

# LATENT TUBERCULOSIS INFECTION IN INDIVIDUALS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION: Comparison of tuberculin skin test to the anti TB-IgM antibodies

Seyed Mohammad Alavi<sup>1</sup>, Mohammad Nadimi<sup>2</sup>, Shahram Shokri<sup>3</sup>, Gholamabbas Zamani<sup>4</sup>

## ABSTRACT

**Objective:** To determine Latent Tuberculosis Infection (LTBI) prevalence and compare TST results to the anti TB-IgM antibodies (ATIA) for the diagnosis of LTBI in HIV infected individuals.

**Methodology:** Sixty two randomized sampled HIV infected subjects from an addict treatment center in Ahvaz southwest Iran underwent TST, using 5 TU of purified protein derivative, and measuring ATIA. Data were analyzed in SPSS (version 16, USA).

**Results:** Of 62 participants, 34 (54.8%) had positive result for TST, whereas 6 (9.7%) had positive ATIA. Overall concordance between TST and ATIA was 45.2% (Kappa= 0.37, P = 0.32). In subjects with positive test results by either TST or ATIA, only 4.8% had positive test results by both tests. Discordant results were found in 54.8% of subjects. Positive results for both tests in subjects categorized in two groups (above and below 200 CD4-cell/mm<sup>3</sup>) had no significant difference (P>0.05).

**Conclusion:** LTBI prevalence among HIV infected individuals in studied area is higher than other parts of the world. TST is a useful test for LTBI diagnosis and prefer to ATIA. Concordance between TST and ATIA is low.

**KEY WORDS:** Human immunodeficiency virus, Latent tuberculosis infection, IgM anti M.tuberculosis antibody, Tuberculin skin test.

Pak J Med Sci January - March 2010 Vol. 26 No. 1 11-14

## How to cite this article:

Alavi SM, Nadimi M, Shokri S, Zamani GA. Latent tuberculosis infection in individuals with human immunodeficiency virus infection: Comparison of tuberculin skin test to the anti TB-IgM antibodies. Pak J Med Sci 2010;26(1):11-14

1. Dr. Seyed Mohammad Alavi, MD.  
Associated Professor,  
Joundishapour Infectious and Tropical Diseases  
Research Center, No: 52, West 11 Avenue,  
Kianabad, Ahvaz, Iran
2. Dr. Mohammad Nadimi, MD
3. Dr. Shahram Shokri, MD
- 1-3: Infectious Disease Ward, Razi Hospital,  
Joundishapour University of Medical Sciences,  
Ahvaz, Iran.
4. Gholamabbas Zamani, BS  
Health Ministry of Iran

Correspondence

Dr. Seyed Mohammad Alavi  
Email:alavi1329dr@yahoo.com

\* Received for Publication: May 13, 2009

\* Accepted: January 1, 2010

## INTRODUCTION

The impact of HIV epidemic on many parts of the developing world is already severe, but it will undoubtedly become worse as the number of people with AIDS and HIV related illness continues to increase over next decades.<sup>1-3</sup> World Health Organization has reported that tuberculosis (TB) is the most important co-infection in the HIV epidemic, with an estimated 13 million people worldwide currently infected with both HIV and TB.<sup>4-6</sup> Latent TB infection (LTBI) detection in HIV-infected individuals is crucial because of a high rate of progression to

active TB, so diagnosis and treatment of latent TB infection (LTBI) are essential to TB control.<sup>7</sup> LTBI traditionally is diagnosed by tuberculin skin test (TST), which is associated with some limitations. HIV-infected patients have a higher rate of anergy, particularly with advanced immunosuppressant.<sup>8-10</sup>

Recent studies have suggested alternative diagnostic tools for LTBI such as interferon- $\alpha$  release assays (IGRAs), QuantiFERON-TB Gold assay, culture filtrate protein 10 (CFP-10) and antibodies detection against mycobacterium antigens<sup>11,12</sup>. Since, there are limited data describing alternative diagnostic tools for LTBI in HIV-infected individuals in Khuzestan, we decided to compare the performance of anti TB-IgM antibodies (ATIA) test with conventional TST for the diagnosis of LTBI in HIV-infected population.

## METHODOLOGY

A total of sixty two documented HIV infected individuals were included in this comparative study which was conducted in Ahvaz capital city of Khuzestan a province south west Iran from Oct to Dec 2008. Study population was randomly selected from available addicted individuals in prisons and addict treatment centers. After a full physical examination and filling a questionnaire (including characteristics, epidemiological data, past history of TB or and variables related to addiction), blood samples of each participant were tested for antibodies against A60 antigen of MTB.

Inclusion criteria were two Elisa-HIV antibody positive and confirmatory western blot. Exclusion criteria were clinical TB, completed treated TB and receiving anti TB drugs during the study. Ten milliliters blood sample was obtained from each case and reserved in two separate tube (5 cc) one citrated and the other without citrate. Citrated samples tested by flow cytometry for CD4 positive cell counting and uncitrated samples were tested for ATIA using commercial kit (Dia-PRO diagnostic, Italy). According to kit's manufacture specimens with values greater than or equal to 1.15 (OD<sub>450nm</sub>=1.15)

were considered positive. All subjects were tested for tuberculin skin test (TST) with 0.1 ml 5TU purified protein derivative (PPD) (Razi Institute, Tehran, Iran). The tests were read after approximately 48-72 hours. For each person maximum transverse diameter of indurations in mm was measured with a ruler by pen-rolled method and recorded. Reactions of 5 mm or larger (for HIV positive) and >2mm (for AIDS patients) were considered positive.<sup>1,3</sup> Finally data were analyzed in SPSS 15. A chi-square test was used to compare proportions, differences with p value less than 0.05 were considered statistically significant. Concordance between TST and ATIA results was evaluated using agreement and kappa statistics.

## RESULTS

Of the total sixty two studied subjects, 59 (95.2%) were men with the mean age of 30.47  $\pm$  6.06 years and 3 (4.8%) were women with the mean age of 34.3  $\pm$  6.65 years, 34 subjects (54.8%) had positive TST results (Table-I). Of subjects with CD4<sup>+</sup> cell counts of more than 200 cells/mm<sup>3</sup>, 56% (28/50) had positive TST results (Table-II), compared with 50% (6/12) with CD4<sup>+</sup> counts of less than 200 cells/mm<sup>3</sup> (p = 0.7). Distribution of TST in age groups showed a significant difference between positive and negative results in age group of 15-25 year (21% vs. 7.5%, p < 0.05) whereas, no difference was observed in age group 26-35 (22.5% vs. 27.5%, p > 0.05) and in age group >35 year (11.5% vs. 7.5%, p > 0.05).

ATIA testing yielded positive results in 9.6% (6/62) of subjects, negative results in 90.4% (56/

Table-I: The results for two studied tests in HIV infected individuals

	ATIA positive N (percent)	ATIA negative N (percent)	Total
TST positive	3(4.8)	31(50)	34(54.8)
TST negative	3(4.8)	25(40.4)	28(45.2)
Total	6(9.6)	56(90.4)	62(100)

TST; tuberculin skin test, ATIA; anti TB-IgM antibodies, HIV; human immune deficiency virus

Table-II: Tuberculin skin test results according to CD4+ Tlymphocyte count in HIV positive individuals

CD4+ count	TST + N (percent)	TST- N (percent)	Total
More than 200	28(45.1)	22(35.5)	50(80.6)
Lower than 200	6(9.7)	6(9.7)	12(19.4)
Total	34(54.8)	28(45.2)	62(100)

TST; tuberculin skin test, CD4+; CD4 positive T lymphocyte count (cell/mm<sup>3</sup>), HIV; human immune deficiency virus

62) of subjects (Table-I). Of those with a CD4<sup>+</sup> cell count of less than 200 cells/mm<sup>3</sup>, 8.3% (1/12) had ATIA positive results (Table-III), compared with 10% (5/50) in subjects with a CD4<sup>+</sup> cell count of more than 200 cells/mm<sup>3</sup> (p = 0.8). Of these, 25 (40.4%) were concordant in their negative results and 3 (4.8%) were concordant in their positive results, for an overall concordance of 45.2% (kappa = 0.37, p = 0.32). TST+/ATIA “ discordant results were found in 50% (31/62) of subjects and TST”/ATIA+ results in 4.8% (3/62) of subjects.

## DISCUSSION

The present study revealed high prevalence of LTBI in HIV infected individuals in the region of study with the prevalence of 59.7% that is significantly higher than the prevalence in the other parts of the world previously reported. The rate of this prevalence ranged between 16.8% in developed countries and 43% in undeveloped area with the mean of 30%.<sup>13-17</sup> Mohraz et al reported 29% prevalence rate of LTBI in Iranian HIV positive patients.<sup>18</sup> The reason for these differences is unclear. Residency in high TB prevalent area (such as India) may be suggested as a reason for this difference, but the prevalence of 43% in India<sup>13</sup> that is lower than the prevalence in our region make it unreasonable. Intravenous injection drug use (the most common route of HIV spread in Iran) and imprisonment<sup>15,18,19</sup> may be suggested for this disagreement of our finding comparing with other studies.

Table-III: Anti TB-IgM anti bodies results according to CD4+ Tlymphocyte count in HIV positive individuals.

CD4+ count	ATIA+ N (percent)	ATIA- N (percent)	Total
More than 200	5(8.0)	45(72.6)	50(80.6)
Lower than 200	1(1.6)	11(17.8)	12(19.4)
Total	6(9.7)	56(90.3)	62(100)

ATIA; anti TB- IgM anti bodies, CD4+; CD4 positive T lymphocyte count (cell/mm<sup>3</sup>), HIV; human immune deficiency virus

In this study LTBI was not affected by age and sex. This finding is in contrast with literature and other reports.<sup>3,8</sup> We believe that HIV epidemiological pattern in Iran (young and male population) is an acceptable reason for this difference.<sup>18,19</sup>

This study revealed that ATIA failed to diagnose LTBI (with 8.8% sensitivity and 11% specificity), so TST in spite of its limitation is yet a useful tool for LTBI diagnosis in the region. This finding is in consistent with the results of studies performed by Imeran and et al (2008) and Song, et al (2007). They reported that serological tests are not useful diagnostic tools for LTBI.<sup>20,21</sup> Our finding is in contrast with some other reports such as the works of Fugita, et al (2005) and Genarro, et al (2007) that recommended serological tests to diagnose LTBI.<sup>22,23</sup> The reasons for this variation are not definitely clear but may be dependent on some factors such as: sample size, kind of used antigen or measured immunoglobulin (IgM vs. IgG, IgM), difference in epidemiological pattern of HIV/AIDS and TB in the various regions and proportion of IVDU in studied population.

## ACKNOWLEDGMENT

The authors wish to thank the research deputy of Jundishapur Faculty of Medicine for approval (MD Dissertation No. P/D/103) and chief and personnel of Jondishapoor Infectious and Tropical Research Center for supporting this study. We also acknowledge Mr. Taei for his valuable cooperation.

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