Active Tuberculosis and Human Immunodeficiency Virus Co-Infection in Israel: A Retrospective Study

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ABSTRACT: **Background:** Tuberculosis is the most common opportunistic infection among people infected with human immunodeficiency virus and its first cause of morbidity and mortality.

Objectives: To analyze the characteristics of a population in Israel with both tuberculosis disease and HIV infection in order to identify factors that contribute to outcome.

Methods: The study group comprised patients hospitalized in the Pulmonary and Tuberculosis Department of Shmuel Harofeh Hospital during the period January 2000 to December 2006. They were located by a computer search of the hospital registry and the pertinent data were collected.

Results: During the study period 1059 cases of active tuberculosis disease were hospitalized; 93 of them were co-infected with HIV. Most of them came from endemic countries (61.2% from Ethiopia and 20.4% from the former Soviet Union; none of them was born in Israel). Ten percent of the cases were multiple-drug resistant and 32% showed extrapulmonary involvement. The response rate to the treatment was good, and the median hospitalization time was 70 days. The mortality rate was 3.2%.

Conclusions: Despite the high prevalence of pulmonary disease in our group, the short-term outcome was good and the Mycobacterium was highly sensitive to first-line drugs. These encouraging results can be attributed to the fact that tuberculosis patients in Israel are identified early and treated continuously and strictly, with early initiation of antiretroviral therapy, which together ensure that the development of drug resistance is low.

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KEY WORDS: human immunodeficiency virus, tuberculosis, Israel, directly observed therapy

About 10 million people are co-infected by human immunodeficiency virus and *Mycobacterium tuberculosis* (11% of them are children), with a rate exceeding 100/100,000 people in Sub-Saharan Africa [1,2]. The interaction between HIV infection and tuberculosis is complex: HIV infection, by decreasing interferon-gamma production, impairs the host's ability to contain infection and increases the risk for the development of active tuberculosis disease. Following the initial exposure, the rate of progression of tuberculosis infection to active disease is higher than 40% in HIV-positive patients compared to approximately 5% in HIV-negative patients [3]. On the other hand, *M. tuberculosis* enhances HIV replication and accelerates the natural progression of HIV infection by increasing cytokine production (in particular tumor necrosis factor-alpha). The risk of death in HIV-infected patients with tuberculosis is twice that in HIV-infected patients without tuberculosis [3-6].

In Israel, the incidence of HIV/AIDS is low, with an estimated number of 4000 patients by the end of 2005. The disease develops predominantly in the immigrant population from Ethiopia (45.4%) [7]. Similar to HIV, tuberculosis comes to Israel mainly from endemic countries such as Ethiopia and the former Soviet Union. The incidence of new cases dropped from 11 cases per 100,000 in 1998 to 7/100,000 in 2006 as a result of directly observed therapy [8] that is administered during the entire period of treatment.

Contagious patients, those with complicated medical problems and those with poor adherence to therapy are hospitalized in the pulmonology department of the Shmuel Harofeh Hospital, the Israeli center for hospitalized tuberculosis patients. The objective of the present study was to evaluate the characteristics and outcome of patients co-infected with active tuberculosis disease and HIV infection

PATIENTS AND METHODS

We conducted a retrospective study of patients hospitalized in the pulmonology department of Shmuel Harofeh hospital from January 2000 to December 2006 with a diagnosis of HIV/AIDS and tuberculosis. Medical charts containing both diagnoses were recorded and the following data were collected: demographic characteristics, medical history, risk factors for HIV infection, immunological status, tuberculosis infection site, laboratory diagnosis, and outcome after the first year. The study population's characteristics were compared to those of the total tuberculosis population in the same period, and after 1 year follow-up the data were obtained from the outpatient tuberculosis clinics.

HIV = human immunodeficiency virus

We included patients with a definitive diagnosis of *M. tuberculosis*: namely, positive culture results (from the sputum, bronchoalveolar lavage, gastric aspirate or other specimen), or pathological changes compatible with tuberculosis (caseating granuloma) and patients with HIV serology positive (by enzyme-linked immunoabsorbent assay and Western blot tests).

RESULTS

Our cohort study included 93 patients, constituting 8.7% of the total number of tuberculosis cases hospitalized in our ward. Tables 1 and 2 show that most of the patients were young (median age 34 years) and most were males (64, 5%). The majority came from endemic countries: 57 patients (61.2%) came from Ethiopia, 19 (20.1%) came from the Former Soviet Union, and the rest were foreign workers, usually from Africa and Asia. No patient was Israeli born.

The pulmonary presentation predominated (86%). The common pulmonary features were ground-glass opacities and lower lobe infiltrates. Only eight patients had cavitary lesions in the upper lobes. Extrapulmonary tuberculosis was detected in 30 patients (32.2%), including 19 (20%) cases with mediastinal or generalized lymphadenopathy, 8 (8.6%) with pleural or abdominal involvement, 2 (2%) with meningitis, and one with bone involvement. In 17 patients (18%) the tuberculosis was found in pulmonary and extrapulmonary sites.

Table 1. Patients' characteristics

	No. (%)
Patients	93 (8.7)
Gender	
Males	60 (64.5)
Females	33 (35.4)
Age (yrs)	
0–25	8 (8.6)
26–45	64 (68.8)
› 45	21 (22.6)
Origin	
Ethiopia	57 (61.2)
Former Soviet Union	19 (20.4)
Other	17 (18,2)
Tuberculosis site	
Pulmonary	80 (86)
Extrapulmonary	30 (32.2)
Both	17 (18.2)
Tuberculosis diagnosis (positive culture for MTB)*	
Sputum	57 (61.2)
Bronchoalveolar lavage	15 (16.1)
Lymphadenectomy	6 (6.4)
Other	15 (16.1)
Susceptibility of MTB	
Partial resistance*	12 (12.9)
MDR-TB	10 (10.7)
Sensitivity (first-line drugs)	71 (76.3)
Outcome	
Death	3 (3.2)
Hospitalization time mean (days)	70 (7–365)
Multiple hospitalizations	11

* Resistance to one of the first-line drugs

MDR-TB = resistance to isoniazid and rifampicin, MTB = *Mycobacterium tuberculosis.*

Table 2. HIV characteristics

	No. of patients
Risk factors	
Immigration country	63
Drug abuse	13
Sexual relations	2
Blood	1
Unknown	14
CD4 (cells/mm3)	
0–50	33
50–200	23
› 200	13
Unknown	20
Diagnosis of HIV infection	
Before hospitalization	56
During hospitalization	37

The sputum smear examination showed the presence of acid-fast bacilli on the Ziels-Nelson stain in 41 patients (44%), and a positive sputum culture for *M. tuberculosis* in 57. Ten patients (10.7%) were multiple drug resistant, and 12 (12.9%) were partially drug resistant (to one of the first-line drugs, usually isoniazid). The median hospitalization time was 70 days (7 days to 1 year).

Multiple hospitalizations due to non-compliance were noted in 11 patients. There were three deaths, one (drug addict) with diffuse pulmonary MDR-TB, and two due to generalized tuberculosis sensitive to the first-line drugs

The mean immunological status was low (CD4 count < 200 cells/mm^3 in 56 patients and < 50 cells/mm^3 in 33 patients). Only 13.9% were intravenous drug addicts. The main risk factor for HIV infection was the country of origin.

In the non-HIV-tuberculosis population, the rate of MDR-TB was high (21%), with typical clinical and radiological presentations and different demographic characteristics (55% were from the Former Soviet Union, 20% from Ethiopia, 11% were born in Israel, and the remainder were foreign workers). The death rate was higher (7%) in the non-HIV population. Factors influencing clinical course and outcome included the presence of alcohol and drug abuse, poor compliance, and drug resistance. Patients who died were drug resistant and had diffuse pulmonary infiltrates.

DISCUSSION

Active tuberculosis disease is an AIDS-defining disease; therefore, all HIV-positive patients with active tuberculo-

MDR-TB = multiple drug-resistant tuberculosis

sis disease meet the criteria for AIDS and should receive antiretroviral therapy independent of the number of CD4 T lymphocytes [9]. Although tuberculosis may appear relatively early in the course of HIV infection, the immune depression induced by HIV modifies the tuberculosis presentation with subnormal clinical and radiological signs and symptoms. Unexplained fever or isolated cough may be the only sign and atypical X-ray features consisting of lower lobe presentation, ground-glass opacities or mediastinal lympadenopathy are found frequently instead of the classical cavitary lesions of the upper lobes. In 20% of cases, the chest X-ray was reported to be normal despite positive sputum cultures [10].

In our study, the patients with HIV infection and tuberculosis were more likely to be immigrants from Ethiopia. This demographic profile has implications for local control strategies since tuberculosis in the Ethiopian immigrant population is characterized by Mycobacterium sensitivity to the first-line drugs, in contrast to the former Soviet Union tuberculosis subpopulation that has a high rate of MDR-TB and has to undergo complex multiple treatment courses.

In our study the rate of presentation of pulmonary tuberculosis was high (86%), while according to the literature, those with HIV infection tend to have increased frequency of a wide spectrum of extrapulmonary involvement [9,10]. We did not find any association between our rate of extrapulmonary tuberculosis cases and the number of CD4 cells, but the radiological examinations of 60% of patients with CD4 < 200 cells/mm^3 were subnormal or normal.

The mortality rate in our study was low (3%) and was related to a markedly depressed immunological status. We initiated antiretroviral therapy during hospitalization, usually 1 month after the start of the tuberculosis therapy. Highly active antiretroviral treatment, known as HAART, is a combination treatment containing at least three antiretroviral drugs, including protease inhibitor and non-nucleoside reverse transcriptase or three nucleoside reverse transcriptase inhibitors [11]. The question of when to administer HAART is controversial. On the one hand, early initiation decreases the mortality rate but is complicated by drug toxicities, drug interactions, and the immune reconstitution inflammatory syndrome. On the other hand, delayed administration leads to HIV progression and opportunistic infections [12-15]. Drug interaction relates to the use of rifampicin, which reduces the therapeutic plasma concentration of the non-nucleoside reverse transcriptase inhibitor and of the protease inhibitor and leads to HIV drug resistance. The common locus interaction occurs within the cytochrome P450 enzyme system and the P glycoprotein. The World Health Organization recommends a regimen that includes efavirenz and rifampicin, based on the results of many trials that demonstrated the efficacy of the standard efavirenz dose in achieving complete viral suppression among patients receiving concomitant rifampicin-based tuberculosis treatment [15]. In cases where protease inhibitor is used, rifampicin must be changed to rifabutin, which has little or no effect on the serum concentration of the protease inhibitor [6,17].

In the first years of the study period, since the normal regimen was a combination of drugs including protease inhibitor and reverse transcriptase inhibitor, rifampicin was replaced by rifabutin. In the last years of the study, we used a new regimen (three non-nucleoside reverse transcriptase inhibitors including efavirenz), which does not require any change in the tuberculosis treatment.

Following the combined therapy, most of the patients suffered gastrointestinal disturbances that were managed with symptomatic treatment. Furthermore, 25% of the patients had immune reconstitution inflammatory syndrome with paradoxical reaction (fever, new lymphadenopathy or pulmonary infiltrates), and 10% of patients had toxic hepatitis. The paradoxical reaction, due to the recovery of the immune system with reconstitution of the antigen-specific T cell-mediated immunity, was managed by a short course of steroids. There was no case of tuberculosis disease as a result of IRIS, but some patients with clinical worsening were difficult to recognize as having IRIS and not as treatment failure. It was always an exclusion diagnosis. The hepatitis resolved after temporary discontinuation of the drugs.

After discharge, we conducted a 1 year follow-up in 62% of the sample (66 patients). Forty-eight patients completed the tuberculosis treatment, 8 patients died, and the remainder did not receive the full treatment because of poor compliance. The 27 patients who were lost to follow-up were mostly foreign workers who left the country or those referred to another national tuberculosis treatment agency.

In conclusion, we have described a specific population of active tuberculosis patients co-infected with HIV. The short-term outcome in this population was good. These promising results are due to the high sensitivity of the Mycobacterium and early initiation of antiretroviral therapy; the expert team that dealt with the complexity of the treatment certainly influenced these results. It is critical that tuberculosis in the setting of HIV infection be diagnosed early, so that patients can be hospitalized to control side effects and improve compliance, and that directly observed therapy be continued for the full treatment period. It is also recommended that an HIV test be routinely administered to all suspected tuberculosis patients since it will modify the management.

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IRIS = immune reconstitution inflammatory syndrome

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