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Treatment outcome, mortality and their predictors among HIV-associated tuberculosis patients

P Tabarsi, MD, MPH[*], **E Chitsaz, MD**[*], **A Moradi, MD**[*], **P Baghaei, MD, PhD**[*], **P Farnia, PhD**[*], **M Marjani, MD, MPH**[*], **M Shamai, MD**[*], **M Amiri, MD, MPH**[*], **S Nikaein, MD**[*], **D Mansouri, MD, MPH**[*], **M Masjedi, MD**[*], and **F Altice, MD**[†]

[*]Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Niavaran Sq, Tehran 1955841452, Iran

[†]Yale University AIDS Program, New Haven, CT, USA

Summary

The risk of death is significantly higher in HIV-infected patients with tuberculosis (TB). 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 tertiary TB centre in Iran. In total, 111 patients were recruited from 2004 to 2007. Mycobacteriological studies and demographic, clinical, and laboratory data from all patients were analysed and predictors of unsuccessful outcomes as well as mortality were determined. The mean age for all 111 TB-HIV patients was 38 ± 9 years (range 22–70) and 107 (96.3%) were men; 104 (93.7%) had a history of drug abuse and 96 (86.4%) had a history of imprisonment. The method of HIV transmission was intravenous drug use in 88 (79.3%). Twenty-three (20.7%) had a history of Category 1 (CAT I) TB treatment and six (5.4%) Category 2 (CAT II) treatment. Combination antiretroviral therapy (cART) was given to 48 (43.2%). No significant associations were found between treatment outcomes or mortality and gender, smoking, drug and alcohol abuse, imprisonment, method of transmission, history of CAT I and CAT II treatments, CD4 counts or adverse effects ($P > 0.05$). Administration of cART led to significantly better outcomes ($P < 0.001$). Lower serum albumin levels and low body weight were significantly associated with mortality.

Keywords

HIV/AIDS; *Mycobacterium tuberculosis*; TB; treatment outcome; mortality; Iran

INTRODUCTION

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 true for the 40 million people currently living with HIV/AIDS. In addition, without proper treatment, 90% of HIV-infected individuals will die within months of contracting TB. Four million people affected with HIV have also TB disease worldwide making TB the major killer in HIV-infected patients.[1] The risk of death from TB is significantly higher in the HIV-infected population, even if the organism is sensitive to and responds well to anti-TB medications.[2–6]

Correspondence to: Payam Tabarsi, tabarsi@nritld.ac.ir.

Studies pertaining to demographic information, route of acquisition and intravenous drug use (IVDU) related to HIV/ AIDS have been conducted in the recent years. In addition, some factors have been proposed as risk factors for mortality in TB/HIV patients.[7,8] However, findings remain controversial mainly due to studies done in different settings in various regions, the major routes of acquisition, diverse demographic characteristics among HIV-positive cases and dissimilar epidemiological patterns of either TB or HIV infections.[7–12]

Similar to its global trend,[13] the number of HIV-infected patients in Iran is on the rise 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 outcomes and mortality of TB/HIV co-infected patients in a tertiary TB centre in Iran.

MATERIALS AND METHODS

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

For all patients, TB and HIV confirmations were undertaken. Primarily, sputum samples (smear and culture) were collected, chest X-rays were performed and patients were tested for HIV antibodies, and in the case of positive results Western blot testing was done for confirmation. After initial confirmation of TB and HIV diagnoses, first-line drug-susceptibility testing (DST) was performed for all culture-positive TB cases. TB treatment was initiated in accordance with standard Category 1 (CAT I) regimens (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol [HRZE] then 4 months of isoniazid and rifampicin [HR]). Until 2005, the Iranian national guidelines for management of TB among HIV-infected patients consisted of the initiation of combination antiretroviral therapy (cART) eight weeks after the start of TB treatment if their CD4+ count was less than 200 cells/μL. Due to the fact that cART consisted of zidovudine, lamivudine and nelfinavir, we replaced rifampicin with rifabutin in their TB regimen to prevent adverse drug interactions in cART-receiving patients. However, in 2005 and thereafter, the protocol was updated by administering cART concurrently with TB treatment for patients with a CD4+ count <100 cells/μL. The new regimen consisted namely of zidovudine, lamivudine and efavirenz, which allowed for the administration of rifampicin as well.

Once DST results were obtained, treatment was modified accordingly. It should be noted that all patients received cotrimaxazole (trimethoprim/sulfamethaxazole) for CD4+ count <200 cells/μL and azithromycin for CD4+ count <50 cells/μL as prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium*-intracellulare infection, respectively.

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

STATISTICAL ANALYSIS

For statistical analysis, we used SPSS software V. 15.1 (Apache Software Foundation, Chicago, Il, USA). Continuous variables were expressed as group means ± standard deviation (SD). Categorical data, such as ethnicity, were expressed as group frequency and

proportion. Statistic 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 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

The mean age for all 111 TB-HIV patients was 38 ± 9 years (range 22–70) and 107 (96.3%) were men. Smokers accounted for 108 (97.3%) of the patients, 104 (93.7%) had a history of IVDU, 53 (47.7%) were alcohol abusers and 96 (86.4%) had a history of imprisonment. The method of transmission of HIV was heterosexual in 11 (9.9%), IVDU in 88 (79.3%), homosexual in one (0.9%) and blood transfusion in nine (8.1%). Pulmonary TB cases accounted for 79 (71.2%) patients, eight (7.2%) had extrapulmonary TB and both pulmonary and extrapulmonary TB were present in 24 (21.6%) patients. Twenty-three (20.7%) had a history of CAT I treatment and 6 (5.4%) had received CAT II treatment. cART was given to 48 (43.2%) patients.

Outcomes were classified into two categories: good outcome and poor outcome. Good outcomes were assigned to all patients who either were cured or had completed treatment, and poor outcome included patients in whom the treatment led to death, failure or default (Table 1). Twenty-one (18.9%) patients died during follow-up (Table 2).

After univariate analysis, a significant association was not found between treatment outcome and gender, smoking, drug and alcohol abuse, imprisonment, and method of HIV transmission ($P > 0.05$). In addition, history of CAT I and CAT II TB treatments were not associated with outcome ($P > 0.05$). cART was started only for patients whose CD4 count was <200 cells/μL. Administration of cART led to a significantly higher rate of good outcome in these patients ($P < 0.001$, 95% confidence interval = 2.1–12.8, odds ratio = 5.2). The mean CD4 counts were 176 and 140 in patients with good outcomes and poor outcomes, respectively. Nonetheless, a correlation was not found between CD4 count and outcome ($P > 0.05$). Furthermore, a CD4 count above 100 and below 100 did not affect treatment outcome.

Although the study did not find an association between body weight and outcome, serum albumin levels were significantly lower in patients with a poor outcome ($P = 0.003$; 30.3 ± 5.2 versus 26.7 ± 4.5 g/L). During the course of treatment, 33 (29.7%) patients developed adverse effects due to either anti-TB or cART medications. However, these adverse effects did not influence the ultimate outcome of the patients ($P > 0.05$).

All the aforementioned variables were also analysed against mortality; however, only age ($P = 0.02$) and albumin level ($P = 0.009$) were found to be significantly associated with mortality. The mean age of patients who died was lower than that of patients who survived (48.6 ± 9 versus 54.9 ± 10.8 years). Similarly, albumin levels were lower in patients who died than in those who survived (25.9 ± 4.5 versus 29.9 ± 5.1 g/L).

DISCUSSION

TB and HIV contribute to each other's progression.[9,16–18] Patients co-infected with TB and HIV have higher mortality rates in comparison with those with one of the two infections alone.[2–6,15,19] In several case series, the main predictor for survival was the prompt initiation of effective anti-TB treatment, cART administration, CD4 count, site of the disease and other previous or concurrent opportunistic infections caused by

immunosuppression.[7–9,20,21] The aim of this study, therefore, was to find risk factors affecting mortality in order to intervene accordingly with our available treatment methods.

All patients were followed through their treatment accordingly; in total, 71 (64%) of the patients achieved a successful outcome but treatment was unsuccessful in 41 (36%) others. In addition, 21 (18.9%) died during the course of treatment. For those who died, we took into consideration the time interval between treatment initiation and death (median = 2.5 months, interquartile range [25–75%] = 1.3–8.5, range = 0.3–18.0).

As the data tables and statistical analyses illustrate, successful outcome is associated with having received cART as well as higher serum albumin levels. Also, mortality in TB/HIV patients was associated with higher body weight and albumin levels. From our data we were unable to demonstrate a significant association between mortality and receiving cART. However, this may be due to the fact that those who died had a short time interval between admission to hospital and death and type 2 error. Therefore, there was no opportunity for receiving effective cART. This is supported by the fact that those who had the opportunity to receive cART showed increasingly better responses to TB treatment and their outcomes were better.

The significant association between albumin levels and treatment outcome and mortality might be explained by those who had more established disease with more recurrent opportunistic infections and severe malnourishment had subsequent lower body weight and albumin levels; hence they were more susceptible to failing anti-TB treatment or to die. This supports the approach to TB-HIV co-infection that requires not only well-administered treatment for both infections but also requires 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, a history of previous opportunistic infection or a history of treatment for TB, not many studies have been done on this topic. Additionally, not many studies have addressed factors such as serum albumin or body weight as predictors of mortality or unsuccessful outcome in TB-HIV patients.

Our study found that TB-HIV cases that presented to our centre were mostly male IVDU. As well, most of the cases (88.1%) had been or were 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 IVDUs or prisoners, in whom there is increased risk of contracting both TB and HIV due to close contacts and more high-risk behaviours.

The strengths of this study included providing standard care for all patients and administering cART and TB treatments within a uniform protocol. All eligible patients received cotrimoxazole/azithromycin prophylaxis against opportunistic infections with less confounding of the outcomes and mortality. Of course, our study had several limitations as well. The first was that our centre is a national referral centre, which means that not all acquired data are necessarily representative of the entire Iranian or other populations. Secondly, the main transmission route of HIV, as is seen in Iran, is IVDU, and the majority of our patients were men; this may restrict the generalizeability of the results obtained.

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

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Table 1

Patients' characteristics with regard to their final treatment outcome

	Outcome					
	Good outcome		Bad outcome		Total	
	Count	Column, *n*%	Count	Column, *n*%	Count	Column, *n*%
Gender						
Male	69	97.2	38	95	107	96.4%
Female	2	2.8	2	5	4	3.6
Route of transmission *						
Heterosexual	7	10	4	10.3	11	10.1
IVDU	59	84.3	29	74.4	88	80.7
Homosexual	1	1.4	0	0	1	0.9
Transfusion	3	4.3	6	15.4	9	8.3
Smoker						
Yes	70	98.6	38	95	108	97.3
No	1	1.4	2	5	3	2.7
Drug abuse						
Yes	67	94.4	37	95.2	104	93.7
No	4	5.6	3	7.5	7	6.3
Alcohol abuse *						
Yes	35	50	18	42.9	53	47.7
No	35	50	24	57.1	58	52.3
Prison *						
Yes	59	85.5	37	95.2	96	88.1
No	10	14.5	3	7.5	13	11.9
History of CAT I treatment						
Yes	15	21.4	8	19.6	23	20.7
No	55	78.6	33	80.4	88	79.3
History of CAT II treatment						
Yes	4	5.6	2	5	6	5.4
No	67	94.4	38	95	105	94.6

	Outcome					
	Good outcome		Bad outcome		Total	
	Count	Column, *n*%	Count	Column, *n*%	Count	Column, *n*%
cART						
Yes	40	56.3	8	20	48	43.2
No	31	43.7	32	80	63	56.8
CD4+ *						
<200	49	71	24	72.7	73	71.6
≥200	20	29	9	27.3	29	28.4
Adverse effects						
Yes	24	33.8	10	25	34	29.7
No	47	66.2	30	75	77	70.3

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

IVDU = intravenous drug use; CAT = category; cART = combination antiretroviral therapy

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Table 2

Patients' characteristics with regard to mortality

	Mortality					
	Yes		No		Total	
	Count	Column, *n*%	Count	Column, *n*%	Count	Column, *n*%
Gender						
Male	19	90.5	88	97.7	107	96.3
Female	2	9.5	2	2.3	4	3.7
Route of transmission *						
Heterosexual	2	9.5	9	10.2	11	9.9
IVDU	16	76.2	72	81.8	88	79.3
Homosexual	0	0	1	1.1	1	0.9
Transfusion	3	14.3	6	6.9	9	8.1
Smoker						
Yes	19	90.5	89	99.1	108	97.3
No	2	9.5	1	0.9	3	2.7
Drug abuse						
Yes	19	90.5	85	95.5	104	93.7
No	2	9.5	5	4.5	7	6.3
Alcohol abuse						
Yes	12	57.1	41	45.6	53	47.7
No	9	42.9	49	54.4	58	52.3
Prison						
Yes	19	90.5	79	87.7	98	88.3
No	2	9.5	11	12.3	13	11.7
Type						
Pulmonary	13	61.9	66	73.3	79	71.2
Extrapulmonary	0	0	8	8.8	8	7.2
Both	8	28.1	16	17.9	24	21.6
History of CAT I treatment						
Yes	2	9.5	21	23.3	23	20.7

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	Mortality					
	Yes		No		Total	
	Count	Column, *n*%	Count	Column, *n*%	Count	Column, *n*%
No	19	91.5	69	76.7	88	79.3
History of CAT II treatment						
Yes	1	4.8	5	5.5	6	5.4
No	20	95.2	85	94.5	105	94.6
cART						
Yes	6	28.6	42	46.7	48	43.2
No	15	71.4	48	53.3	63	46.8
CD4+ *						
<200	16	84.2	58	70	74	72.5
≥200	3	15.8	25	30	28	27.5
Adverse effects						
Yes	7	33.3	27	30	34	30.7
No	14	66.7	63	70	77	69.3

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

IVDU = intravenous drug use; CAT = category; cART = combination antiretroviral therapy