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Incidence of Active Tuberculosis Among Human Immunodeficiency Virus (HIV)-Positive Patients and Evaluation of Their Responses to Usual Anti-Tuberculosis Medications in Shiraz, South West of Iran

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Abstract

Background: Human Immunodeficiency Virus (HIV) makes infected cases prone to opportunistic infections like Tuberculosis (TB) due to impaired immunity of the body, especially Multi Drug Resistant (MDR) ones which are a major concern. With HIV outbreak starting late in the 20th century, the international health community is observing a huge rise in the incidence of this complex disease. Herein, we estimated the incidence of TB among HIV-positive individuals and their responses to anti-tuberculosis medications in Shiraz, Southwest of Iran. **Materials and Methods:** 840 HIV-positive patients were included in this cross-sectional study. During the first examination CD4+ count and PPD test was obtained, patients were checked for other symptoms too. Patients, if diagnosed with TB, received proper medication. If therapy failed, second-line therapy was prescribed for them. Type of resistance was studied and recorded. Patients continued their routine anti-viral therapy during the study.**Results:** Of 840 participants, 29 were diagnosed with Active TB (3.4%), 76% of them were diagnosed with PCR and culture and other with acid fast. Males were the majority of TB positives (82.8%). Most patients suffering from TB had CD4+ count lower than 200 (55.1%); 17.2% of the cases were MDR-TB. **Conclusion:** Low CD4+ count makes the patient vulnerable to TB. It is necessary to maintain patient's immunity in order to treat and prevent tuberculosis; so, anti-viral therapies still play important roles in preventing TB in HIV-positive patients.**[GMJ.2015;4(2):115-20]**

Keywords: Tuberculosis; Drug resistance; Human Immunodeficiency Virus (HIV); Incidence; Iran

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is an infection caused by Human Immunodeficiency Virus (HIV) which affects the normal function of immune system [1]. HIV is a retro virus infecting some of the main cells of immune system including those having CD4+ markers and also antigen presenting cells like macrophages and dendritic cells. As a consequence of infection, the number of CD4+ cells falls to a dangerous pathological level [2]. Lack of CD4+ cells will make the patient prone to opportunistic

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infections which are one of the main causes of mortality among HIV-infected patients [3]. HIV can be found in most of the body fluids. Unprotected sexual contact, exposure to infected body fluids and vertical transmission are the three main transmission routes around the world [4].

Tuberculosis (TB) is the most prevalent bacterial infection among HIV patients. The numbers published by WHO is quite shocking [5]; approximately one third of the world population is thought to be infected with TB [6]. TB (in the past also called Phthisis or Phthisis pulmonalis) is caused by different strains of mycobacteria genus and mostly by Mycobacterium tuberculosis. It is usually transmitted by inhaling airborne particles [7]. Once, it was believed that TB was disappearing eventually due to worldwide vaccination programs and vast improvements in public health. But, by the emersion of HIV, a huge increase in TB infection was observed and yet it is very common in communities with high HIV prevalence. Most infections do not have any significant symptoms (Latent Tuberculosis) which can eventually turn into active TB and can be a killer if left untreated [8]. Due to immune deficiency, HIV patients can easily get infected by contacting bacteria which makes the disease complex [9].

There are four drugs known as the first-line therapy for TB, if it failed, there would be second line medications. Considering high prevalence of TB in HIV patients, it is important to compare the effectiveness of the regimens between HIV+ and HIV- patients.

Multiple Drug Resistant Tuberculosis (MDR-TB) is caused by a bacteria that is resistant to at least Isoniazid (INH) and Rifampin (RMP), two of the main first-line anti-tuberculosis drugs [10]. The occurrence rate of MDR is consequently rising globally [11]. One of the main concerns regarding TB is the incidence of a disease which is resistant to most of the second- line treatment drugs called XDR-TB [12, 13] also found in Iran [14].

MDR-TB is quite prevalent in Iran and is thought as an endemic potential in a mega-city like Tehran, the capital of Iran [15]. While HIV rates are rising all over the country, this study was designed to evaluate the incidence of TB among HIV patients in Shiraz, another major city in Iran. The prevalence of MDR and XDR was also checked here. We found small literature on this issue in Iran, so it was necessary to perform this study in order to help specialists in diagnosis and treatment of these patients.

Materials and Methods

It was a cross-sectional study conducted under the observation of Shiraz University of Medical Sciences from December 2012 to December 2013. More than two thousand individuals infected by HIV and confirmed by ELISA and Western Blot tests, were selected in this study. All patients were HIV positive. They were regularly followed up by Shiraz HIV/AIDS Research Center (it is a referral center for all cities of Fars province, south west of Iran). All HIV-positive individuals are registered in this clinic, followed clinically and para-clinically and treated if needed. PPD Skin test (0.1 ml of purified protein derivative solution; PPD) and Chest X-Ray are done for all of them as screening methods of tuberculosis (Reaction >5 mm was considered as PPD positive). CD4 T-cell count was measured and recorded in their charts. Consent form was completed for all participants. All demographic data, asking about their age, sex, and job and how they got infected, physical findings and probable rout of transmission were recorded in a questionnaire by our consultant. Sample size in the study is 840 HIV-positive persons that were selected using randomized sampling technique from patients' record. All 840 persons remained in the study were followed for one year. During this year if the physician detected any tuberculosis signs (severe coughing, fever, sputum, hemoptysis, headache, dyspnea, significant lymph nodes, etc.), other tests were performed to see if the patient is really un-infected or infected. PCR, Sputum Acid-Fast stain, Mycobacterial culture were done for all participants with respiratory symptoms (cough, fever, sputum, hemoptysis, sweating, anorexia, etc.), and PCR, tissue sampling, Mycobacterial culture and Acid-Fast staining were used for the documentation of extra-pulmonary tuberculosis

in symptomatic patients. First-line treatment was started for TB- positive patients. First-line HRZE regimen consisted of Rifampin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E). Treatment success rate was evaluated by monthly sputum test and if the acid fast coloring after five months or bacterial culture after three months were still positive, it was considered as a treatment failure. If treatment failure had occurred, an antibiogram test was performed on the sample to see if the bacteria are resistant to any of the drugs in the study and to detect MDR-TB patients. After antibiogram test, appropriate second-line treatment was started for those patients. Every detail was recorded closely. Everyone in the study received free health care services and laboratory tests. In monthly check-ups, if patient was confirmed to be TB positive, proper first-line medications were prescribed and the outcome was closely observed. At the end of this study, every case was checked again to evaluate the final outcome of treatments.

Data was sent to a biostatistician for further analysis. SPSS analytical software version 15.0 was used for the analysis. Data were described and Chi-Square test and T-test were used for comparison. $P<0.05$ was defined as statistically significant.

The study protocol was approved by the medical ethics committee of Shiraz University of Medical Sciences and an informed consent form was filled by each participant.

Table 1. Primary PPD Results and CD4+ T-Cell Count in Both Pulmonary and Extra-Pulmonary Patients

TB Type			PPD results		
			Positive	Negative	Total
Pulmonary	CD4+ count	>400	2	1	3
		300-400	1	2	3
		200-300	2	3	5
		50-200	2	6	8
		50>	3	1	4
		Total	10	13	23
Other	CD4+ count	>400	0	2	2
		50-200	1	0	1
		50>	1	2	3
		Total	2	4	6

Table 2. CD4+ T-Cell Count and Drug Response

TB Type			Treatment type		
			Non Drug Resistant	Drug Resistant	Total
Pulmonary	CD4+ count	>400	3	0	3
		300-400	1	2	3
		200-300	4	1	5
		50-200	6	2	8
		50>	4	0	4
		Total	18	5	23
Other	CD4+ count	>400	1	1	2
		50-200	1	0	1
		50>	1	2	3
		Total	3	3	6

Results

Out of 840 patients, 29 were diagnosed with active TB (3.4% per year), 23 with pulmonary (79.3%) and 6 extra-pulmonary (20.7%) (Table 1).

4 had a positive history of TB. Of these patients with confirmed TB infection, 75.6% were diagnosed with PCR and Culture and the rest (24.4%) were diagnosed with acid-Fast (Table 3). 41.4% of patients (12 patients) were PPD positive and 17 patients (58.6%) were PPD negative at the beginning of the present study. (Table 1). A majority of TB positives were males with 24 cases (82.8%), while only 5 females were diagnosed (17.2%). TB patients aged 25 to 55 years old with the mean age of 37.2±8.3. Regarding the table 1 five patients had CD4+ count more than 400 (17.2 %) at the first visit, 8 had a count between 200 and 400 (27.5%) and the other 16 were under 200 (55.1%). Among these 29 patients, 25 were on anti-viral drugs (86.2 %) and 4 did not have any history of consuming such drugs (13.8%). Twenty one cases were treated with classic HRZE regimen but the other 8 were diagnosed as drug-resistant TB so 27.6% of TB patients were suffering from drug-resistant

TB. The occurrence of drug-resistant TB was significantly related to primary CD4+ count (P>0.05) (Table 2). From 8 patients with drug resistance, 1 was only resistant to Isoniazid, 2 only resistant to Rifampin and 5 to both of them (INH and R) (MDR), from 6 Patients that were resistant to Isoniazid, three of them had a history of consuming Isoniazid in the past. 55.2% of TB patients were exposed to HIV through septic needle, 34.5% was due to unprotected sexual activity and 10.3% was due to other reasons.

Discussion

As declared, TB is an endemic disease among HIV patients. In a major study by Corbett et al., they reviewed published literature regarding the relation between HIV and TB. The occurrence rates were quite huge and they concluded that TB is becoming a global health concern in association with HIV pandemic [5]. HIV can help the transformation of latent TB to its active form [16]. A study in southeast of Iran determined the occurrence rate of TB as 135/10,000 [17]. In comparison to our data, TB occurrence rate is quite higher in HIV patients than the whole community of Iran. Males were the majority of TB positives among our samples that can be due to the higher prevalence of HIV in Iranian males than females [18].

PPD test was used to diagnose latent TB but it was negative in almost half of the participants at first examination. It may indicate inaccuracy of PPD in detecting latent TB. Ewer et al. compared PPD test with a sensitive enzyme-linked immunospot (ELISPOT) method in a TB outbreak in England; 535 students were tested for tuberculosis infection with both TST and ELISPOT. They found that ELISPOT was a better and more accurate method in detecting TB [19].

During a cross-sectional study from January 2004 to December 2006, 459 HIV-positive individuals in Shiraz, southern Iran were enrolled. 28.5% of HIV-positive individuals had a positive PPD skin test, among whom 89.3% showed a latent tuberculosis infection and 10.7% active tuberculosis [20]. In our study, active TB was detected in 3.4% of patients. Interferon-gamma release assay is more specific and more helpful to obtain epidemiological data to determine the appropriateness of isoniazid chemoprophylaxis.

A cross-sectional study used interferon-gamma release assay (T-SPOT.TB-immunospot) to detect tuberculosis infection in 520 patients in a U.K. HIV clinic with a large sub-Saharan population. 542 patient samples were tested. Median CD4 count of them was 458 cells/µl. A positive test was found in 10% (50/502) individuals. A negative test was found in 452 samples and an indeterminate results in 40 (7.4%). Neither was associated with a low CD4 count [21]. In our study, most PPD negative patients has cd4 count lower than 200(52.9%).

In another study in Denmark, QuantiFERON-TB In-Tube test (QFT-IT) was performed for 590 HIV-positive individuals. 27/590(4.6%) of individuals showed positive QFT-IT, indicating the presence of latent TB infection [22].

A cross-sectional study was carried out at an anti-retroviral therapy (ART) clinic of Pravara Rural Hospital, India from June 2011 to May 2012. A total of 1012 HIV-positive patients, receiving ART during the study period, were included in the analysis. The prevalence of pulmonary tuberculosis among HIV-positive patients was 17%. Low CD4 count (< 50/µl) had statistically significant association with HIV/TB co-infection as compared to HIV infection only (P < 0.0001) [23].

HIV will reduce CD4+ count in mean time, so the immune system will slowly go toward a breakage point. Patients with CD4+ count lower than 200 enter AIDS step of HIV infection. According to our results, the majority of TBs occurred in patients suffering from AIDS or having a CD4+ count lower than 200. It is mostly due to low prognosis potential in these patients. Pilheu et al. conducted a study on seventeen HIV-negative patients with severe pulmonary tuberculosis and 10 other TB patients with milder symptoms. The mean CD4+ count for patients with severe condition was 341.25±142.73 while, patients whose conditions were better, had a CD4+ count of 721.40±272.20. They concluded that patients with lower T-cell count were more prone to TB infection and had worse symptoms [24].

In a hospital-based cohort study, 346 HIV-infected patients receiving HAART between 1996 and 2005 in Cape Town were followed for TB disease. TB incidence density rate was 3.5/100 person-years in the first year of anti-retroviral therapy and significantly decreased during follow-up reaching 1.01/100 person-years in the fifth year. TB incidence, during the study, was highest among patients with baseline CD4 cell counts < 100 cells/ml and those with World Health Organization (WHO) clinical stages 3 or 4 disease aged <33 years had highest TB incidence rate. Plasma viral load, previous history of TB, low socioeconomic status and gender were not related risk factors for TB. Blood CD4 cell counts increased slower among TB patients than those who remained free of TB, though virologic response to HAART was similar [25].

In a South African cohort study by Lawn et al., 346 HIV-positive patients were followed from 1996 to 2005. They concluded that using highly active antiretroviral therapy (HAART) will lower the annual incidence of TB among HIV-positive patients. They also noted that TB is mostly prevalent among patients with CD4+ count lower than 100. It was also mentioned that the incidence of TB is not directly related to plasma viral load, positive history of TB or patient's sex [26]. In a study by Farnia et al., 1074 TB-positive patients, Iranian and Afghan residents of Tehran, Iran, were studied. The goal of the study was to evaluate the strains responsible for MDR-TB and to assess the prevalence of MDR-TB among patients with TB infection in Iran. Among 1074 patients in their study, two hundred and sixty three patients (15%) were confirmed to have MDR-TB [15]. In this study, 17.2% of our cases were diagnosed as MDR-TB; it is a small increase in comparison to their data.

Conclusion

Nowadays, MDR-TB is becoming more and more prevalent. It is necessary to set our policies in order to control this issue. The occurrences of MDR-TB and TB in HIV patients are related to CD4+ count which is an already-believed fact, so it is important to keep CD4+ count at a reasonable level in HIV patients. As a result, HAART and other anti-viral therapies may come in handy to prevent TB and its related complications in HIV-positive patients.

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Conflict of Interest

None declared.

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