FREQUENCY OF POSITIVE PURIFIED PROTEIN DERIVATIVE TEST IN THOSE INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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Background: The objective of this study was to determine the frequency of positive purified protein derivative (PPD) skin test in those infected with human immunodeficiency virus (HIV) and to investigate its association with CD4-positive T cell count, demographic factors, and possible routes of transmission in Iran.

Methods: Fifty-one (36 males and 15 females) patients from an HIV clinic were selected and tested by a 5-tuberculin unit PPD.

Results: The mean ± SD age of patients was 32.2 ± 7.9 years. The probable route of HIV transmission was intravenous drug using in 21 (41%, CI95%: 28 – 54%) and sexual transmission in 17 (33%, CI95%: 20 – 46%) patients. Thirteen (26%, CI95%: 14 – 38%) patients had other risk factors. There were 13 (25%; 10 males and 3 females) PPD-positive patients among HIV-infected patients when a cut-off value of 5 mm was used; there were 15 (29%; 11 males and 4 females) when a cut-off point of 2 mm was employed. In addition, there was no significant correlation between the PPD test using both cut-off values of 5 and 2 mm, and none of the three probable routes of HIV transmission including intravenous drug using, sexual, and others. The mean ± SD CD4+ T cell count was 674 ± 487/mm³ in men and 573 ± 327/mm³ in women (P > 0.05). No significant correlation could be demonstrated between the patient’s PPD positivity rate and CD4+ T cell count.

Conclusion: Considering the high rate of tuberculin reactivity, more attention should be paid to the importance of PPD test and isoniazid preventive therapy against tuberculosis in HIV-infected patients.

Tuberculin skin test is the only readily available test to detect previous infection with Mycobacterium tuberculosis. It is widely used in epidemiologic surveys, clinical evaluation of patients with suspected tuberculosis (TB), and assessing indications for isoniazid therapy. The degree of sensitization is clearly affected by multiple factors. Infection with the human immunodeficiency virus (HIV) type-1 results in a decreased cell-mediated immunity, which includes a decreased and delayed hypersensitivity reaction to various skin tests, e.g., purified protein derivative (PPD). The immunosuppression that develops with progressive HIV infection has been associated with anergy. Because of this association in HIV-infected individuals, the usefulness of the Mantoux test has been questioned.

There was a significant association between results of the tuberculin skin test and CD4 T-lymphocyte count in HIV-infected patients. It

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means that destruction of the immune system with HIV results in a lower response to PPD. On the other hand, TB is endemic in our country and vaccination with Bacillus Calmette-Gurine (BCG) is routinely given to all newborns in Iran. Therefore, age is a factor which could interfere with the size of induration in PPD test. PPD-positive HIV-infected patients are recommended to have isoniazid preventive therapy (IPT) against TB. In a recent study of HIV-infected patients, the prevalence of tuberculin reactivity varied directly and that of anergy indirectly with the absolute CD4\(^+\) T cell count. At present, limited information is available on delayed-type hypersensitivity (DTH) skin test responses in HIV-infected patients in Iran. Considering the above points and regarding the importance of this issue, this study was conducted to investigate the existing problem, the frequency of PPD positivity and its correlation with demographic factors, and CD4\(^+\) T cell count.

**Patients and Methods**

The data obtained from a database on 150 HIV-positive patients between 1992 and 2004. We selected records of 150 HIV-positive patients in a private infectious diseases clinic. They all underwent the PPD test (Pasteur Institute of Iran) as well as the 5TU test, by intradermal injection of 0.1 mL of PPD on the volar aspect of the forearm. Induration was read 48 – 72 hr later. All the necessary details of patients including the age, sex, intravenous drug use (IVDU), and other probable routes of transmission, as well as the laboratory tests including the CD4\(^+\) T cell count were retrieved from their records. Fifty-one patients fulfilled the inclusion criteria and enrolled into this study. The retrieved data from these 51 patients were statistically analyzed, using the SPSS version 10. Comparison between groups was made using the \(\chi^2\) test, analysis of variance (ANOVA), Student’s \(t\)-test, and Pearson correlation coefficient.

The PPD positivity was defined as an induration >5 mm, set by the Scientific Committee of the Center for Disease Control (CDC) of Iran for starting IPT in HIV-infected patients, considering the high endemicity of TB in Iran and routine BCG vaccination in all newborns. In some countries, however, the cut-off level of 2 mm is considered positive. We used both of these cut-off values and evaluated the effect of this difference on the frequency of PPD positivity and the number of patients needing IPT.

**Results**

We recruited 51 (15 women and 36 men) HIV-infected patients. The mean ± SD age of our patients was 32.2 ± 7.9 (range: 14 – 57) years. The probable route of HIV transmission was intravenous drug using in 21 (41%, CI\(_{95%}\): 28 – 54%) and sexual transmission in 17 (33%, CI\(_{95%}\): 20 – 46%) patients. Thirteen (26%, CI\(_{95%}\): 14 – 38%) patients had other risk factors, including dialysis and blood transfusion in one case, needlestick in another case, tattooing while in prison in one, use of shared blades in prison in another one, history of blood transfusion in Thailand in one case, blood transfusion in two patients, surgery in two, and hemophilia in three patients.

The mean ± SD CD4\(^+\) T cell count was 645 ± 445 (range: 122 – 2877) cell/mm\(^3\). PPD test became positive in 13 (25%, 10 males and 3 females) and in 15 (29%, 11 males and 4 females) HIV-infected patients when a cut-off point of 5 and 2 mm were used, respectively (Table 1).

There was an inverse correlation between the age and CD4\(^+\) T cell count (\(r = -0.2\)); that between age and tuberculin induration was direct (\(r = 0.05\)). No significant correlation was observed between the PPD test positivity employing either the cut-off values of 5 or 2 mm and none of the three probable routes of HIV transmission (i.e., IVDU, sexual, and others) (Table 2).

The mean ± SD CD4\(^+\) T cell count in those patients who possibly had been infected by IVDU, by sexual route, and by other routes was 558 ± 376, 564 ± 314, and 559 ± 376/mm\(^3\), respectively; there was no statistically significant differences between the groups. The mean ± SD CD4\(^+\) T cell count was 674 ± 487 in men and 573 ± 327 in women (\(P > 0.05\)).

**Table 1.** Distribution of HIV-positive patients, based on the CD4\(^+\) T-lymphocyte count and the tuberculin test response.

<table>
<thead>
<tr>
<th>PPD cut-off/Results</th>
<th>2 mm</th>
<th>5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative CD4 &lt; 500</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Positive CD4 &lt; 500</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Negative CD4 ≥ 500</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Positive CD4 ≥ 500</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Negative CD4 ≥ 500</td>
<td>13</td>
<td>38</td>
</tr>
</tbody>
</table>
We found that using a cut-off value of 2 mm, 29% of HIV-infected patients were PPD positive. Significant correlation was not observed between the PPD size and none of the CD4+ T cell count, age, sex, IVDU, sexual transmission, and other routes of HIV transmission.

In a study performed by Portu et al on IVDUs in Spain, PPD was positive in 35% of HIV-infected patients and in 65% of those who were HIV-negative. In the HIV-infected group, there was a significant correlation between the results of tuberculin test and the CD4+ T cell count; when CD4+ T-lymphocyte count was 500 cells/mm³, the rate of positive PPD test was similar in both HIV-positive and HIV-negative patients (47% vs. 65%). However, when the CD4+ T cell count was <500 cells/mm³, a positive PPD test occurred in only 21% of HIV-positive patients. PPD test, then showed a low sensitivity for detecting TB infection in HIV-infected IVDUs, with a CD4+ T cell count <500 cells/mm³.3

In fact, these results are not similar to our study and we did not demonstrate any correlation between the PPD size and the CD4+ T cell count. Similarly, in a study on HIV-infected patients in Hong Kong, 47 patients were administered the PPD test (5 TU). Seventeen percent of patients were positive, employing a cut-off value of 5 mm. No significant correlation could be demonstrated between the patient’s CD4+ T cell count and the PPD positivity.4

In a population-based study in Africa, the prevalence of PPD positivity was 22 – 25%.3 In this study, a cut-off value of 5 mm was used. The frequency of PPD positivity in Africa is consistent with our study.

In a study carried out by Mandalakas et al on HIV-infected Ugandan children, results showed a lack of reaction to PPD test, which was associated with lower CD4+ T-lymphocyte counts and progression of the HIV disease.1

In Markowitz et al’s study on 1,171 HIV-positive patients and 182 HIV-seronegatives, the prevalence of tuberculin reactivity was higher among the IVDUs than the homosexual men in both the HIV-seronegative (19.1% vs. 6.8%, \( P = 0.03 \)) and HIV-positive individuals (15.1% vs. 2.5%, \( P < 0.001 \)). Among the HIV-infected patients, the prevalence of tuberculin reactivity varied directly and that of anergy inversely with the CD4+ T cell count; the prevalence rates were 1%, and 72%, respectively, in patients with <200 CD4+ T cells/mm³ and 8.4% and 25.5%, respectively, in those with CD4+ T cell count of 600 cells/mm³ (\( P < 0.001 \) for both comparisons). The strongest predictors of tuberculin reactivity were IVDU, black race, and a previously-positive PPD test. The strongest predictor of anergy was the HIV-seropositivity.6

In Garcia-Garcia et al’s study on 801 HIV-positive clients in Mexico, reactivity to PPD among HIV-positive subjects was seen in 174 (22%), 261 (32.6%), and 269 (37.1%) of patients, using PPD cut-off values of >10, >5, and >2 mm, respectively. Variables associated with PPD reactivity were CD4+ T cell count, BCG scar, and age.7

Graham et al reported anergy to be higher in HIV-positive group and found to increase as the CD4+ T cell count fell. An inverse correlation between PPD positivity and CD4 count was also observed.8

In our study, similar to what found in the Hong Kong survey, we found no significant correlation between the PPD size and none of the CD4+ T cell count, IVDU, sexual transmission, and other routes of transmission.

Our findings are in contrast with the studies conducted in Mexico and Spain. This difference could be related to a small population used in our study (52 vs. 810 in Mexico). Further studies on larger samples are necessary to detect the reason for this difference. In this study, using PPD, we determined the frequency of latent TB in HIV-infected population. We also showed the importance of this test for detecting latent TB, as well as the number of subjects requiring IPT.

### Table 2. Distribution of HIV-infected patients, based on the probable route of HIV transmission and their tuberculin test situation.

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<tbody>
<tr>
<td>Source</td>
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<td>Negative</td>
</tr>
<tr>
<td>IVDU</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Sexual</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>9</td>
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### Discussion

We found that using a cut-off value of 2 mm, 29% of HIV-infected patients were PPD positive. Significant correlation was not observed between the PPD size and none of the CD4+ T cell count, age, sex, IVDU, sexual transmission, and other routes of HIV transmission.

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### References

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