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Treatment outcome and mortality: Their predictors among HIV/TB co-infected patients from Iran

Payam Tabarsi [a,b,*], *Ehsan Chitsaz* [a], *Ahmadreza Moradi* [a], *Parvaneh Baghaei* [a], *Majid Marjani* [a], *Davood Mansouri* [a]

[a] *Clinical TB and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[b] *Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Background: The risk of death is significantly higher in TB/HIV-infected patients than in those patients with just one disease or the other. This study aims to evaluate the impact of demographic, clinical and laboratory characteristics on the treatment outcome and mortality of TB/HIV co-infected patients in a TB tertiary center in Iran.

Materials and methods: The study was conducted at Iran's National Referral Center for Tuberculosis. In total, 111 patients were recruited between 2004 and 2007. Mycobacteriology studies were performed for all patients. Demographic, clinical, and lab data of all patients were analyzed, and predictors of unsuccessful outcomes, as well as mortality, were determined.

Results: The mean age for all 111 TB/HIV patients was 38 ± 9 years (range 22–70) and 107 patients (96.3%) were male; 104 patients (93.7%) had a history of drug abuse, and 96 patients (86.4%) had a history of imprisonment. The route of transmission of HIV was intravenous drug use in 88 of the patients (79.3%); 23 patients (20.7%) had a history of Category 1 (CAT-1) (5.4%) and CAT-2 treatment. Highly Active Antiretroviral Therapy (HAART) was given to 48 patients (43.2%). There was no significant association found between treatment outcome or mortality with sex, smoking, drug and alcohol abuse, imprisonment, route of transmission, history of CAT-1 and CAT-2, cluster of differentiation 4 (CD_4), and adverse effects ($p > 0.05$). Administration of HAART led to a significantly higher rate of good outcome ($p < 0.001$). Lower Albumin levels and body weight were significantly associated with mortality.

Conclusion: Albumin levels and weight can be predictors of mortality and an unsuccessful outcome. Administration of HAART led to a better outcome.

Introduction

Infection by Human Immunodeficiency Virus (HIV) kills more than 8000 people daily, while more than 5000 people die of tuberculosis (TB) every day. It is estimated that one third of the world's population are infected with TB, and this is consequently true for about 40 million people currently diagnosed with HIV/AIDS. In addition, without the proper treatment, 90% of the HIV-positive patients will die within months of contracting TB. Four million people affected with HIV also have TB worldwide making TB the main killer in HIV-infected patients [1]. The risk of death is significantly higher in the

* Corresponding author at: Masih Daneshvari Hospital, Darabad, Niavaran Sq, Tehran 1955841452, Iran. Tel.: +98 21 20109590; fax: +98 21 20105050.
E-mail address: tabarsi@nritld.ac.ir (P. Tabarsi).

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HIV-infected population, even if the mycobacterium is sensitive and responds well to anti-TB medications [2–6].

As well, some mortality risk factors have been proposed among TB/HIV patients [7,8]. However, in this regard, there remain controversies which are mainly owing to different settings in various regions, the major route of acquisition, diverse demographic characteristics among HIV-positive cases and dissimilar epidemiologic patterns of infections of TB and HIV [7–12].

Similar to its global trend [13], the number of HIV-infected patients in Iran is escalating with many of them being co-infected with TB [14,15].

This study aims to evaluate the impact of demographic, clinical and laboratory characteristics on the treatment outcome and mortality of TB/HIV co-infected patients along with identifying risk factors affecting mortality to determine whether or not to continue with the available treatment methods in a TB tertiary center in Iran.

Materials and methods

All National Research Institute of Tuberculosis and Lung Disease (NRITLD) TB/HIV patients were studied who have been hospitalized at Masih Daneshvari Hospital, Tehran-Iran, at the National Referral Center for Tuberculosis between 2004 and 2007. The study comprised a total of 117 patients; 111 of them have completed follow-up procedures. For this purpose, retrospectively, data was extracted from the patients' medical records.

For all patients, TB and HIV confirmation was undertaken. Primarily, sputum samples (smear, culture) were collected, chest X-rays were undertaken, and patients were tested for HIV antibodies; in the case of positive results, Western Blot testing was done. After initial confirmation for TB/HIV, first-line drug-susceptibility tests (DST) were performed for all culture-positive cases. TB treatment was initiated in accordance with standard CAT-1 regimens. Until the year 2005, the Iranian national guidelines for management of TB among HIV-infected patients consisted of the initiation of HAART eight weeks after the start of TB treatment if their CD4+ count was less than 200 cells/ml. In order to prevent adverse drug interactions in HIV-infected patients receiving the HAART treatment, Rifampin was replaced with Rifabutin in their TB treatment. However, in 2005 and thereafter, the protocol was updated by administering HAART concurrently with TB treatment for patients with a CD4+ < 100 cells/ml. The new regimen consisted of Ziduvudin, Lamivudine and Efavirenz, which allowed the administration of Rifampin as well.

Once DST results were acquired, treatment was modified accordingly. It should be noted that all patients received Cotrimoxazole (trimethoprim/sulfamethoxazole) for CD4+ < 200 cells/ml and Azithromycin for CD4+ < 50 cells/ml as prophylaxis against opportunistic infections such as *Pneumocystis carinii pneumonia* (PCP) and *Mycobacterium avium* complex (MAC), respectively.

Monthly checkups were undertaken for follow-up until the completion of the treatment. TB treatment outcomes were measured in accordance with standard definitions.

Statistical analysis

For statistical analysis, SPSS software V.15.1 (Apache Software Foundation, Chicago, Illinois) was used. Continuous variables were expressed as group means ± SD. Categorical data, such as ethnicity, were expressed as group frequency and proportion. Statistics without Yates' correction, Fisher's exact test, Student's *t*-test and the Mann–Whitney U test were used as appropriate. All reported *p*-values are two-sided. A *p*-value of less than 0.05 was considered statistically significant.

The protocol of the study was reviewed and approved by the Scientific and Ethics Committee of the NRITLD.

Results

Totally, the mean age for all 111 TB/HIV patients was 38 ± 9 years (range 22–70), and 107 patients (96.3%) were male. Smokers accounted for 108 (97.3%) of the patients, 104 of the patients (93.7%) had a history of drug abuse, 53 patients (47.7%) were alcohol abusers, and 96 patients (86.4%) had a history of imprisonment. The method of transmission of HIV was heterosexual in 11 patients (9.9%), intravenous drug use in 88 patients (79.3%), homosexual in 1 patient (0.9%), and transfusion in 9 patients (8.1%). Pulmonary TB cases accounted for 79 (71.2%) patients, while 8 patients (7.2%) had extra-pulmonary TB, and simultaneous pulmonary and extra-pulmonary TB was present in 24 (21.6%) patients; 23 patients (20.7%) had a history of CAT-1 treatment and 6 patients (5.4%) had received CAT-2 treatment. HAART was given to 48 (43.2%) patients.

Outcomes were classified into two categories: good outcome and bad outcome. Good outcomes were assigned to all patients who either were cured or had completed treatment, and bad outcomes included the patients in whom the treatment led to death, failure, or default (Table 1). Death accounted for 21 (18.9%) patients (Table 2).

Having performed a univariate analysis, a significant association was not found among treatment outcome and sex, smoking, drug and alcohol abuse, history of imprisonment, and route of transmission ($p > 0.05$). In addition, history of CAT-1 and CAT-2 treatment were not associated with outcome ($p > 0.05$). HAART was started only for patients whose CD_4 count was less than 200. Surprisingly, administration of HAART led to a significantly higher rate of good outcomes in these patients ($p < 0.001$, CI 95% = 2.1–12.8, OR = 5.2). The mean CD_4 count was 175.8 and 140.09 in patients with good outcomes and bad outcomes, respectively. Nonetheless, a correlation was not found between the CD_4 count and outcome ($p > 0.05$). Furthermore, a CD_4 count above 100 and below 100 did not affect treatment outcome.

Although the study did not find an association between weight and outcome, albumin levels were significantly lower in patients with a bad outcome ($p = 0.003$; 3.03 ± 0.52 vs. 2.67 ± 0.45). During the course of treatment, 33 (29.7%) patients developed adverse effects due to either anti-TB or HAART medications. However, these adverse effects did not influence the ultimate outcome of the patients ($p > 0.05$).

All the aforementioned variables were also analyzed against mortality; however, only age ($p = 0.02$) and albumin le-

Table 1 – Patients' characteristics with regard to their final treatment outcome.

	Outcome					
	Good outcome		Bad outcome		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Gender						
Male	69	97.20	38	95	107	96.40
Female	2	2.80	2	5	4	3.60
Route of transmission[*]						
Heterosexual	7	10	4	10.30	11	10.10
IVDU	59	84.30	29	74.40	88	80.70
Homosexual	1	1.40	0	0	1	0.90
Transfusion	3	4.30	6	15.40	9	8.30
Smoker						
Yes	70	98.60	38	95	108	97.30
No	1	1.40	2	5	3	2.70
Drug abuse						
Yes	67	94.40	37	95.20	104	93.70
No	4	5.60	3	7.50	7	6.30
Alcohol abuse[*]						
Yes	35	50	18	42.9	53	47.7
No	35	50	24	57.1	58	52.3
Prison[*]						
Yes	59	85.50	37	95.20	96	88.10
No	10	14.50	3	7.50	13	11.90
History of CAT-1						
Yes	15	21.40	8	19.6	23	20.70
No	55	78.60	33	80.4	88	79.30
History of CAT-2						
Yes	4	5.60	2	5	6	5.40
No	67	94.4	38	95	105	94.60
HAART						
Yes	40	56.30	8	20	48	43.20
No	31	43.70	32	80	63	56.80
CD4+[*]						
<200	49	71	24	72.7	73	71.6
⩾200	20	29	9	27.3	29	28.4
Adverse effects						
Yes	24	33.80	10	25	34	29.70
No	47	66.20	30	75	77	70.30

[*] The values were not available as the factor's status was unknown for some cases.

vel ($p = 0.009$) were found to be significantly associated with mortality. The mean age of patients with mortality was lower than that of patients without mortality (48.6 ± 9 vs. 54.9 ± 10.8 years). Similarly, albumin levels were lower in patients who died than in those who survived (2.59 ± 0.45 vs. 2.99 ± 0.51).

Discussion

It is now recognized that both TB and HIV contribute to each other's progress [9,16–18]. Patients co-infected with TB and HIV have higher mortality rates in comparison with those infected with one or the other [2–6,15,19]. In several case series, the main predictor for survival was the prompt initiation of effective anti-tuberculosis treatment, HAART administration, CD4 count, site of the disease, and other previous or concurrent opportunistic infections caused by immunosuppression [7–9,20,21].

All patients were followed throughout their treatment accordingly; totally, 71 (64%) of the patients reached a successful outcome, whereas the same treatment led to an unsuccessful outcome in 41 (36%) others. In addition, 21 patients (18.9%) died during the course of treatment. For those who died, the time interval between treatment initiation and death was taken into consideration. A median was then calculated. (Median = 2.50 months, IQR 25–75% = 1.25–8.50, Range = 0.30–18.00.)

As the data tables and statistical analyses illustrate, a successful outcome is associated with having received HAART treatment and higher albumin levels. Furthermore, the analysis of mortality in TB/HIV patients is associated with higher

Table 2 – Patients' characteristics with regard to mortality.

	Mortality					
	Yes		No		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Gender						
Male	19	90.50	88	97.70	107	96.30
Female	2	9.50	2	2.30	4	3.70
Route of transmission[*]						
Heterosexual	2	9.50	9	10.2	11	9.90
IVDU	16	76.20	72	81.8	88	79.30
Homosexual	0	0	1	1.1	1	0.90
Transfusion	3	14.30	6	6.9	9	8.10
Smoker						
Yes	19	90.50	89	99.10	108	97.30
No	2	9.50	1	0.90	3	2.70
Drug abuse						
Yes	19	90.50	85	95.50	104	93.70
No	2	9.50	5	4.50	7	6.30
Alcohol abuse						
Yes	12	57.10	41	45.60	53	47.70
No	9	42.90	49	54.40	58	52.30
Prison						
Yes	19	90.50	79	87.70	98	88.30
No	2	9.50	11	12.30	13	11.70
Type						
Pulmonary	13	61.90	66	73.30	79	71.20
Extra-Pulmonary	0	0	8	8.80	8	7.20
Both	8	28.10	16	17.90	24	21.60
History of CAT-1						
Yes	2	9.5	21	23.30	23	20.70
No	19	91.5	69	76.70	88	79.30
History of CAT-2						
Yes	1	4.80	5	5.50	6	5.40
No	20	95.20	85	94.50	105	94.60
HAART						
Yes	6	28.60	42	46.70	48	43.20
No	15	71.40	48	53.30	63	46.80
CD4+[*]						
<200	16	84.20	58	70	74	72.50
⩾200	3	15.80	25	30	28	27.5
Adverse effects						
Yes	7	33.30	27	30	34	30.70
No	14	66.70	63	70	77	69.30

[*] The values were not available as the factor's status was unknown for some cases.

weight and albumin levels. In accordance with the collected information, mortality has no significant association with receiving HAART treatment. However, this may be owing to the evidence that those who died experienced a very short time interval between their time of admission to the hospital and death. Therefore, there was no opportunity for receiving an efficacious HAART treatment. This is supported by the fact that those who had the opportunity to receive HAART showed an increasingly better response to TB treatment, and their outcome significantly improved.

Furthermore, the significant association between albumin levels and treatment outcome and mortality can be rationalized as those who had more developed disease, more recurrent opportunistic infections and more severe malnourishments had lower weight or albumin levels, and hence were more liable to have anti-TB treatment failure or to die. This may support the fact that a thorough combat against TB-HIV co-infection not only requires a well-administered treatment plan for both infections, but also mandates the presence of a relatively competent immune system, which may be adversely affected by malnutrition.

Despite the many factors affecting the risk of mortality in TB/HIV patients, such as the site of culture-proven TB at presentation, the history of previous opportunistic infection, history of treatment for tuberculosis, etc., not many studies have been done on this topic.

Additionally, not many studies have addressed the factors such as albumin or weight as predictors of mortality or a unsuccessful outcome in TB/HIV patients.

This study denotes that TB/HIV cases presenting to the center were mostly male IV drug users. As well, most of the cases (88.1%) have been or are currently imprisoned. This confirms and emphasizes the importance of implementing efficient plans for preventing, screening, and treating TB/HIV in high risk groups such as IV drug users or prisoners, in whom there is increased risk of contracting both TB and HIV owing to close contact and more high-risk behaviors.

The purpose of this study consisted of providing standard care for all patients and administering HAART and TB treatments with a uniform protocol. All eligible patients received co-Trimoxazole/Azithromycin as prophylaxis against opportunistic disease. This helps with interpreting the findings with a more direct relation to the outcomes and mortality. Of course, this study had several limitations as well. The first was that the center is a national referral center, which means that not all acquired data is necessarily a representation of the entire Iranian society. Secondly, the main pattern of the transmission route of HIV, as is seen throughout the country, is intravenous-drug abuse, and the majority of the patients were male. This may confine the researchers from considering the obtained results as the exact representative of the Iranian population.

However, it seems that, with regard to the health concern prompted by increasing TB-HIV infections, it is crucial to conduct more comprehensive studies on this issue; particularly on the predictors and risk factors for unfavorable outcomes or mortality. These should be preferentially undertaken in different settings worldwide and with a larger sample.

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