulmonary involvement (less parenchymal and cavitary lesions in the former). In a study in Hong Kong including 60 TB patients, fever, night sweat and diarrhea were the most common symptoms (5). In another study, among 60 HIV/TB co-infected patients and 120 tuberculosis patients without HIV infection in Brazil, fever, weight loss, chronic cough (77.9%, 41.5%, 23.7% each) in the HIV positives and productive cough (84.8%) followed by fever (64.5%) in the HIV negatives were the most predominant symptoms (15).

It seemed that the presentation of tuberculosis depends upon the degree of immune suppression in HIV infected individuals. "Among our HIV seropositive patients, typical radiological features of post-primary tuberculosis, i.e. upper zone infiltration and cavitary lesions were less common, while atypical features such as mid and lower zone infiltrates, exudative lesions and mediastinal lymphadenopathy were more common." (15)

denopathy were more common in seronegative patients" (16). In our patients, except bilateral lesions which were more frequent among patients with CD4 count  $< 200/\text{mm}^3$ , there was no statistically significant difference in the association between the radiological features and patient categories of CD4 count (CD4 count  $< 200/\text{mm}^3$  vs.  $\geq 200/\text{mm}^3$ ). Like the infiltrates, cavitary lesions were more often bilateral and this suggested that more than one lobe was involved in most of the cases. Therefore, a diffused pattern in a chest film in a patient with known pulmonary TB should alert the physician of the possibility of concurrent HIV infection and would probably harden the differential diagnosis with other opportunistic infections.

In a study (17), cavity and upper lobe infiltration were less common in the HIV positives, which is similar to the present study. Pozniak et al. (18) failed to show any characteristic patterns differentiating HIV positive and negative patients, except for the predominance of cavitation in HIV negative patients. This was contrary to a previous report (19) which had indicated that individuals co-infected with TB and HIV were more likely to have cavitary lesions than those with only TB.

Comparing other studies (5, 20), less miliary patterns and more pleural effusion and primary TB were observed among our HIV/TB patients (Table 2). Pleural effusion occurred in 23.2% of the cases in this study and could present on its own or bilaterally. This was more than the 7% reported earlier (21). Lymphadenopathies have been reported by other workers as an unusual mode of presentation of pulmonary TB in adults (22, 23), and in this study lymphadenopathy was found in only seen in the HIV positive group.

In our study, normal CXR was reported in 18% of the HIV/TB group. Long et. al. reported normal CXR in 30% of the HIV infected and 11.5% of the HIV negative patients with tuberculosis (24). The rate of normal CXR ranged between 6% and 11% in other studies (5). It could be concluded that the clinicians should be cautious about the fact that normal chest radiography does not always rule out Tuberculosis; thus, other imaging techniques such as lung computerized tomography

(CT) scan or other laboratory diagnostics may be more helpful.

In the current study, the mean hemoglobin level, leukocyte and lymphocyte were lower in the HIV/TB patients. Another study investigating hematologic changes in 67 TB/HIV+, 39 TB/HIV- and 40 asymptomatic HIV+ patients had comparable results (25). The mean ESR was higher in the HIV+ patients, which can be explained by the presence of anemia in these patients. Therefore, a high ESR in an HIV-positive patient may buttress the assertion that a high ESR raises the index of suspicion for TB; in such cases, a thorough investigation for the possible focus of TB should be pursued. In line with previous studies, tuberculin skin testing was reactive in only one third of the HIV positive patients, which may be attributed to HIV-induced immunosuppression (8, 26). Therefore, such a test, although inexpensive may be of scant relevance in the diagnosis of TB in the late stages of HIV. The ability to respond to tuberculin skin test correlates with the degree of cell-mediated immunity and decreases as the CD4 cell count decreases. The CD4 cutoff below, the TST of which is unreliable, is not well defined, but clinical experience suggests that high false negative rates occur at CD4 cell counts  $< 400$  cells/ $\mu\text{L}$ . Moreover, results obtained from the recent study highlight the fact that clinical and radiological manifestations of tuberculosis depend directly on the immunity status of the patients. The classic form of the disease is mainly seen in those with a competent immunity system or in other words, in those with high CD4 cell count. Those with CD4 count less than 200, mostly show atypical CXR findings. In addition, normal and traditional typical findings of tuberculosis are not sensitive indicators of the disease in this special group of patients.

In conclusion, this study shows that several clinical, laboratory and radiographic features occur in different proportions in patients infected with both HIV and TB compared with TB patients not infected with HIV. These differences are of paramount importance when considering areas of relatively high TB prevalence like developing countries, and should be taken into account when

considering a diagnosis of HIV infection and its potential for TB co-infection, and vice-versa.

### Ethical Considerations

Ethical issues including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc. have been completely observed by the authors.

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