

Negative Impact Factors in HIV-Tuberculosis

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ABSTRACT

About one quarter of all tuberculosis (TB) deaths are among people living with HIV. Tuberculosis is a leading infectious cause of death among persons infected with HIV and the outcome of TB treatment is poorer in these patients.

Objective: To identify the factors associated with a poor tuberculosis outcome in patients with HIV-TB coinfection

Material and methods: This is a retrospective cohort study using data from the local TB registry for 2009–2016. We performed descriptive statistics as well as univariate and multivariate analysis.

Results: During the study period we identified 86 patients (4.76% of all patients registered for TB treatment) with HIV-TB who had a mean age of 35.05 ± 9.10 years and were mostly male (73.25%). More than half of patients were current drug users (51.16%) and 22.10% homeless. The mean CD4 value was $179.11 \pm 204.76/\text{mm}^3$ and 69.76% of patients received antiretroviral treatment during TB treatment. Viral hepatitis was present in 61.62% of cases, and 77.9% of patients were new TB cases. Pulmonary TB was noted in 72 cases, with confirmation by culture being obtained in 84.44% of cases. Treatment success was achieved in 63.95% of cases, 22.09% of patients died, 8.13% abandoned treatment, and 5.81% were lost to follow up. Several factors related to poor outcome were identified by univariate analysis, including drug use (OR=3.14, $p=0.027$), homeless status (OR=3.01, $p=0.039$) and viral hepatitis (OR=2.93, $p=0.045$). Multivariate analysis revealed marginal insignificance for homeless status ($p=0.06$) and drug use ($p=0.86$).

Conclusions: A special attention and dedicated programs should be considered for patients who are intravenous drug users or those without a stable home.

Keywords: tuberculosis, HIV infection, treatment outcome.

INTRODUCTION

Despite huge advances in tuberculosis (TB) epidemiology, TB remains one of the top ten causes of death worldwide (1), being responsible for 1.2 million deaths in 2019 (2).

Almost a quarter of those deaths (251 000) were among HIV positive patients (2).

The incidence of TB in Romania has been continuing to fall since 2002 (3). However, from a total of 991 cases of HIV-tuberculosis coinfection reported by ECDC in 2018 for 30 European Union and European Economic Area countries, Romania is responsible for 254 cases (one quarter) (4). The proportion of all tuberculosis patients tested for HIV in Romania is 83.9%; 2.5% of the tested patients are HIV infected (4). Coinfection

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Article received on the 11th of February and accepted for publication on the 18th of May 2021

Age – Mean (±standard deviation)	35.05 (±9.10)
Gender	
Male – Number (%)	63 / 86 (73.30)
Female – Number (%)	23 / 86 (26.70)
Provenience	
Urban – Number (%)	75 / 86 (87.20)
Rural – Number (%)	11 / 86 (12.80)
Occupation	
No occupation – Number (%)	59 / 86 (68.60)
Retired – Number (%)	21 / 86 (24.40)
Employee – Number (%)	6 / 86 (7.00)
Homeless	
Yes – Number (%)	19 / 86 (22.10)
No – Number (%)	67 / 89 (77.90)
Intravenous drug use	
Active – Number (%)	44 / 86 (51.16)
Former – Number (%)	3/86 (3.49)
No – Number (%)	39 / 86 (45.35)

TABLE 1. Demographics for all patients

represents a real challenge due to high morbidity and mortality and massive resource consumption. TB and HIV infection are two diseases influencing each other. The depletion of CD4+T lymphocytes increases the risk of achieving a new TB infection, but also the risk of reactivation of a latent TB and the presence of viral particles impairs a normal macrophage bactericidal action (5). On the other hand, *Mycobacterium tuberculosis* increases HIV replication. Multiple mechanisms have been described (6).

Overall success of TB treatment is poorer for HIV patients (in the European region, in, 2018, 60% for new and relapsed cases versus 75.5% in the same category of patients but without HIV infection) (7).

Because of this, identifying factors that might influence the treatment outcome to an even greater extent would be of utmost importance. □

MATERIAL AND METHODS

This is a descriptive, retrospective study based on the information collected from the unique registry of patients treated for tuberculosis in 4th District TB Unit, in Marius Nasta Institute of Pneumology, Bucharest, Romania. This district represents one sixth of the population living in Bucharest and in nearby villages.

The study was performed with the approval of the Ethic Committee of the Institute.

We searched in the registry of patients with TB those patients with HIV infection treated during the years 2009-2016. Data regarding demo-

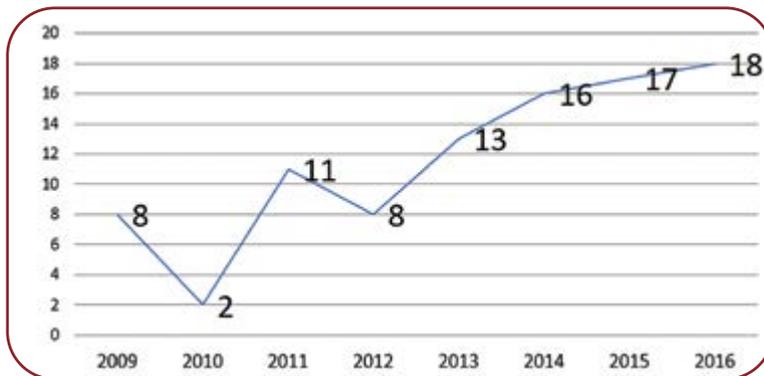


FIGURE 1. Number of patients with TB-HIV coinfections during the years of research

graphics (age, gender, living area, occupation), intravenous drug use, medical data regarding HIV (severity according to CD4 number, presence of antiretroviral treatment, complications, adverse reactions) and TB infection (TB form and localization, type of case, results of sputum smears and cultures, antibiotic sensitivities), treatment, comorbidities, evolution and outcome were noted. Data were stocked in a Microsoft Office Excel database and statistical analysis was performed using R 3.4.4 (2018-03-15) - Copyright (C) 2018 The R Foundation for Statistical Computing Platform R Core Team (2018). R A language and environment for statistical computing. (Univariate and multivariate) logistic regression was performed to assess the factors influencing the outcome of TB treatment. Findings were considered statistically significant if $p < 0.05$.

RESULTS

During the years of our study, out of a total of 1806 patients registered with TB treatment, 86 (4.76%) had a documented HIV infection. The number of patients with coinfection had an upward trend over time, as illustrated in Figure 1. Patients had a mean age of 35.05 ± 9.10 years and 63 of them (73.25%) were male. While six patients had a stable occupation, 22 were retired and 54 (62.79%) jobless. More than half of patients (44, 51.15%) were active intravenous drug users and three former users. Almost a quarter of patients (19, representing 22.10% of all patients) were homeless persons (Table 1).

Pulmonary tuberculosis was diagnosed in 72 cases (49 of them were pulmonary only, with the remaining being both pulmonary and extrapulmonary sites). Miliary tuberculosis was present in 15 cases. Among extrapulmonary forms, tuberculous adenitis prevailed (24 cases), followed by meningoencephalitis tuberculosis (five cases) and tuberculous pleurisy (four cases). Osteoarticular tuberculosis (two cases), peritonitis (two cases), pericarditis, spleen, liver and intestinal tuberculosis (one case each) have been also identified.

Sixty seven patients (77.9%) were new cases, relapse was noted in 14 cases, and in five cases treatment was restarted after having been previously abandoned.

Microbiological confirmation was obtained by culturing *Mycobacterium tuberculosis* in 73 cases (84.88%); 59 cases (68.60%) had posi-

tive smear for acid-fast bacilli. Tuberculosis was diagnosed using histopathological evaluation in six cases, and seven cases had no confirmation. It should be noted that, during the studied period, the genetic investigation (PCR-DNA *Mycobacterium tuberculosis*) was not common for the diagnosis of TB in our unit.

Antibiogram was available in 66 of the 73 positive cultures (90.41%). Eleven patients were identified with multidrug-resistant tuberculosis (MDR-TB).

Sixty patients (69.76%) received an antiretroviral therapy (ART) during the TB treatment, with more than a half (32) of them being under ART at the moment of tuberculosis diagnosis. The mean number of CD4 cells was 179.11 ± 204.76 per mm^3 , with 23 patients having $\text{CD4} < 50$ cells/ mm^3 .

Viral hepatitis was a leading comorbidity and was found in 53 (61.62%) cases (hepatitis C virus in 47 cases, hepatitis B+C virus in five cases and hepatitis B virus in one case) and 28 patients were cachectic.

Treatment success was achieved in 54 cases (63.95%): 38 cases (44.18%) were cured, with the remaining completing their treatment (17, 19.76%). Nineteen patients (22.09%) died during treatment, seven (8.13%) patients abandoned treatment, and five (5.81%) subjects were lost to follow up.

To identify the factors predicting the risk of treatment failure, univariate binary simple logistic regression analysis was used, with treatment failure as dependent variable and demographic,

TABLE 2. Univariate analysis of risk factors for negative tuberculosis treatment outcome

Variable	Odds ratio	P value	95% Confidence interval
Age	0.98	0.574	0.93 la 1.03
Homeless	3.01	0.039	1.05 la 8.58
Male	1.15	0.779	0.42 la 3.12
Rural provenience	1.48	0.546	0.43 la 5.31
Recurrences	1.43	0.546	0.44 la 4.63
Pulmonary cases	1.59	0.468	0.45 la 5.56
Extrapulmonary cases	1.43	0.427	0.58 la 3.51
Positive AFB	1.76	0.274	0.63 la 4.87
Positive culture	1.65	0.481	0.40 la 6.78
MDR	2.16	0.248	0.58 la 7.97
CD4 number	0.99	0.060	0.99 la 1.01
Intravenous drug use	3.14	0.027	1.13 la 8.67
Viral hepatitis	2.93	0.045	1.02 la 8.38
Cachexia	2.05	0.132	0.80 la 5.27

TABLE 3. Multivariate analysis of risk factors for negative tuberculosis treatment outcome

Factor	Odds Ratio	P value	IC95% for Odds Ratio
Homeless	4.03	0.060	0.94 la 17.19
Intravenous drug use	4.25	0.086	0.81 la 22.19

clinical and paraclinical variables as independent variables. The analysis revealed that homeless cases (OR = 3.01, $p < 0.05$), intravenous drug use (OR = 3.14, $p < 0.05$) and chronic viral hepatitis (OR = 2.93, $p < 0.05$) were associated with a risk of negative treatment outcome. All results are listed in Table 2. The following risk ratio (RR) were found: 2.99 for homeless cases, 3.12 for drug use and 2.91 for chronic hepatitis.

Factors with a $p < 0.20$ were considered for multivariate binary logistic regression, via a backward selection algorithm. Important factors, even though marginally insignificant, included homeless cases (OR = 4.03, RR 3.99) and intravenous drug use (OR = 4.25, RR 4.22) (Table 3). □

DISCUSSION

There are many reasons that contribute to a poorer treatment outcome in HIV infected TB patients. However, efforts should be made to identify modifiable factors or at least the situations in which the risk of failure is high; also, more implication and motivation is needed.

A number of studies identified some factors influencing treatment outcome.

During the years of intensified fight against tuberculosis, female gender and treatment were identified as significant determinants of successful TB treatment outcome, according to a study in Cameroon (8). Two Ethiopian studies reported that patients with advanced age and those with smear positive pulmonary TB (9) as well as TB-HIV patients with a history of previous TB treatment, smear-positive pulmonary TB, late HIV stage, history of opportunistic infection and not being on co-trimoxazole prophylaxis therapy (10) had unfavorable treatment outcomes. Other factors associated with unfavorable TB treatment outcomes included WHO stage IV, age greater than 45 years and baseline CD4 count less than 200 cells/ μ L (11).

The results of our study revealed that homeless subjects, intravenous drug users and patients

with viral hepatitis had the highest risk of treatment failure. However, homeless status and intravenous drug use were not demonstrated to be independent variables, with results obtained from multivariate analysis being marginal insignificant ($p=0.06$ and $p=0.08$, respectively). Also, the presence of viral hepatitis was found to be related to this risk in univariate analysis, while multivariate analysis showed that it was a non-significant relationship. One possible explanation is that viral hepatitis may be a confounding factor, given that, according to the literature, 50-90% of intravenous drug users are coinfecting with hepatitis C virus (HCV) (12). A Romanian study notes that 92.4% of patients with HIV-HCV coinfection are intravenous drug users (13).

In Romania, in 2016, 2.2% of patients with known HIV status had a HIV positive test (14). In our unit, 4.76% of all treated patients are infected with HIV, which may be related to both a higher detection rate and a higher prevalence of HIV infection (one reason could be related to drug use in Bucharest and also to a high TB frequency among intravenous drug users (15). However, this result should be treated with caution and efforts to identify HIV infection in TB patients should be intensified in Bucharest.

In Romania, treatment of TB among HIV infected patients was successful in 70.4% of cases, as notified in 2016 (14). In our unit, the level of therapeutic success was lower. However, this is a result of all the studied years and the values should not be compared.

The authors believe that this analysis is important because it enables us to do a risk assessment in our own patients, and a similar study has not been performed in Romania yet. Moreover, identifying intravenous drug users as one of the factors influencing the outcome of TB treatment should raise the alarm, given the increasing proportion of patients using intravenous drugs since the beginning of the last decade (16). We should not forget that these patients (drug users as well as homeless persons) are vulnerable populations,

and all efforts should be made to maintain their adherence to treatment.

The present study accounts for the sixth part of patients with TB in Bucharest, but it has a rather local relevance, because we cannot state that this population is representative for either Bucharest or Romania. However, it has managed to raise some concerns and problems that could be widely evaluated.

We believe that identifying intravenous drug users and homeless persons as special problems did arise our awareness, and we should focus our future studies on this issue too. □

CONCLUSIONS

In univariate analysis, homeless persons, use of intravenous drugs and presence of chronic hepatitis were identified as risk factors for tuberculosis treatment failure, which should receive special attention and set in motion the whole available therapeutic arsenal (including counseling, support organizations, incentives, etc.). □

Conflicts of interest: none declared.

Financial support: none declared.

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