Original Paper

The Profile of the Patients with Double Infection HIV and TB in South West of Romania

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ABSTRACT: Background: Co-infection with human immunodeficiency virus (HIV) / tuberculosis (TB) raises important diagnostic and treatment problems as the lung is one of the target organs for HIV. Studies have shown that an HIV patient is 5-15 times more likely to switch from Koch's bacillus-infected status to active tuberculosis. Material and method: Retrospective study on 207 patients with HIV/TB coinfection in the Oltenia area registered in the Regional Center for Monitoring and Evaluation of HIV/AIDS infection in Craiova to define the profile of patients with double TB-HIV infection in southern Romania for cases registered between 2005-2015. Results: 53.14% of patients were females. Most cases were from rural areas (56.10%) Half of them are born between 1988 and 1990 but only 5% graduated university. 66.18% don't have a job and are supported by state with a monthly minimum income. 29.4% are smokers. More than 60% of cases had pulmonary TB and other 25% had concomitant pulmonary and extrapulmonary TB. TB and HIV have been diagnosed almost at the same time in 25% of cases. At the time of TB diagnosis 75% of patients had CD4+lymphocytes count <200cel/ml. We also noticed the absence of prophylaxis for TB in patients infected with HIV (PIH) and high incidence of hepatitis B (30.43%). Conclusions: Clinical expression, radiological and bacteriological aspects are often atypical in HIV/TB coinfected patients. The lack of TB prophylaxis and TB endemicity in the studied area may justify the large number of TB cases in HIV-infected patients.

KEYWORDS: Pulmonary tuberculosis, HIV, co-infection, immunosuppression.

Introduction

Human immunodeficiency virus (HIV)/ tuberculosis (TB) co-infection is a huge burden on health systems.

Every year, several million people worldwide become infected with tuberculosis, among other things, due to the increasing incidence of HIV infection. Since 1993, pulmonary TB in adults has been a criterion for classifying the case as AIDS.

TB can occur at any stage during HIV infection, being negatively influenced by the degree of immunosuppression and positively influenced by effective antiretroviral therapy (ART).

For patients infected with HIV (PIH), the risk of developing active TB increases by about 10% per year. Active tuberculosis defines the entry into stage IV of HIV infection (AIDS disease) [1,2].

HIV is a determining factor in tuberculosis epidemics by increasing the number of patients with latent TB and active disease accompanied by an increase in TB-related deaths in a population of immunodeficient individuals [3].

HIV co-infection affects the ability of the immune response to control TB and increases the likelihood of developing active TB in the early period of *M. tuberculosis* infection [4].

The degree of TB infectivity varies greatly for patients with TB-HIV co-infection and is correlated with sputum positivity, pulmonary cavity, laryngeal TB, cough frequency, sputum volume and consistency.

HIV can affect TB transmission by altering these determinants [5-9].

Observational and retrospective studies have suggested that TB accelerates disease progression for PIH [10-12] and increases mortality and incidence of opportunistic infections that define AIDS for HIV/TB coinfection patients compared to HIV-infected patients without active TB in similar groups for the number of CD4 cells [12].

Other studies [13-15] suggest that the average duration of TB infectivity may be significantly affected by access to health services and the time of diagnosis [16].

If PIHs have access to care and treatment, with periodic evaluation for the active detection of TB, the average duration of TB infectivity is shorter than that of TB in people without HIV.

According to a 2010 ECDC report, most cases of HIV/TB co-infection (85.6%) in Europe have been reported in the Eastern region of the continent, where the percentage of HIV-infected patients diagnosed with tuberculosis has risen from 3.4% in 2008 to 5.5% in 2010, totaling 16,000 cases.

Romania has a special cohort of PIH made mostly of children born between 1988 and 1990 parenterally infected with HIV and is a country with a low prevalence of HIV/AIDS of 0.04%.

The data published by the National Commission for the Fight against AIDS (CNLAS) at the end of 2013 present TB in Romania as the most frequent opportunistic infection associated with HIV infection.

Also, Romania is considered a country with increased endemicity for tuberculosis. HIV testing of patients diagnosed with TB is mandatory in Romania but in 2013 only about 60% of them knew their HIV status.

A WHO monitoring in 2016 on cases in 2014 in Romania reports 15,906 patients in treatment for tuberculosis (regardless of form) of which 69% were investigated for HIV status (3% positive for HIV infection) [17,18].

Material and Method

We have analyzed retrospective data of 207 patients with HIV/TB coinfection in the Oltenia area registered in Regional Center for Monitoring and Evaluation of HIV/AIDS in Craiova.

These cases for cases were registered between 2005 and 2015, from four counties: Dolj, Olt, Mehedinţi and Gorj.

The register is located at the Hospital for Infectious Diseases and Pneumology Victor Babes Craiova.

Our analysis included demographic, immunological, clinical, radiological and bacteriological data at the time of TB diagnosis, associated infections and TB prophylaxis measures in HIV-infected patients and treatment of both diseases.

Our aim was to identify a profile of the patient with double HIV/TB infection at PIH in southern Romania.

The diagnosis of TB was established based on clinical symptoms, radiological examination, confirmed by specific acid fast bacilli (AFB) sputum examinations on microscopy and culture and/or anatomo-pathological examination with evidence of tuberculous granuloma for extrapulmonary TB.

The diagnosis of HIV infection or AIDS disease was established by serological confirmations-Elisa and Western-Blot tests.

We included patients regardless of the order of diagnosis of the disease: TB preceded HIV/AIDS, was followed by HIV/AIDS, or the detection of the two diseases was performed in the same time.

Being a retrospective study, we obtained an exception from the Ethical Board of the Hospital, since only demographical patient data was collected.

Results

Females represented 53.14% of cases, with a slight predominance of those in rural areas (56.04%).

Most patients were Romanian, with only 8.21% of patients being rroma.

Most cases were from Dolj (40.1%) and Olt (40.5%) counties.

Almost 50% of the patients in the group were born between 1988 and 1990 (part of the Romanian cohort of PIHs with a parenteral HIV transmission at that time).

At the time of TB diagnosis, 35.71% of patients were between 11 and 20 years old and another 33.33% were between 21-30 years old.

In the analyzed group there were other PIHs born between 1942-2002, who have various forms of contracting HIV (sexual, vertical or unknown).

More than half of the patients (55%) were unmarried.

About 42% graduated from high school and only 5.31% graduated university.

The incomes of these patients were minimal: 66.18% were socially assisted and had a minimal income and only 14% were employed.

Of our study lot, 29.4% were smokers and 2.41% admitted alcohol consumption.

Only 41 cases (20%) of TB were detected by symptoms (passive detection), the rest were identified by early screening during monthly visits to the Regional Center for Monitoring and Evaluation of HIV/AIDS Craiova.

Most patients diagnosed with TB identified the presence of TB-associated symptoms (cough, sweating, loss of appetite, weight loss, physical asthenia) two weeks (35.26%) and three weeks (28.02%) before the diagnosis of tuberculosis.

Patients presented only some of these symptoms, rarely associated with all of them or associated with hemoptysis.

There were only 6 patients (2.89%) who had symptoms for more than 8 weeks.

At the time of diagnosis of TB, 47.82% of PIH in this group were in the category of C3 disease (some by concomitant diagnosis of double infection) and other 28.50% were category B3, a category with severe immunosuppression.

Another 31 PIHs were part of category B2 (14.97%), a category of patients with CD4 lymphocyte count <500 cells/μl (Table 1).

Table 1. Repartition according to initial HIV/AIDS status at the time of a diagnosis of TB in HIV/TB patients.

HIV status (prior to TB)	Number of patients	Percentage of total
B1	1	0.43%
B2	31	14.97%
B3	59	28.50%
C1	3	1.45%
C2	14	6.76%
C3	99	47.82%

Only 39% of the HIV/TB group had at the time of TB diagnosis an average viremia below 0.5 mil copies/ml. Data on viremia were missing in one third of the analyzed group.

The mean CD4 lymphocyte count at the time of TB diagnosis was analyzed for 146 HIV/TB patients for whom data were available.

For three out of 10 patients the mean CD4 lymphocyte value was <100 cells/μl.

Only 5% had previous contact with a person diagnosed with TB and had TB chemoprophylaxis.

The new TB cases represented 79.22% of the group, and another 16.4% subsequently presented a recurrence of TB in the analyzed period.

There were 6 patients with MDR (2.90%) and one patient with XDR who needed to continue treatment for up to 18 months.

TB cases were distributed as follows: 60% of cases were pulmonary TB, another 25.12% of cases had concomitant pulmonary and extrapulmonary TB (affecting lymph node, central nervous system (CNS), pleural, digestive, bone).

The rest of the cases with extrarespiratory TB affected similar organs: 11 cases with lymph node TB (6 cases with mediastinal localization), 7 cases with CNS TB, 8 cases with pleural TB and 5 cases with TB of digestive tract (Tables 2 and 3).

Table 2. Distribution of HIV / TB cases with lung damage.

Concomitant TB	Total	Percentage
P	124	59.9%
P, DIG	8	3.86%
P, GGL	14	6.75%
P, GGL, CNS	2	0.96%
P, OS	1	0.48%
P, PL	10	4.80%
P, PL, DIG	2	0.96%
P, PL, PERIC	1	0.48%
P, PL, CNS	1	0.48%
P, CNS	12	5.79%
P, CNS, DIG	1	0.48%

Table 3. Distribution of HIV / TB cases without lung damage.

TB location	Total	Percentage
DIG	5	2.41%
GGL	11	5.31%
PL	8	3.87%
CNS	7	3.38%

P-pulmonary, CNS-central nervous system, PL-pleural, DIG-digestive, GGL-ganglia, OS-osseous, PERIC-pericardiac

In half of the cases with TB with changes on the chest X-ray, we predominantly encountered infiltrative-nodular type and of infiltrative-ulcerated type radiographic changes.

Military pattern was described in 32 cases (15.2%).

Cavity changes were described in another 44 patients (21.25%) often concomitant with other changes described before.

Patients in this group recognized certain symptoms associated with TB: 91.8% presented cough, 82.1% had weight loss, and hemoptysis was identified among 5.3% of those with HIV/TB.

The mentioned symptomatology was present especially for those who had CD4 lymphocyte counts <300 cells/μl at the time of TB diagnosis.

Patients who accused cough and weight loss had pulmonary radiological changes predominate of nodular infiltrative type (15-20%) simultaneously or not with other changes, of which more numerous seem to be those of infiltrative-ulcerated type (approximately 10%).

The most common pulmonary radiological changes for those with hemoptysis were infiltrative-ulcerated and cavitary changes in 27.3% of HIV/TB patients.

83 cases (40.1%) had sputum AFB negative on microscopy and culture.

They were patients with extrarespiratory TB or minimal changes on lung radiography or

military TB. Of these, 56 cases (27%) had symptoms for 2-3 weeks.

Another 47 people with HIV/TB infection were negative on AFB microscopy but positive on the specific culture.

Many PIHs were diagnosed early with TB due to permanent screening for TB symptoms.

These are, therefore, those with sputum with a low number of bacilli (<5000 bacilli/ml), which can be diagnosed by culture for *M. tuberculosis* on Lowenstein-Jensen solid medium.

Another 75 patients with HIV/TB (36.2%) were positive for AFB on both microscopy and culture (M+C+), cases that required immediate hospitalization and the start of antibacterial treatment under direct observation (DOT).

After two months of treatment only 3 patients had positive microscopy and culture.

Sensitivity to antibacterial medication identified seven cases with drug resistance (3.38%). Of these, 5 were recurrences, 2 cases were the first antibacterial treatment. Only one case showed extended chemoresistance (XDR).

71.5% of patients received concomitant treatments for HIV and TB (antibacterial treatment was introduced before or after starting ART in a maximum of 4 weeks), while 26.6% had successive treatments.

During the period analyzed in our study, 19 patients (9.17%) died of TB during treatment.

The administration of antituberculous treatment to PIH with TB was done taking into account the recommendations of the National Guidelines, daily, for at least 12 months; except for children, for whom the duration of treatment is 6 months.

The duration of treatment was on average 11.41 months (0-18). 89.85% underwent treatment for 12 months.

The clinical evolution and drug tolerance of concomitantly administered drugs was good for most of the patients we had data on (only 27 patients).

86% of patients (178 PIH) received treatment according to the recommendations, they were evaluated as cured patients with completed treatment.

We also analyzed concomitant diseases in HIV/TB patients for which these patients required treatment or regular monitoring.

We notice that approximately 3 out of 4 patients (73.91%) have malnutrition and 4 out of 10 patients (40.58%) also presented with Candidiasis (included all possible locations for candidiasis).

A number of 48 patients have various neurological conditions at the same time; another 15 patients have digestive disorders.

The distribution of all the diseases analyzed is found in tables 4 and 5.

Table 4. Distribution of concomitant diseases in the HIV / TB group.

Other diseases	Number	Percentage	Other diseases	Number	Percentage
Cardiac	7	3.38%	Neurological	48	23.18%
Surgical	12	5.79%	Psychiatric	10	4.8%
Diabetes	9	4.34%	Renal	6	2.89%
Digestive	15	7.24%	Syphilis	2	0.96%
Hepatitis D	1	0.48%	Acute weight loss	8	3.86%
Lipodystrophy	7	3.38%	Candidosis	84	40.58%
Neoplasm	3	1.45%	Malnutrition	153	73.91%

Table 5. Distribution of Hepatitis, Toxoplasma and CMV Cases in HIV / TB Patients.

Illness	Number	Percentage
Hepatitis B	63	30.43%
Hepatitis C	8	3.86%
Toxoplasma	104	50.24%
Cytomegalovirus	33	15.94%

All HIV/AIDS patients from the records of the Craiova Regional Center for Monitoring and Evaluation of HIV/AIDS Infection were investigated for concomitant infections with Toxoplasma, Cytomegalovirus (CMV), Hepatitis B and C.

Approximately half of the patients analyzed had a Toxoplasma infection (50.24%) and 63 patients (30.43%) had Hepatitis B. 22.70% of the HIV/TB group received chemoprophylaxis for Pneumocystis carinii.

Discussions

Low CD4 lymphocyte counts are associated with more severe systemic symptoms [19].

In all stages of HIV infection, pulmonary TB is the most common form of TB [20].

PIH with TB frequently have subacute systemic and respiratory symptoms, including fever (88%), weight loss (79%), cough (79%),

and diarrhea, with a mean duration of 6 weeks [21].

In our study those with low values of CD4 <300 cells/μl presented cough and weight loss had and also pulmonary radiological changes of nodular infiltrative type simultaneously or not with other changes, of which more numerous seem to be those of infiltrative-ulcerated type.

Also, 15% presented millary TB.

In other studies chest Xrays for PIH with CD4 of>350 cells/μl and pulmonary TB frequently show upper lobe infiltrates, cavities, and/or pleural damage, similar to aspects of reactivated pulmonary TB in HIV-infected patients. [21-23]

Atypical radiological changes are associated with deficient immunity in primary reactivations and infections with TB in PIH [24].

For PIH with CD4 <200 cells/μl radiological changes are atypical including pleural fluid collection, infiltrative changes located in the lower or middle lobe, mediastinal lymphadenopathy, interstitial nodules or even normal radiography [20,25,26].

Chest radiography is used for screening and monitoring, but has no specificity, and the definitive diagnosis of TB disease requires a microbiological method.

Patients with HIV infection may have a paucibacillary sputum, so the sensitivity and specificity of the microscopy for AFB is low, and the culture can take up to 8 weeks to confirm a diagnosis [27].

Using a combination of symptoms to monitor TB appears to be effective and practical in excluding active TB in HIV-infected patients.

Cough, fever or night sweats lasting more than 3 weeks had a sensitivity and specificity of 93%, respectively 36% in various studies.

In addition, the absence of symptoms such as fever, night sweats, weight loss and cough had a negative predictive value of 97.7% to exclude active TB [28-30].

PIHs with active TB have fewer or no TB-specific symptoms, and cough-only screening will not detect all patients [31].

For pulmonary TB diagnosis, the revised case definitions emphasize clinical reasoning along with the use of at least two sputum samples for AFB, HIV test, chest radiography, and sputum culture, if possible [32].

For extrapulmonary tuberculosis, revised case definitions and diagnostic algorithms for TB emphasize HIV testing, microscopic examination of sputum, chest radiography, clinical reasoning, sample testing for different

fluids and biopsies from the affected site for AFB detection and immediate initiation of TB treatment for disseminated TB, TB meningitis, pleurisy or bacillary pericarditis [32-34].

In our study we had positive microscopy for AFB results in 20.7% of PIH with TB and bacteriological confirmation of TB by culture in approximately 60% of the analyzed samples.

The yield of microscopic sputum results decreases with reduced CD4 count.

In PIH, sputum microscopy detects 22-43% of those with active TB disease.

With the high number of negative results for BAAR on sputum microscopy, culture is essential for the confirmation of tuberculosis and for drug sensitivity testing in PIH [33,34].

Sensitivity to antibacterial medication was performed using also rapid biomolecular tests, such as Xpert MTB/RIF and identified drug resistance in 3.38% of the group with only one case of extended chemoresistance (XDR).

According to the recommendations of the national HIV/TB treatment guidelines the reporting of cases with TB multiple locations is made first for pulmonary TB if the patient has concomitant pulmonary and extrarespiratory TB.

In the case of TB coinfection (any location) associated with HIV/AIDS, treatment will be instituted by the pulmonologist in collaboration with the infectious disease physician who treats the HIV patient according to the recommendations of the guidelines [35].

The high number of extrarespiratory TB diagnosis in PIH from our study has been more often associated with low CD4 lymphocyte counts and associated comorbidities such as malnutrition, the presence of candidiasis, and Toxoplasma and Hepatitis B infections.

22.70% of the HIV/TB group received chemoprophylaxis for PCP but only 5% received TB chemoprophylaxis, although WHO (2016) recommends prophylactic treatment with Isoniazid for at least 6 months in PIH, especially in poor countries with a high incidence of tuberculosis, regardless of degree of immunosuppression.

The risk of developing active TB disease remains twice as high in HIV-positive people, even if the number of CD4+T cells is within the normal range and they receive ART [36-38].

We had simultaneously diagnosis for TB and HIV in 1 of 3 cases due to the success of screening program in our country.

This is why 71.5% of patients received concomitant treatments for HIV and TB (antibacterial treatment was introduced before or

after starting ART in a maximum of 4 weeks) and only 19 PIH (9.17%) died of TB during treatment in the same period.

There are overlaps in the toxicity of antiretroviral, antituberculosis medication and cotrimoxazole therapy, and therefore vigilance is required in monitoring adverse reactions.

Conclusions

Poverty, standard of living and education maintain an increased frequency of TB in poor communities.

Active TB in patients with HIV infection is a sign of disease progression to AIDS and is correlated with severe immunosuppression and a significant plasma viral load, low income, atypical radiological aspects, several cases of extrapulmonary TB.

In these patients, the early antituberculosis treatment is imperative.

There is also a need to for chemoprophylaxis with Izoniazid in those infected with HIV with a low number of CD4 lymphocytes.

The success of national prevention programs for those with HIV and TB is noteworthy.

Furthermore, all patients newly diagnosed with tuberculosis (new case or recurrence) should be encouraged to accept HIV testing.

Acknowledgements

Conflict of interests

None to declare.

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