Peculiarities of persons who inject drugs among patients with HIV–tuberculosis coinfection registered in 4th District TB Unit Bucharest during 2009–2018

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Abstract

English:
Introduction: Human immunodeficiency virus (HIV)–tuberculosis (TB) coinfection is a worldwide problem and a subject of concern, being associated with high mortality and risk of complications. Intravenous drug use is a way of getting infected with HIV that continues to rise, especially in the big cities. We aimed to study the peculiarities of persons with HIV–TB who inject drugs.

Methods: We performed a retrospective, observational study, among patients treated for TB in the 4th District TB unit, Bucharest, during a 10-year period. A unique registry of patients with TB was used, and data of all patients with HIV–TB were noted (demographics, medical, treatment outcome). A comparison between drug users (people who inject drugs [PWID]) and nondrug users (non-PWID) was assessed.

Results: We identified 122 patients with HIV–TB: 60 PWID, 58 non-PWID, and 4 former users. The mean age was 36.4 ± 9.8 years, 75% were males, and 73% were using antiretroviral treatment (ART). After comparing PWID with non-PWID patients, the following differences were noted: age (33.0 ± 6.0 years in PWID vs 40.5 ± 11.3 in non-PWID, P < 0.0001), gender (87% vs 66% males, P = 0.0034), presence of chronic hepatitis (97% vs 21%, P < 0.0001), CD4 number (156.1 ± 204.5 cells/mm³ vs 260.8 ± 248.9 cells/mm³, P = 0.0409), ART (65% vs 84%, P = 0.0075), and evaluation at the end of TB treatment (P = 0.0373).

Conclusions: PWID represent a vulnerable population of those with HIV–TB coinfection, whose outcome in TB treatment is significantly poorer and who are at risk of abandonment, death, and comorbidities. They should be included in dedicated programmes that are aimed at increasing adherence to treatment and care, additionally assessing the dependence problem.

Keywords
HIV • tuberculosis • coinfection • drug users

Particularităţile persoanelor ce îşi injectează drogu din rândul pacienţilor cu coinfeţie HIV–tuberculoză înregistrați în Dispensarul TB Sector 4 Bucureşti în 2009-2018

Rezumat

Romanian:
Introducere: Coinfeccia HIV–tuberculoza (TB) reprezintă o problemă globală și un subiect de interes, fiind asociată cu mortalitate mare și risc crescut de complicații. Consumul de droguri injectabile intravenoase este o posibilitate de contractare a infecției HIV, în special în orașele mari. Ne-am propus să studiem particularitățile persoanelor cu HIV–TB consumatoare de droguri injectabile.


Rezultate: Am identificat 122 pacienți cu HIV–TB: 60 PWID, 58 non-PWID și 4 foști consumatori. Vârsta medie a fost 36.4 ± 9.8 ani, 75% dintre ei erau bărbații, 73 primeau tratament antiretroviral (ARV). După compararea pacienților consumatori cu cei neconsumatori am obținut următoarele diferențe semnificative: vârsta (33.0 ± 6.0 ani la PWID vs 40.5 ± 11.3 ani la non-PWID, P < 0.0001), sexul (87% vs 66% bărbați, P = 0.0034), prezența hepatitii cronice (97% vs 21%, P < 0.0001), numărul de celule CD4 număr (156.1 ± 204.5 celule/mm² vs 260.8 ± 248.9 celule/mm², P = 0.0409), ARV (65% vs 84%, P = 0.0075) și evaluarea la finalul tratamentului TB (P = 0.0373).

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Introduction

Tuberculosis (TB) in patients infected with human immunodeficiency virus (HIV) represents a stringent problem worldwide. It was reported that Romania registered in 2019 one-quarter of all European cases of patients with TB–HIV coinfection (1), and approximatively 1.9% of patients with TB reported in our country are HIV-infected (1). The coexistence of both diseases represents a huge impact on a patient’s prognosis, as each infection influences the other and TB gets to be one of the leading death causes in HIV patients (2,3). Under these conditions, we emphasise the need to identify and provide early treatment for patients with HIV and TB.

Intravenous drug use is one of the routes of HIV infection, and people who inject drugs (PWID) are a special vulnerable population due to their needs, low treatment adherence, and high abandonment, death, and failure risks. When compared to a cohort of HIV persons not using drugs, HIV-infected PWID had more often a history of TB treatment, and in follow-up were more often treated for active TB (4). When comparing the TB incidence of PWID with that of men who have sex with men (MSM), the adjusted incidence rate ratio was five times higher in male PWID patients, and six times higher in female patients (5). A study that addressed almost 600 PWID with HIV in Bucharest identified a proportion of 28.5% of patients with TB (a proportion that kept increasing during the years of study); the mortality among these patients with TB was higher (6).

A study performed in Bucharest, 4th District TB Unit, by the same authors as the present study identified injection drug use as one of the factors associated with unfavourable TB treatment outcome in a cohort of HIV-infected patients treated for TB (7).

Against this backdrop, and considering the peculiarity of data published in Romania regarding this vulnerable and difficult-to-address group, we aimed to study the demographics, medical history, and treatment outcome peculiarities of PWID among HIV patients treated for TB in our unit and to compare them with those of non-PWID HIV–TB patients, considering that the results could help define this special vulnerable population; and by that we would be able to influence the future decisions regarding treatment options.

Materials and methods

This is a retrospective, observational, and nonrandomised study based on the information collected from the unique registry of patients treated for TB in the 4th District TB Unit, in Marius Nasta Institute of Pneumology, Bucharest, Romania (a unit where treatment is provided for persons with TB from one-sixth of the population living in Bucharest and nearby villages).

For realising this study, we searched in the registry of all TB patients for those with HIV during the years 2009–2018. We aimed to identify the persons who inject drugs (PWID), and to compare them with the patients with HIV–TB coinfections, but without drugs’ consumption. We explored demographic variables, as well as variables related to TB (diagnosis and treatment) or HIV infection (severity of immunodepression and the presence of antiretroviral treatment [ART]). Patients were divided into two lots, the injectable drug users (PWID), and the nonusers (non-PWID), and the differences regarding the variables noted were investigated. We included in the PWID group all patients injecting drugs, regardless of the substance injected. Most users were using heroin, ethnobotanical drugs (so called “legal drugs”), or an association of the two.

Collected data were stored in a Microsoft Office Excel database and the needed 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], Vienna, Austria). R provides a language and an environment for statistical computing. A descriptive analysis was performed; for the continuous variables the mean and standard deviations (SD) were calculated, whereas for the categorical variables the absolute and relative frequencies were computed. An interferential analysis was performed; for continuous variables bidirectional Welch tests were used for two independent samples, whereas for categorical variables...
bidirectional $\chi^2$ (chi-square) tests for two independent proportions were used; and Fisher’s exact test was used for two independent proportions and the G test of independence. The statistical significance was considered for $P < 0.05$.

**Results**

During the 10 years’ analysis, we identified 122 patients with TB–HIV coinfection (5.47% of all 2227 patients treated in our TB unit during this period). The mean age of these patients with TB–HIV coinfection was 36.41 ± 9.85 years, three-quarters of them were males, and 87.7% declared that they lived in an urban area (even if 23.8% had no stable home). Regarding TB localisation, 81.9% had lung involvement, and 19.7% had an association of both pulmonary and extrapulmonary involvement. The CD4 mean value was 203.94 ± 230.12 cells/mm$^3$ and 73.8% used ART during the TB treatment (Table 1).

After excluding 4 patients who were former drug users, the remaining 118 were divided into one lot for PWID (60 patients) and another one for those that had never used injectable drugs (non-PWID, 58 patients). In Figure 1, the annual number of patients with TB–HIV coinfection, PWID or non-PWID, can be observed.

In PWID, pulmonary TB was present in 51/60 patients, and extrapulmonary TB in 21/60, most frequently adenitis (13 cases), pleurisy (4 cases), and meningoencephalitis (3 cases). A total of 10 cases were disseminated military TB. A positive smear was present in 43/60 cases, and a positive culture in 52/60. Antibiogram was performed and its result was available in 47 cases, and six cases (10%) were MDR cases. Although the new cases had a higher proportion in the PWID group (80% vs 72.41%), treatment success (cured cases or treatment completed) was better in the non-PWID group (77.58% vs 51.66%). A high mortality is observed in the PWID group (30% vs 12%) (Figure 2).

The differences between the two lots are noted in Table 2. The following variables have a statistically significant difference: age ($P < 0.0001$), gender ($P = 0.0034$), presence of chronic hepatitis ($P < 0.0001$), CD4 number ($P = 0.0409$), ART ($P = 0.0075$), and evaluation at the end of the treatment ($P = 0.0373$).

**Discussion**

This study represents our first attempt to assess the population of drug users in our unit. Active drug users represent 49.18% of all patients with HIV–TB treated in the study years, and 2.69% of all patients treated in our unit, and thus this constitutes an important issue needing to be assessed. The annual number of patients who use injectable drugs kept rising in the years of the study (Figure 1). It is estimated that in Romania the prevalence of HIV among PWID is 15.9% (data from 2017 (8)), and thus the current study represents only one part of the problem of PWID. However, HIV condition is an important

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years), mean ± SD</td>
<td>36.41 ± 9.85</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (75.4)</td>
</tr>
<tr>
<td>Environment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>107 (87.7)</td>
</tr>
<tr>
<td>Homeless status, n (%)</td>
<td>29 (23.8)</td>
</tr>
<tr>
<td>TB, n (%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>100 (81.9)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>46 (37.7)</td>
</tr>
<tr>
<td>Associated</td>
<td>24 (19.7)</td>
</tr>
<tr>
<td>Mean CD4 value (cells/mm$^3$)</td>
<td>203.94 ± 230.12</td>
</tr>
<tr>
<td>Antiretroviral therapy, n (%)</td>
<td>90 (73.8)</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; TB, tuberculosis.

**Figure 1.** Annual number of patients with HIV–TB coinfection treated for TB in our unit. HIV, human immunodeficiency virus; TB, tuberculosis.
Figure 2. Treatment outcome in the two groups.

Table 2. Differences between PWID and non-PWID.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PWID/60</th>
<th>Non-PWID/58</th>
<th>Difference (CI 95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>33.05 ± 6.01</td>
<td>40.57 ± 11.34</td>
<td>−7.51 [−10.85 to −4.18]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>52 (86.66)</td>
<td>38 (65.51)</td>
<td>21.15 [5.80 to 36.50]</td>
<td>0.0034†</td>
</tr>
<tr>
<td>Male</td>
<td>7 (28.34)</td>
<td>12 (20.69)</td>
<td>7.65 [−0.07 to 0.23]</td>
<td>0.674</td>
</tr>
<tr>
<td>Homeless, n (%)</td>
<td>17 (28.34)</td>
<td>12 (20.69)</td>
<td>75.97 (N/A)</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Chronic hepatitis, n (%)</td>
<td>58 (96.66)</td>
<td>12 (20.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (35.00)</td>
<td>21 (36.21)</td>
<td>−1.21 [−18.49 to 16.07]</td>
<td>0.4455‡</td>
</tr>
<tr>
<td>CD4 (cells/mm³), mean ± SD</td>
<td>156.10 ± 204.56</td>
<td>260.86 ± 248.98</td>
<td>−104.76 [−205.10 to −4.42]</td>
<td>0.0409</td>
</tr>
<tr>
<td>ART, n (%)</td>
<td>39 (65.00)</td>
<td>49 (84.48)</td>
<td>−19.48 [−35.20 to −3.77]</td>
<td>0.0075†</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (35.00)</td>
<td>21 (36.21)</td>
<td>−1.21 [−18.49 to 16.07]</td>
<td>0.4455‡</td>
</tr>
<tr>
<td>Extrapulmonary case, n (%)</td>
<td>4 (6.67)</td>
<td>12 (20.00)</td>
<td>−13.33 (N/A)</td>
<td>0.0575‡</td>
</tr>
<tr>
<td>Adverse reactions, n (%)</td>
<td>23 (38.33)</td>
<td>29 (50.00)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (16.66)</td>
<td>6 (10.34)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Evaluation, n (%)</td>
<td>9 (15.0)</td>
<td>16 (27.58)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>18 (30.00)</td>
<td>7 (12.06)</td>
<td>−</td>
<td>0.0373§</td>
</tr>
<tr>
<td>Ab./lost</td>
<td>29 (50.00)</td>
<td>6 (10.34)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Treat. comp.</td>
<td>6 (10.34)</td>
<td>16 (27.58)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7 (12.06)</td>
<td>N/A</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>

Ab., abandonment; ART, antiretroviral therapy; lost, lost in follow-up; PWID, persons who inject drugs; SD, standard deviations.

*Welch t test.
†c² test.
‡Fisher’s exact test.
§G independence test.

risk factor for TB: given that the risk of TB among people living with HIV is 16–27 times higher (9), for this very reason, our study stopped at PWID living with HIV treated for TB. In our unit, the proportion of patients with HIV from among all patients treated was 5.47%, which is thrice the national proportion reported in 2019 and published in 2021 (1). This might be related to the proximity of the two greatest infectious disease centres in the country, to an intensified HIV testing, or maybe to a local outbreak. The use of injectable drugs became a problem related to HIV endemics in Romania, and especially in Bucharest from 2011 onwards (10–12). If, in 2010, 1.5% of all newly diagnosed HIV cases were attributed to injectable drug consumption, in 2013 the percentage had risen to 31% (13). A similar trend might be
observed in Figure 1, where the year 2012 can be observed as being a crucial year that serves as a turning point, in that commencing from this year onwards, most cases of HIV–TB have belonged to the PWID category (excepting 2017). Notably, the characteristics of patients identified with HIV–TB are the following: mostly male, young patients (Table 1), and patients at risk for both HIV infection and drug use. The later comparison between PWID and non-PWID proved that the PWID are younger and more frequently males (Table 2). Also, a worthy-of-mention aspect is the proportion of patients being treated with ART. Even if the recommendations are to treat with ART any HIV patient with TB diagnosis, only a proportion of 73.8% of patients are treated. This is related to a low compliance to ART treatment, but also can be explained by the long study period (as in the beginning of the 2010s access to ART was not that easy and PWID were not always included in a treatment programme – this assumption was tested in the present study and it confirmed that only 65% of PWID were treated, vs 84.48% of those not using drugs, \(P = 0.0075\)). The lower frequency of ART in the PWID is an extra-risk factor for these patients, as the delay of ART in HIV patients is related to poor outcome, as well as high complication and mortality rate (14). However, we should recognise that a chronic antiviral treatment in a noncompliant, less-motivated patient is a sure way to antiviral drug resistances, and all efforts should be made for an integrated service assessing all patients’ problems.

Also, a stringent issue regarding PWID is hepatitis C virus (HCV) coinfection. The data from the National Antidrug Agency revealed that, in 2019, 52% of all tested PWID were HIV-infected and 64% HCV-infected (15). A Romanian study from 2016 revealed that 80.8% of PWID have HIV–HCV coinfection, and in 26.9% of PWID cases there is a triple infection with HIV-HCV-hepatitis B virus (HBV) (16). This coinfection was often facilitated by drug injection, which explains the statistic difference between PWID and non-PWID regarding chronic hepatitis presence.

TB in HIV-infected persons represents a poor prognosis factor. This was also proved for PWID (17); diagnosis of TB was associated with high mortality rate in HIV-infected PWID. Mortality was also related in these patients with extrapulmonary TB and extensively drug resistant TB (17). In our patients, the main TB localisation in both PWID and non-PWID is pulmonary (81.9% in all patients, with no differences regarding the drug use). However, PWID have a more severe HIV infection (mean CD4: 156.10 ± 204.56 cells/mm\(^3\) vs 260.86 ± 248.98 cells/mm\(^3\), \(P = 0.0409\)) and it is estimated that TB forms are more severe. However, TB severity was not assessed in the current study. The lower CD4 number might be explained by the lower rate of ART use, but also the delay in the presentation of the PWID, which is more than double in the literature compared to the non-PWID (18). There are many reasons that explain this delay, from fear of narcotic withdrawal related to a possible hospitalisation, to stigma (19) or lack of health insurance.

The outcome of TB treatment represents an important finding of this study. The success of treatment (cured or treatment completed) is statistically lower in PWID (\(P = 0.0373\)), and also treatment outcome is worse in each evaluation category (Figure 2). A high mortality rate is observed in the PWID group (30% in PWID vs 12.06% in non-PWID). The first reason for all these is a poor adherence to treatment and care. Some possible explanations, namely lack of motivation, unstable lifestyle, alcohol use (20,21), and a possible way to maintain the retention in treatment, could be integrating TB–HIV care and substance use services (22,23).

An interesting issue is represented also by the adverse reactions declared during the TB treatment. Less adverse reactions are declared in the PWID group (marginal insignificance, \(P = 0.0575\)), even if it is expected that more severe patients, with more comorbidities and more substance use, would experience more frequent adverse reactions. We think that this is also related to the poor adherence to medical care, and also to treatment (both TB and ART).

This study confirms our previous study (7), which stated that the use of intravenous drugs is associated with a worse TB treatment outcome, but also comes to complete the full image of this vulnerable group. The problem of PWID is extremely important for TB specialists, as injecting drugs seems to be predictable for active TB in people living with HIV (24). Also, there are countries where TB prevalence in PWID was noticed to be extremely high in the last period (25), and thus it is expected that the proportion of PWID in the TB units would rise; having realistic expectations and knowing how to act in these conditions might introduce an important avenue of help in treating these patients. There are recommendations based on reviews regarding drug injecting and integrated HIV–TB care (23), but they should be individualised according to the local peculiarities. Studies in Romania concerning the HIV–TB problem are lacking; also, the interest in PWID is very low, even if in some parts of the country (such as Bucharest and surroundings) the number of PWID is high and continues to rise. Unfortunately, since TB is an air-transmitted disease, the problem of TB in PWID represents a social problem, which, left unattended, will continue to increase the numbers of the TB endemic in Romania (which has already been negatively influenced by the COVID-19 pandemic).

**Conclusion**

PWID are more often male, of younger age, and, in a very high proportion, HCV-infected. The ART is less frequent in this group and HIV infection has a higher severity (evaluated with...
CD4 value). TB treatment outcome is significantly poorer in this group, with a high mortality rate. Special attention should be paid to this vulnerable group by including programmes dedicated to increasing adherence to treatment and care. A problem that should not be neglected is that of drug addiction.

Acknowledgments

Not applicable.

Conflict of interest

The authors declare that there are no conflicts of interest.

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