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CLINICAL EPIDEMIOLOGY OF HIV-TUBERCULOSIS COINFECTION

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Abstract. HIV screening of tuberculosis patients has been a common practice in Romania, since1998. Compared to the national statistics, the Galaţi county has similar prevalence of HIV/AIDS but higher prevalence of TB. The study is a retrospective analytic study assessing the epidemiology and clinical characteristics of HIV tuberculosis coinfection in Galaţi during 1998-2008. A number of 98 cases of HIV/TB were recorded out of the total 324 HIV cases. The average annual incidence of tuberculosis was over 30 times higher in HIV positive patients (5.2%) than in HIV negative ones and it displayed a tendency of increasing. HIV was acquired vertically (11%), sexually (19%) or horizontally during early childhood (70%). 44% of the patients had tuberculosis as the primary AIDS defining event, while 26.5% developed tuberculosis after HIV diagnosis. 45% of the cases had extra-pulmonary tuberculosis involvement and correlated with lower CD4 count, older age and mortality rate. 50% had microbiological criteria for tuberculosis diagnosis. The rate of microbiological evidence was lower in the primary pulmonary tuberculosis than in the secondary one and correlated with younger age. 27% of the patients received antiretroviral treatment (ARV) at the time of tuberculosis diagnosis and 2 developed tuberculosis as immune reconstruction event. Out of 98 HIV/ tuberculosis patients, 67 were cured, 11 relapsed and 21 died. The risk of death is related to the severity of the immunosuppression at the time of tuberculosis diagnosis (median CD4 count of 219 in survivors vs. 42 in the case of deceased patients, $p< 0.001$). The risk factors for death in HIV/ tuberculosis co-infection are low CD4, extra-pulmonary involvement and older age. A new strategy for the improvement of tuberculosis diagnosis in HIV patients should allow earlier medical involvement in order to decrease the HIV- tuberculosis mortality in Galaţi - Romania.
Keywords: HIV, tuberculosis, prevalence, diagnosis, death

Background

TTuberculosis (TB) is the most frequent co-infection among HIV infected patients worldwide. TB is responsible for the death of one out of every three people with HIV/AIDS worldwide. People who are HIV-positive and infected with TB are 30 times more likely to develop active TB than people who are HIV-negative.

Mycobacterium tuberculosis enhances HIV replication and might accelerate the natural progression of the HIV infection.

The use of antiretroviral therapy (ART) may significantly influence the clinical presentation, management and prognosis for HIV patients co-infected with *Mycobacterium tuberculosis* and the incidence of this disease. The optimal management of TB in the HIV-infected patient is not well defined, because of the interactions between HIV and TB therapies, the overlapping toxicity of these treatments, and the role of prophylaxis against TB.

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The best time to initiate ART and TB therapy in relation to each other remains controversial. There may be major regional diversities in clinical issues related to TB.

HIV screening of tuberculosis patients has been a common practice in Romania, since1998. Compared to the national statistics, the Galați county has higher prevalence of HIV/AIDS (50/100000 vs. 20/100000) and also of TB (163.7/100000 vs. 110.1/100000).

Objectives

The objectives of the study are:

- Assessment of the epidemiology of HIV tuberculosis co-infection (HIV/TB) in the Infectious Diseases Hospital Galați – Romania.
- Recognition of the clinical and evaluative peculiarities of TB in HIV patients.

Materials and methods

This is a retrospective analytic study based on medical reports on HIV/TB co-infected patients, followed up for at least 12 months after TB diagnosis in the Infectious Diseases Hospital Galați, during 1998-2008.

The diagnosis of tuberculosis was supported by clinical, epidemiological, imagistic (radiology, computed tomography, echography) and/or laboratory criteria (bacteriologic exam - microscopy, culture, cytological and biochemical exam of pleural effusion, CSF). Considering the potential of atypical tuberculosis in severe immunosuppressed HIV infected patients, diagnosis through therapeutic proof (ex juvantibus) was accepted for a few of the patients.

The end point of the anti-tuberculosis treatment was death, abandonment or finalization of the complete regimen, of 6 – 18 months, depending on the severity and the anatomic site of tuberculosis.

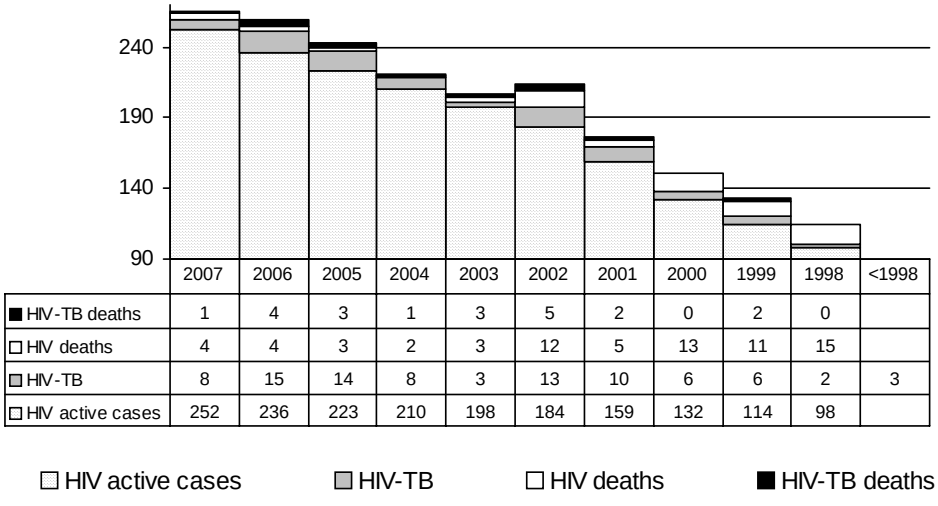
Microsoft EXCEL - Statistical Analysis Tool Pack software was used for statistical analysis.

Results and discussion

The peculiarity of the Romanian HIV epidemic is the development of two patterns: the adults' pattern, with slow but constant arising and the pediatric pattern. The pediatric epidemic is characterized by predominance of patients born between 1987 and 1990, most of them non-vertically infected in the early childhood. Nowadays, the pediatric HIV infected patients have grown up to adult age.

HIV mortality and AIDS defining diseases have been significantly reduced in Romania after 1998, due to the availability of ARV. Nevertheless, TB is the most frequent HIV associated disease in Romania, as criteria for HIV testing, but also as AIDS defining disease after HIV diagnosis. The average annual incidence of TB was over 30 times higher in the HIV positive patients (5.2%) from Galați than in the HIV negative ones.

A number of 98 HIV/TB co-infected patients from the 324 follow-up HIV cases were recorded in the Infectious Diseases Hospital, in the past 10 years (figure 1).



	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	<1998
HIV-TB deaths	1	4	3	1	3	5	2	0	2	0	
HIV deaths	4	4	3	2	3	12	5	13	11	15	
HIV-TB	8	15	14	8	3	13	10	6	6	2	3
HIV active cases	252	236	223	210	198	184	159	132	114	98	

Figure 1. HIV-TB co-infection in Infectious Diseases Hospital Galați

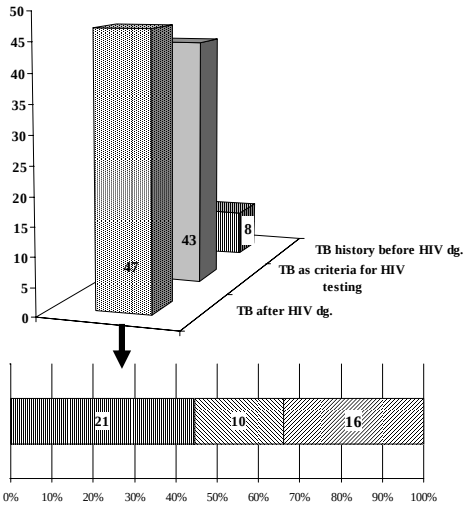


Figure 2. Sequence of TB, HIV and ART

History of TB before 1998 was found in 8% of the HIV cases. During 1998 – 2008, tuberculosis was the primary AIDS defining event in 44% of the cases or was developed after HIV diagnosis in 26.5%. TB as HIV testing criteria was recorded in 13.5% of all patients and in 44% of the HIV-TB co-infections (figure 2).

The general characteristics of patients with HIV-TB co-infection are: sex ratio M/F 1.32, rural area (54%), median age 12 [1; 57] upon HIV diagnosis and 14 years old [2; 57] upon TB diagnosis (table I).

biological criteria in 50% of the cases. The rate of microbiological evidence is lower in primary TB than in secondary pulmonary TB (p<0,001; OR= 120.75) and is related to younger age.

Calcifications of the spleen were associated to late evolution of TB (p<0,001; CI [3.93; 18.63]; OR=8.56).

The pulmonary TB involves 75.5%. Pulmonary primary TB was related to younger age (p<0,001; CI [10-17]). Atypical pulmonary TB and extrapulmonary involvement was the main characteristic

Sex ratio (Male / Female)	1.32
Aria (Urban / Rural)	1.17
Median age at time of HIV diagnosis	12 [1; 57]
Median age at time of TB diagnosis	14 [2; 57]
Immunity (CD4 Ly) on TB diagnosis (82/98 available data)	Med 177/mm^3 CI [186; 278]
Viral load on TB diagnosis (44/98 available data)	Med 161000 c/mm^3 CI [79500 c/ml; 293075 c/ml]

Table I. Characteristics of HIV-TB co-infected patients

The transmission ways of the HIV infection were: 11% vertically, 19% sexually or 70% horizontally during early childhood. The median age of HIV diagnosis suggests long term survival of the pediatric cases.

The median age upon TB diagnosis points out an immune decline through the natural HIV history, but also a possible immune vulnerability around the age of puberty. The median immunity corresponding to TB diagnosis is 177/mm^3 and it expresses severe immunosuppression.

The diagnosis of TB was supported by micro-

of most the patients. The frequency of single or multiple extra-pulmonary TB involvement was 45% (Table II).

Compared to the single pulmonary involvement, the extra-pulmonary HIV involvement correlated with lower CD4 count (median 77/uL vs. 233/uL, p<0.001), older age (median 16.5 vs. 14, p=0.002) and mortality rate (p<0.001).

Antiretroviral treatment (ARV) at the time of TB diagnosis was received by 27% of the patients and correlated with ARV failure (8/26), immune reconstruction (2/26) or undefined reasons. Anti-

Pulmonary involvement: 74 patients	
A. Acute miliary: 9	
B. Primary tuberculosis: 22	Classic: 13 Atypical: 9
C. Secondary tuberculosis: 43	Classic ulcerous-caseosis-cavitary: 9 Atypical (pneumonia, multilobar infiltrates, bronchial involvement, lower or middle lobe): 34
Single or multiple extra-pulmonary involvement: 46 patients	
Osteoarthritis (Spondyles L1-2): 1	
Meningoencephalitis: 7	
Adenitis	Peripheral: 9 Abdominal (mesenteric): 9 Mediastinal: 22
Serositis	Pleural effusion: 9 Polzserositis: 6
Pulmonary and extra-pulmonary involvement: 34 patients	

Table II. Clinical patterns of TB on HIV infected patients

TB treatment was associated with ARV in 55% of the cases, either PI (13%) or INNRT (32%) (Table III).

ARV status upon TB diagnosis	ARV management after TB diagnosis	Evolution	Observations
65: Naive	46: begin ARV after median time 3 months [1 month; 6 months]	7 deaths 57 favorable 1 failure TB	NNRTI: • 35 EFV • 11 NVP
7: Experienced but no current ARV (non-compliant)	3: change ARV regimen 4: remain free of ARV	3 deaths 1 favorable 3 failure TB	Non-compliant
26: under ARV • 10 PI regimen • 16 NNRTI regimen	6: remain on PI regimen 4: change PI ◊NNRTI 13: remain on NNRTI regimen	11 deaths 9 favorable 7 failure TB	3 Rifabutin 6 failure ARV

Table III. TB framework for ARVT

The most frequent secondary reactions under anti-tuberculosis treatment were liver toxicity 42.85%, allergies (19.38%) and renal toxicity (4%).

A progression of the immunologic suppression after TB was recorded in 41% of the patients. Out of the 98 HIV/TB patients, 67 were cured, 11 relapsed and 21 died. The risk of death correlates to the severity of immunosuppression at the time of TB diagnosis (median CD4 count of 219 in survivors vs. 42 in the case of deceased patients, p< 0.001) (Table IV).

Length of treatment	Median: 6 months [1; 18]
Evolution	65 cured 11 relapses 21 deaths
Liver toxicity	42/98 • 10 - III/IV • 18 - II • 14 - I
Renal toxicity	4/98
Allergic reactions	19/98

Table IV. HIV framework on TB treatment

Mortality was similar on TB negative (22%) and TB (all types) positive (21.5%) HIV patients, even if 29.2% of the deaths were related to TB.

Conclusions

1. HIV/TB co-infection in Galați has high incidence, especially in pediatric cohort.
2. Adults' HIV/TB co-infection has delayed diagnosis and severe prognostic.

3. The risk factors for death in HIV/TB co-infection are low CD4 levels, extra-pulmonary involvements and older age.
4. A new strategy for improvement of TB diagnosis in HIV patients should allow earlier medical involvement in order to decrease the HIV-TB mortality in Galați - Romania.

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