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Clinical and Sociodemographic Risk Factors for Tuberculosis in Human Immunodeficiency Virus Infected Patients

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ABSTRACT

To identify clinical and sociodemographic factors associated with the risk of tuberculosis in HIV-infected patients. A case-control study in a cohort of hiv-infected patients. Cases: patients coinfected with HIV and pulmonary or extrapulmonary tuberculosis. Controls: no clinical tuberculosis and PPD negative, matched for age and sex. Primary data were obtained from medical records and personal interviews. We identified 47 cases and 94 controls. The main risk factors identified were: underweight (malnutrition) (BMI ≤ 18.49), abscence of antiretroviral therapy, CD4 + cells count ≤ 199 cells/mm^3, RNA HIV-1 viral load ≥ 100,000 copies/mL. Tuberculosis is associated to multiple risk factors in HIV infected patients, clinical factors are more important that sociodemographic ones. CD4+ cells count < 200 cells/μL, malnutrition IMC < 18.9 and RNA HIV-1 viral load > 100,000 copies/mL are associated with tuberculosis in HIV infected patients.

Keywords: HIV, Tuberculosis Risk Factors, Clinical, Sociodemographic

1. INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, is considered one of the most common opportunistic infections in individuals infected with Human Immunodeficiency Virus (HIV) and is the leading cause of death which is estimated at 13% of individuals with Acquired Immunodeficiency Syndrome (AIDS) worldwide (Blanc *et al*., 2011; Alvarez-Uria *et al*., 2013; Kyeyune *et al*., 2010).

Global estimates suggest that one in three people living with HIV are infected with TB and 40-60% of these will develop active Tb (Kaplan *et al*., 2009). The risk of developing active TB in HIV patients is 5-15% per year, due to reactivation of latent infection which generally depends of the inmunocompromised degree (Fox *et al*., 2013).

Mexico recorded a prevalence of HIV infection of 0.3% in the population aged 15-49 years old, ranked third in the Americas, with an estimated incidence of 267 per 100,000 habitants (Bautista-Arredondo *et al*., 2013; De Luca *et al*., 2010). Coinfection HIV/Tb varies between 4 and 9% in the different Mexico states (Zenteno-Cuevas *et al*., 2011). The mortality rate associated with HIV reported by the Mexican Social Security Institute (IMSS) in 2009 was 3.35 per 100,000 patients (Vazquez-Martinez *et al*., 2011).

Factors traditionally associated with acquisition of infection, disease development and mortality from *M. Tuberculosis* are complex. Factors most frequently found are: poverty, malnutrition, overcrowding, lack of ventilation and lighting in homes, alcohol, smoking and other drugs, pregnancy, corticosteroids use, lack of access to merg services and presence of other associated conditions such as diabetes (Gomes *et al*., 2013). Household contacts with TB infected merg also a known and risk factor for development tuberculosis, especially in endemic areas (Fox *et al*., 2013). HIV infection has joined the long list of risk factors and confers increased risk for active Tb (Gomes *et al*., 2013).

HIV has facilitated the re-emergence of TB in over three decades and has also helped to change the clinical

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and epidemiological spectrum of it, leading to the mergente of new risk factors, higher rates of relapse and mortality as well as a high percentage of extrapulmonary clinical forms (Sterling *et al*., 2010).

The aim of this study was to identify demographic and clinical factors that are associated with risk of tuberculosis in HIV-infected patients treated at the Hospital de Infectologia "La Raza" National Medical Center, IMSS.

2. MATERIALS AND METHODS

A case-control study was conducted from March 1 to June 30, 2012, in a cohort of 700 patients infected with HIV, diagnosed by ELISA and confirmed by Western blot, treated at the Hospital de Infectologia "La Raza" National Medical Center, Mexico City. We included 47 patients aged ≥ 16 years, diagnosed with pulmonary or extrapulmonary TB, they were tested by smear, culture, histopathology or PCR and in whom the symptoms, physical signs, diagnostic aids and therapeutic response suggested the existence of Tb with initial negative bacteriological results. 94 controls were recruited, two per case, matched for age and sex (± 5 years) with no clinical evidence, microbiological or molecular of Tb and tuberculin skin test (PPD) negative. PPD test was performed using 0.1 mL of purified protein derivative of tuberculin of 2.0 IU mL^{-1}, given intradermally on the forearm by the Mantoux method and measured 72 h after application. The positive cutoff for this test was considered as induration ≥ 5 mm. We excluded patients who could not complete the questionnaire and/or had a history of non-tuberculous mycobacterial infection. Among the potential controls 3 patients were removed, for having tested positive to PPD.

Demographic, social, economic, illicit drug use, alcohol and smoking were obtained through a questionnaire administered to the patient during a personal interview, in that moment, PPD application was made, for the presence of latent TB, to controls. Sociodemographic factors were composed of the following variables: Sex, age, occupation, education level, socioeconomic status (SES AMAI index 10×6), marital status and county of birth, place of residence and stay in high-risk sites. High-risk demographic entity of Tb was considered those states where the incidence of TB is higher than 16.7 per 100,000 population (by reference to the national incidence of TB in 2009).

Degree of marginalization for municipality of birth was scored according to published by the National Population Council (CONAPO), in count II Population and Housing 2005 National Survey of Occupation and Employment (ENCE) 2005 (fourth quarter) and consists of a summary measure to differentiate states and municipalities as the overall impact of the deficiencies that affect the population as a result of lack of access to education, residence in inadequate housing, the perception of insufficient monetary income and those related to the residence in small towns.

Host clinical factors considered for the study were: living with tuberculosis patients, contact with chronic coughers, nutritional status, smoking, alcohol, illicit drug use, use of Highly Active Antiretroviral Therapy (HAART), CD4+ cells count and HIV-1 RNA viral load.

Frequencies were obtained; we verified the type of distribution by the Kolmogorov-Smirnov test. Continuous variables were analyzed with getting normal distribution mean and standard deviation and as median and interquartile range for different distribution than normal. In nominal or ordinal qualitative variables frequencies and percentages were obtained using SPSS version 15.0.

Bivariate analysis was performed with chi square test. Odds Ratio (OR) with confidence intervals 95% was calculated to measure the effect of each risk factor. To adjust for the effects of potential confounders, we used logistic regression models $p \leq 0.05$ were considered significant, it was calculated using STATA statistical software version 11.1.

2.1. Ethical

The study was approved by the Local Committee for Health Research 35021 Hospital de Infectologia "La Raza" National Medical Center, with corporate registration number R-2010-35021-3. Writed informed consent was obtained from all participants for the implementation of PPD.

3. RESULTS

The study cohort consisted of 700 HIV-infected adult patients aged 16 years or older who were receiving ART between March 1st to 30 June 2011.

Table 1. Description of HIV-Tb cases (n = 47)

Tuberculosis localitation	No.	(%)
Extrapulmonary	20	42.5
Disseminated	14	29.8
Pulmonary	13	27.7
Extrapulmonary TB (Localization) (n = 20) *		
Meningeal	10	50.0
Lymph node	9	45.0
Bone	1	5.0

*Extrapulmonary TB cases, HIV: Human Immunodeficiency Virus, Tb: Tuberculosis

Table 2. Socio-demographic variables

Variable	ORp	$CI_{95\%}$	p*
Schooling			
superior education	Ref	-	-
Medial superior education	0.85	0.36-2.00	0.712
Basic education	0.86	0.33-2.22	0.766
Actividad laboral			
Managers, professional and administrative activities	Ref	-	-
Education workers/art/entertainment/sports and technical	1.64	0.53-5.06	0.392
Artisans and industry workers/employees/trade and services personals	1.81	0.67-4.85	0.24
Heavy and mobile machinery operators/laborers/scrutiny	2.64	0.80-8.70	0.111
Do not work	2.2	0.68-7.13	0.189
Marital status			
Bachelor	Ref	-	-
Married	1.61	0.67-3.88	0.283
Widowed/divorced/separated	4.46	0.64-31.03	0.131
Socioeconomic level			
High	Ref	-	-
Medium	1.25	0.59-2.65	0.554
Low	1.28	0.40-4.06	0.672
Tuberculosis Incidence ¶ (State of birth)			
Low incidence (≤ 16.7)	Ref	-	-
High incidence (> 16.7)	1.67	0.62-4.49	0.308
Marginalization Degree			
Low	Ref	-	-
Medium/ High	3.03	0.88-10.43	0.078
Working in nursing homes			
No	Ref	-	-
Yes	2	0.12-31.97	0.624

ORp: Paired odds ratio, *Chi square test, Ref: Reference, ¶ Rate of tuberculosis per 100,000 Population

Table 3. Clinical variables

Variable	ORp	CI95%	p*
Contact with a patient with pulmonary tuberculosis			
Negative	Ref	-	-
Positive	1.75	0.57-5.42	0.332
Contact with people with chronic cough			
Negative	Ref	-	-
Positive	2.19	0.58-8.36	0.249
Body mass index (BMI) ¤	0.74	0.64-0.86	<0.01
Body mass indez (BMI)			
Low weight	3.69	1.14-11.97	0.03
Normal weight	Ref	-	-
Overweight / obesity	0.28	0.09-0.88	0.03
Antiretroviral treatment (ARVT)			
Yes	Ref	-	-
No	3.87	1.83-8.19	< 0.01
CD4+ T lymphocytes Ψ §	0.46	0.32-0.65	< 0.01
CD4+ T lymphocytes			
≤ 199 cells/mm^3	38.64	4.03-370.51	< 0.01
200 – 499 cells/ mm^3	2.02	0.22-18.29	0.53
> 500 cells/ mm^3	Ref	-	-
Viral load (HIV-1) Ψ §	1.29	1.13-1.48	< 0.01
Viral load (HIV-1)			
< 10,000 copies/ml	Ref	-	-
10,000 – 100,000 copies/ml	2.09	0.48-9.13	0.324
>100,000 copies/ml	9.74	3.12-30.38	< 0.01
Viral load (HIV-1)			
Undetectable (< 40 copies/ml)	Ref	-	-
Detectable (≥ 40 copies/ml)	4.89	1.64-14.54	<0.01

ORp: Paired odds ratio, *Chi square test, Ref: Reference, ¤ Media with standard deviation, Ψ Mediana with interquartile range, § Analysis with elimination of outliers (r Pearson)

Table 4. Clinical risk factors with largest Association for the occurrence of tuberculosis in HIV patients

Variable	ORp	$CI_{95\%}$	p
Body mass index (BMI) *	0.69	0.57 0.82	< 0.01
CD4+ *	0.25	0.13-0.47	< 0.01
Viral load *	1.39	1.17-1.67	< 0.01

Conditional logistic regression model, * Continuous variables

Table 5. Association between addictive substances consumption and occurrence of tuberculosis

Variable	RORp	$CI_{95\%}$	p*
Tobacco use			
No	Ref	-	-
Yes	1.04	0.51-2.13	0.903
Smoking			
Never smoking	Ref	-	-
Use to Smoke	1.39	0.65-2.94	0.395
Current smoking	0.46	0.16-1.36	0.162
Intensity of smoking (cigarettes/day) (n=28 cases y 55 controls)			
Mild smoker (< 5)	Ref	-	-
Moderate smoker (6-10)	1	0.09-11.03	1
Severe smoker (≥ 11)	1.26	0.25-6.360	0.782
Alcoholic beverages consumption			
No	Ref	-	-
Yes	1.05	0.48-2.33	0.894
Alcoholism			
No	Ref	-	-
Use to drink	0.89	0.32-2.47	0.831
Current drinker	1.14	0.49-2.67	0.756
Drug use			
No	Ref	-	-
Yes	0.83	0.29-2.34	0.732

ORp: Paired odds ratio, *Chi square test, Ref: Reference

A total of 47 of 700 patients (6.71%) had active pulmonary or extrapulmonary TB disease. The most frequent location was extrapulmonary with 42.6% (20 cases), followed by disseminated with the 29.8% (14 cases) and pulmonary with the 27.7% (13 cases); of the total of extrapulmonar cases, 50% were meningeal (10 cases), 45% lymph node TB (9 cases) and 5% bones and joints (1 case) (**Table 1**).

TB patients tended to be younger, 26 to 35 years of age (44.7%) and higher proportions of male (97.9%). The type of work (heavy and mobile machinery operators, laborers and security guards), marital status (widowed, divorced or separated) and low socio-economic level presented ORp = 2.64(95% CI: 0.80 - 8.70); ORp = 4.46 (95% CI: 0.64-7.13) and ORp = 1.28 (95% CI: 0.40-4.06) respectively.

Greater proportions of TB were originated in a high TB incidence States (ORp = 1.67, (95% CI: 0.62 -4.49) and marginalized regions ORp = 3.03 (95% CI: 0.88-10.43) (**Table 2**).

The clinical factors associated with increased risk were: low body mass index (BMI ≤ 18.49) ORp = 3.69 (95 CI 1.14-11.97%); history of contact with a patient with pulmonary tuberculosis ORp = 1.75, (95% CI: 0.57-5.42); and contact with people with chronic cough ORp = 2.19, (95% CI: 0.58-8.36).

The lacking of ARV-Therapy increased the risk for developing TB almost 4 times ORp = 3.87, (95% CI: 1.8-8.19), patients with 200 or lower CD4 counts had an ORp = 38.64, (95% CI: 4.03-370.51) and the HIV-1 RNA viral load >100,000 copies/mL conferred risk of ORp = 9.74, (95% CI: 3.12-30.38). Detectable viral load (≤ 40 copies/mL) has an ORp = 4.89, (95% CI: 1.64-14.54) (**Table 3**).

In multivariate analysis only lower CD4 count (ORp = 4.0(CI95% 2.13-7.69), p<0.01), detectable viral load (ORp = 1.39 (CI95% 1.17-1.67), p>0.01) and lower body mass index (ORp = 1.45 (CI95% 1.22-1.76). p< 0.01), were related with screening acceptance. Statistical significance was assumed for p-values ≤ 0.01 (**Table 4**).

4. DISCUSSION

Tuberculosis is a disease caused by M. tuberculosis; there are several factors that are associated with its development and presentation. TB disease can occur at any stage of HIV disease and its manifestations depend largely on the level of immunosuppression.

Prevalence of TB/HIV-coinfected patients was 6.1% in the institution studied. Maximum patients in our study were in the age group of 26-35 years (44.7%) and majority (97.9%) were males. Descriptive analysis showed that TB patients were more likely to be immunosuppressed and live in particular geographical regions like Baja California, Guerrero, Veracruz, Tabasco, Chiapas and Oaxaca, were has 67% more risk of Tb, less than that reported by (Zhou *et al*., 2009) in the Asia-Pacific region, where the risk was 3 times more. On the other hand high grades of marginalization have 3 times more risk of developing Tb in comparison to the low grade.

Our Findings showed that lower CD4 (<200/mm^3), lower BMI and detectable viral load had more probability to develop TB confection. The mean CD4 + lymphocyte difference was statistically significant with p value of 0.01.

BMI could indirectly describe human immunity function, which influence the progress of the disease. In many publications before, TB- HIV patients have BMI significantly lower than TB or HIV alone. Moreover, lower BMI could become strong predictor to HIV patient's mortality. In our results each unit of BIM increased confers 35% more protection for not developing TB, result consistent with Hanrahan *et al*., 2010 who noted that overweight and obesity are associated with reduction in the risk of developing TB; they showed that BMI < 17.0 represents 3.8 more risk of having Tb.

Most of the subjects (42.6%) in our study coursed with extrapulmonary TB. While pulmonary TB is a common presentation in HIV negative cases, it was present in only 27.7% of HIV-TB coinfected cases in our study. Disseminated TB involving both pulmonary and extrapulmonary sites was also frequent (29.8%) in this study population, contrary to what was reported by (Girardi *et al*., 2012) where 80% were pulmonary location. On the other hand the 2012 WHO reported similar data, which describes 60% of extrapulmonary tb in HIV patients.

Schooling was not related as a risk factor to develop TB in our population, contrary to the data of (Miranda *et al*., 2009), who describes 3 times more risk in developing TB in people with ≤ 3 years of education.

In relation to employment, patients who work as heavy equipment operators, drivers, workers of construction as pawns and vigilant, although it was not significant, have tendencies almost 3 times more risk as opposed to those who engage in activities managerial or professional. This is something new in our study because the labor activity as a risk factor for Tb only has been studied worldwide in free HIV health workers and miners (Khayyam *et al*., 2010).

No association was found between consumption of addictive substances such as alcohol and tobacco, probably due to the small number of patients. There is evidence showed in a study carried out in 2 rural areas China (Wang and Shen, 2009) where smoking was found to be associated in 93% of the patients with TB disease; as well, a study in the South of India 21, reporting 2 times more risk of TB in alcoholic beverages consumers.(**Table 5**).

Patients without ART have higher risk (ORp 3.8) to develop TB. Consistent with other studies, (Girardi *et al*., 2000; Tabarsi *et al*., 2012) find that using ART, with 2 or 3 drugs, has a protective effect (RR = 0.16 and 0.08 respectively) in relation to those who did not use any scheme or used monotherapy.

Tabarsi *et al*. (2012), showed protection through the use of art (P <0.001). Another cohort study conducted in Europe and North America 25, in cities with high incidence of Tb (20 cases per 100,000 population), shows that use of art is a protective factor (RR = 0.87), only when ART start with high CD4 count.

5. CONCLUSION

In our study, CD4 + lymphocyte count was found strongly associated with the development of Tb, with counts < 200 cells/mm3 (ORp = 38.6); being higher and consistent with the report by (Antonucci *et al*., 1995), in a multicenter cohort study in 23 hospitals in Italy, where the risk was almost 5 times higher in patients with less than 200 cells/mm^3. In addition, (Hanrahan *et al*., 2010), in another cohort study reported 14 times more risk in HIV-infected population.

HIV-1 RNA viral load was found strongly associated with TB development (ORp = 9.7), mainly with >100,000 copies/mL, consistent with the cohort of South Africa held by (Wang and Shen, 2009), who reports a risk of almost 4 times more when de viral load was >5,000 copies/mL.

The strengths of our study are based in the analysis of socio-demographic and clinical risk factors exclusively in infected HIV patients in Mexico. In addition, there are few studies that involve variables such as TB incidence and marginalization degree of as risk factors.

Our study have problems with precision, we obtained wide confidence intervals on variables of interest, mostly because the small sample size. Matching and conditional logistic regression model controlled the validity. So it is a study that has internal validity and therefore we can infer our results could be used in other groups of HIV infected patients.

These results highlight the need for effective monitoring procedures in AIDS patients and the continuous training of health personnel to ensure data collection, complete and accurate:

- Declaration of conflict of interest
- No conflicts of interest

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