

# Profile of Respiratory and Extra-Respiratory Tuberculosis in Patients Living with HIV in Dolj County between 2005-2015

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**ABSTRACT:** Introduction: Tuberculosis (TB) is the commonest and the deadliest opportunistic infection in patients living with HIV/ AIDS. Purpose: The paper aims to assess patients with and without TB-HIV coinfection in Dolj county registered in Regional and National database in order to identify risk factors for progression to active TB for immunodepressive patients. Material and method: We performed a retrospective descriptive study using records of 336 patients infected with HIV (PIH)-data from medical charts between 2005-2015 and we compared with the data for 1120 patients without HIV between 2005-2012. Results: 64,1% were females and 35,89% were males. Most cases were from rural areas (61,54%) most of them graduating primary (17,94%) and secondary school (48,71%). Most of them don't have a job (87%) and are supported by state with a monthly minimum income. Majority is born between 1980-1990 (64,1%), with predominance of Romanians (92.31%) compared to the Roma. Regarding all TB diagnoses (pulmonary and extrapulmonary) 117 had at least one episode of active TB. TB and HIV have been diagnosed almost at the same time in 25,64% cases. At the time of TB diagnosis 87% of patients had CD4+lymphocytes count <200cel/ml. We also noticed the absence of prophylaxis for TB in PIH, high incidence of hepatitis B among those with HIV/TB coinfection (34%). Conclusions: Active TB in patients with HIV infection is correlated with severe immunosuppression, poor education, and atypical clinical expression and radiological findings and more cases of extrapulmonary TB.

**KEYWORDS:** tuberculosis, HIV, pulmonary, lymphocytes

## Introduction

The dual infection between HIV and TB is known as “accursed duet”[1]. In the last 30 years, incidence of tuberculosis increased across the globe mostly due to increasing human immunodeficiency virus (HIV) incidence, low economic status of nations, migration and the appearance of resistant strains of *Mycobacterium tuberculosis*-MDR and XDR cases [2].

About 8-9 million persons are diagnosed with active TB every year and approximately two million people die of TB or its complications all around the world [3]. The two epidemics: HIV and TB act together like a syndemy that is also responsible for major economic costs around the world. As a form of early treatment and prevention it is necessary to screen for tuberculosis in HIV infected people and *vice-versa*.

Literature proves that of all the opportunistic infections for PIH, TB is the fist as incidence and the deadliest [2,3]. According to data published by WHO the risk of developing active TB is about 20-37 times higher among PIH especially in endemic countries with HIV and/or

TB compared to people without HIV (10% risk). Every year, about 25% of deaths are due to TB in PIH every year, especially in low and middle income states where TB is the leading cause of death for PIH [4].

Today, the value of the global incidence (new cases and relapses) of tuberculosis in our country is the highest in the European Union and one of the highest in the *World Health Organization* (WHO) European Region (5th place after Kazakhstan, Moldova, Georgia and Kyrgyzstan). Also, high rate of HIV cases for children infected in late 1980s and at the beginning of 1990s (>90% of the cases are F1 subtype) configured a unique cohort of patients infected with HIV in Romania. Six thousand cases of PIH are still alive. They are those that have a history of multiple therapeutic regimens of ART and are considered long term survivors.

In Romania, the majority of the population is considered as having latent infection with *M. tuberculosis*. In about 10% of cases this infection could progress to a form of active TB (pulmonary or extra-respiratory) more often in the first two years of exposure (6-24 months). The origin of extrapulmonary tuberculosis is usually in the hematogenous metastatic

outbreaks developed after primary infection period. Extra-respiratory TB diagnosis is difficult and is established excluding other pathological conditions by the physicians in specialties involved. The main factors that contributed to the increasing the number of extra-respiratory tuberculosis cases are the increased number of immunocompromised persons, aging and growing numbers of population. Extra-respiratory TB is more common in children than in adults [5].

HIV and *M. tuberculosis* amplify each other at cellular and molecular levels, where they disturb specific mechanisms of defense, leading to accelerated disease in PIH [6].

Object of many studies, the depletion of CD4 T cells from secondary lymphoid tissues, blood, and other sites in PIH leads to opportunistic infections such as TB and cytomegalovirus, hepatitis and more [7,8]. The loss of CD4 effector memory cells decreases immune control of latent infections and is responsible for the progression of latent to active TB along with other opportunistic infections [9].

Due to HIV infection the function of the remaining CD4 T cells is also affected. Studies prove that CD4 cells in PIH who had undetectable HIV in plasma after at least 1 year of ART presented defective IFN secretion after contact with *M. tuberculosis* purified protein derivative (PPD) [10].

The dual infection Tuberculosis and HIV often has atypical symptoms, especially in patients with advanced immunosuppression. This is why extra-pulmonary TB is more common in PIH compared to non-HIV/TB patients [4].

Fortunately, tuberculosis in HIV/AIDS is curable as in immunocompetent hosts [6].

## Material and Methods

We performed a retrospective descriptive study using records of 336 patients infected with HIV (PIH), analyzing data existing in medical charts between 2005-2015. Data were collected from medical charts of PIH still alive that are actively monitored and treated in Regional Center for Monitoring and Evaluation of HIV/AIDS in Craiova. We searched for demographics, associated comorbidities, clinical symptoms, immunologic evaluation for the moment of TB diagnose, TB type, TB related number of treatments, radiological aspect, if positive AFB (acid-fast bacilli) smears supported TB diagnosis and other possible factors that could influence progression of

tuberculosis form stage of latent infection to the stage of active. From 336 patient still alive 117 (34, 82%) had at least one episode of active TB that was treated and cured.

We analyzed patients registered with TB-HIV searching for risk factors in immunodepressed patients trying to establish a profile of the patient co-infected with HIV and TB. We focused on the data around the moment of TB diagnosis (+/- 6 months).

We collected detailed demographic data and also data regarding medical and therapeutic history and all data regarding the date of TB diagnosis (within a +/- 6 months period). Data regarding TB included: form of TB (pulmonary and extra-pulmonary or both), number of active TB episodes treated, clinical symptoms, radiological aspect, simultaneous diagnosis with tuberculosis, CD4 + lymphocytes count, HIV type before diagnosis, confirmed diagnosis by smears for AFB from different types of pathological products or confirmed diagnosis by histopathological examinations.

Sputum was examined for acid-fast bacilli (AFB) and also for other possible microorganisms. In cases of extra-pulmonary TB pathological tissue, secretions and fluids were sent for mycobacterial and histopathological exams. For lymph node tuberculosis the diagnosis was possible due to microbiological evidence of tuberculosis or histopathological examinations of removed lymph nodes. Pleural effusion was thoroughly examined for bio-chemical, microbiological and cytological data. In cases of meningitis CSF analysis was done to prove the etiology.

Important imaging results (chest X-ray, CT, RMN) for these patients were also noted.

We were also particularly interested to see culture results for *Mycobacterium tuberculosis*, phenotype sensitivity to antibiotics and presence of MDR resistance or XDR resistance to TB drugs.

We also searched for evidence of prophylaxis for TB in PIH examined.

Presence of other coinfections was also noted as all PIH examined have been tested for Hepatitis B and C, and for presence of *Toxoplasma* or *Cytomegalovirus* (both for Ig M and Ig G).

## Results

The study involved a total of 336 PIH all of them being confirmed at diagnosis by both ELISA and Western Blot tests. Out of these

117 (34,82%) were at least once treated for active TB.

TB cases were found mostly in women (75 cases), mostly in rural part of Dolj county (61,54%).

Most of the patients come from the cohort of people infected in the late 1980s. Distribution of cases by age groups shows that most PIH were born between 1980 and 1990-considered as part of the Romanian cohort of PIH, another 28,20% were born before 1980, and just 7,7% were born between 1990-2000.

60 cases were diagnosed as seropositive in the period 1990-2000, and the rest of 57 cases after 2000.

Majority of patients are unemployed (87%) and are supported by state with a monthly minimum income, others have different jobs like in constructions, accountants, farmers and more and 3 of them are students.

As specific to Romanian cohort of PIH most of them (69, 27%) were HIV infected by parenteral route, other 28% being infected after sexual contact. Only 1 of the PIH had a history of drug abuse. PIH born before 1980 had a higher rate of HIV infection through sexual contact.

We noticed predominance of Romanians (92,31%) compared to the Roma people.

As in literature the level of poor education for PIH is also high for this group: 48,71% finished secondary school, 17,94% finished primary school, and 23% finished high school. This is probably because of the fear for stigma rejection due to disease or just because most of them couldn't afford going to high school from countryside areas.

At the time of TB diagnosis 46,2% were underweight, other 43,5% had normal weight and 5,3% were overweight.

TB and HIV were almost simultaneous diagnosed (+/-6 months period) in 26,64% (30 cases). Just 35,89% of all TB cases have been confirmed by AFB smears and cultures or by histopathological exams of other tissue samples.

Most of the PIH with TB history had just one episode of active TB treated representing 61,54% of all cases examined, other 35,89% had two episodes of active TB treated and only three cases (2,564%) were registered with 3 episodes of active TB that needed therapy.

CD4 count under 200 cells/mm<sup>3</sup> at the moment of TB diagnosis was associate with 87,17% of the cases, some of them having less than 50 cells/mm<sup>3</sup> at the moment of TB

diagnosis. Other 7% had CD4 count value between 200-500 cells/mm<sup>3</sup> and only in 5% of the cases the CD4 count was more than 500cells/mm<sup>3</sup> at the time of TB diagnose.

We also looked for TB location and we have observed interesting data: 54 cases had just pulmonary TB (46,15%), 30 cases (25,64%) had pulmonary and extrapulmonary TB at the same time, the rest of the cases having just extrapulmonary TB diagnosis affecting lymph nodes, pleural effusion, peritoneal ascites TB, gastrointestinal TB, laryngitis TB, meningitis TB.

Symptoms were atypical as debut for TB. Cough not always with expectoration, low-grade fever with night sweats that were not influenced by other treatments, anorexia, or weight loss >10% of initial body weight, were the most common symptoms associate with pulmonary TB. AFB smears were positive for 28,20% of patients (microscopy and/or culture for M. Tuberculosis), for the rest pulmonary TB diagnosis was established according to clinical symptoms, radiological aspect, and other biological data. 8 cases presented MDR and 1 case presented XDR TB.

Atypical chest X-ray (CXR) findings are specific for altered immunity and for reactivation of primary TB infection in HIV-infected patients. Out of the CXRs examined patients with pulmonary evidence of tuberculosis 33% had only one side infiltrates, 35,89% had bilateral infiltrates and only 5% presented lung cavitation associated with higher CD4 counts. Miliary pattern and intra-thoracic lymphadenopathy were observed in 5 patients (13%).

Extra-respiratory TB involved 53% of all TB cases: intra-thoracic lymph nodes (13 cases) and peripheral lymph nodes (8 cases), pleural involvement was seen in 15 patients, followed by gastrointestinal TB (10 cases), 9 cases meningitis TB and 3 cases of bone and joint TB and other types of extra-respiratory TB. All of them had low CD4+counts (<200cells/ml). Most of them (78%) were also underweight at the moment of TB diagnosis. Half of them also associated pulmonary tuberculosis. Just 10 cases had been confirmed histopathologically or by AFB smears.

For lymph node tuberculosis the diagnosis was possible due to microbiological evidence of tuberculosis from discharged secretions of affected lymph nodes or histopathological examinations of removed lymph nodes. Pleural effusion was thoroughly examined for

bio-chemical, microbiological and cytological data. In cases of meningitis CSF analysis was done to prove the etiology. For patients with extra-pulmonary TB relevant biological samples were collected for both mycobacterial and histopathological exams.

As regarding to their multiple therapeutic regimen history of ART more than 64% (75 cases) of the cases had at least 5 therapeutic ART regimens changed, also almost 25% had 3-4 therapeutic ART regimens changed.

The presence of other co-infections was also noted: 48 cases (34%) had Hepatitis B evidence and 6 had Hepatitis C evidence. Ig G for Toxoplasmosis was also positive for 34% of the cases. Only 15 cases (12,82%) had evidence for cytomegalovirus. Another frequent infection was oral candidiasis observed in 64% of cases analyzed.

Only 20 of the 336 medical charts examined had received Isoniazid prophylactic therapy for TB in this period. None of the cases with TB examined for PIH had received prophylaxis for TB.

All TB cases for PIH received therapies (DOTS) according to national guidelines and WHO guidelines.

No data regarding mortality is available.

## Discussion

HIV related immunodepression among TB infected people is the greatest risk factor for progression to active TB. [11] Coinfection HIV/TB is associated with lower CD4 counts leading to progression of HIV to AIDS as also evidenced in our study. Research studies also support that CD4 counts are lower among HIV/TB coinfecting patients compared PIH without TB. Severe immune suppression is mostly found in patients with CD4 count lower than 200 cells/mm<sup>3</sup>. TB therapy has a positive influence on CD4 counts, and directly observed treatment for TB will prevent and even reverse possible MDR-TB occurrence. HIV-infected patients have a higher risk for TB mostly because of their affected capacity develop or sustain long-lasting protective immune responses [4,12,13].

Origin of extrapulmonary TB lies in hematogenous dissemination developed during TB primary infection. Evolution of TB can be in early state, before spontaneous healing of the primary TB infection, or later in lifetime when initial lesions can reactivate due to immunosuppressive factors, diseases or treatments.

PIH with latent TB have a 50-70% lifetime risk of developing active TB compared to a 10% risk in people without HIV [4].

In our study most cases were from rural areas (61,54%) most of them graduating primary (17,94%) and secondary school (48,71%). The most of them don't have a job (87%) and are supported by state with a monthly minimum income. Illiteracy and poverty could also influence the development of TB in PIH.

Majority of PIH is formed of those born between 1980-1990 (64,1%) as part of the Romanian unique cohort of PIH that have been infected with HIV by parenteral route, with predominance of Romanians (92.31%) compared to the Roma.

Regarding all TB diagnoses (pulmonary and extrapulmonary) 117 had at least one episode of active TB almost 64% of cases involving extra-respiratory forms of TB sometimes with atypical symptoms or CXR aspect.

Extrapulmonary TB is more common in coinfecting HIV/TB patients than in non-HIV/TB individuals, frequently associated with advanced immunosuppression [3].

As the CD4 count falls under 200 cells/mm<sup>3</sup>, PIH with pulmonary TB often have atypical CXR aspect, including pleural effusion, infiltrates nonspecific for TB interesting lower or middle lobes, mediastinal enlarged lymph nodes or a normal CXR [14,15].

TB and HIV have been diagnosed almost at the same time in 25,64% cases (30 cases) especially in the last 8 years due to intensified HIV testing for all TB cases.

WHO recommends screening for active TB in PIH, but there is no guidance for what is more significant to screen for. Studies applied for symptoms, chest X-ray and CD4 value. Cain et al. designed an algorithm for TB screening in PIH using three signs: cough and/or fever of any duration, or night sweats >3 weeks during the last month [16-19].

For smear-negative pulmonary TB, WHO emphasize clinical judgment associated with at least two sputum AFB staining and culture, HIV testing and chest X-ray. For extrapulmonary TB algorithm includes HIV testing, sputum smears, chest X-ray, clinical judgment, AFB staining for different pathological samples, and recommends immediate TB treatment for disseminated TB, TB meningitis, or TB-associated serositis [4,16-19].

In our study only 35,89% of all TB cases have been confirmed by AFB smears and cultures or by histopathological exams of other

tissue samples and most of the PIH had just one episode of active TB treated (61,54%), other 35,89% had two episodes of active TB that needed therapy mostly because their ineffective immune system and association with other infections.

We also noticed the complete absence of Isoniazid prophylaxis for TB in PIH diagnosed with TB and high incidence of hepatitis B among those with HIV/TB coinfection (34%).

*Patients without HIV diagnosed with extrarespiratory TB in Dolj county between 2005-2012*

We have compared our data presented above with data from a retrospective analysis of a number of 1120 cases of extra-respiratory tuberculosis from Dolj county area during 1st January 2005-31st December 2012 using the data entered in National Tuberculosis Register. Extra-respiratory tuberculosis represents for the studied period and area just 13.92% of all cases of tuberculosis, significant less than 53% presented for PIH.

As referring to demographic aspects 57.95% were men and 42.05% were women and most cases were from urban areas (60.18%).

New cases represented 89.91% of all cases.

The most frequent locations for tuberculosis involved pleura and peripheral lymph nodes. Just 12.77% of cases were confirmed histopathologically and 5.45% were confirmed by smears for AFB from different types of pathological products.

Symptoms included loss of weight (more than 10% of body weight), night sweats, cough, pain, tiredness, sometimes fever and chills, and also other symptoms specific to TB locations such as nausea, chest pain, abdominal pain, enlargement of peripheral or intra thoracic lymph nodes. Most of the cases patient received one or two antibiotic treatments but without response.

Chest X-rays were normal for more than half of cases with extra-respiratory TB. Other aspects included nonspecific opacities or fluid pleural collections but also widened mediastinum.

Of all patients 74.82% had completed tuberculosis treatment.

Diagnosis of some TB extra-respiratory locations was difficult because of lack of laboratory accessible techniques and was sustained on symptoms, lack of response to other treatments, and also on the biochemical and cytological characteristics of samples analyzed.

## Conclusions

Active TB in patients with HIV infection is a sign of progression to AIDS and is correlated with severe immunosuppression, poor education, atypical clinical expression and radiological findings, more cases of extrapulmonary TB and lack of prophylaxis treatment for TB especially for those with low CD4 count.

Physicians treating HIV-infected patients should early identify those at risk for active TB as to reduce the associated morbidity, considering multidrug-resistant and extremely drug-resistant TB that mounting around the world. Early diagnosis and treatment for TB in PIH are important and will reduce TB associated mortality. WHO also suggests to use of Xpert MTB/RIF test for PIH who have TB signs and symptoms.

Evidence based guidelines and multidisciplinary approaches must consider coinfection HIV/TB as together, not separate diseases, and are necessary stop the rapid worsening of the HIV-TB syndemic.

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