Original Article

Human immunodeficiency virus infection amongst newly diagnosed tuberculosis patients and their clinico-radiological profile: A prospective study from Western India

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Abstract

Background: Since time immemorial tuberculosis (TB) has been and continues to be one of the most significant infections causing human disease. In tropical countries, TB remains a leading cause of death. Human immunodeficiency virus (HIV) epidemic continues to fuel this global TB epidemic. The rapid growth of the HIV epidemic in many countries has resulted in an equally dramatic rise in the estimated number of new TB cases, which present therefore the integration of HIV and TB testing at the primary level is need of the hour. **Methods:** A prospective study was conducted on newly diagnosed, untreated TB patients aged 15-45 year and patients were screened for HIV infection. Clinico-radiological spectrum of TB among HIV seropositive and seronegative patients was evaluated. **Results:** Out of a total of 307 patients screened, 17 (5.54%) were found to be HIV seropositive. Seroprevalence was found significantly ($P < 0.01$, χ^2 9.301) more common in 26-35 year age group and higher in Extrapulmonary TB (EPTB) patients than that in pulmonary TB (PTB) patients (9.90% vs 3.4%). Fever was the most common presenting symptom for TB in HIV seropositive patients. On examination pallor (58.82% vs. 15.86%), oral ulcer (35.3% vs. 0.35%) was found more common and on chest X-ray mid-lower zone involvement and mediastinal lymphadenopathy were more common in HIV seropositive patients. **Conclusion:** HIV seropositivity rates among newly diagnosed TB patients aged 15-45 year was 5.54 percent. The presentation of TB was more often atypical among these patients. Thus, an integrated model of TB and HIV at primary healthcare service delivery is an efficient use of resources that would address the two very important co-epidemics and thereby result in better management.

Keywords: EPTB (Extra Pulmonary TB), HIV, HIV TB co-infection, primary health care, PTB (Pulmonary TB)

Introduction

Human immunodeficiency virus (HIV) continues to fuel the global tuberculosis (TB) epidemic. The estimated TB incidence in India is about 27 lakhs. TB remains the leading cause of death among people infected with HIV, accounting for around one in three acquired immunodeficiency syndrome (AIDS)-related deaths. In 2017, an estimated 10.0 million [9.0-11.1 million] people had active TB, approximately 9% were living with HIV. It is estimated that 49% of people living with HIV and TB are unaware of their coinfection and are therefore not

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receiving care.[1,2] In the developing countries, more than 75% of TB patients are in the economically productive age group of 15-45 years with a very frequent association of TB and HIV and the varied clinico-radiological characteristics of TB depending on the degree of immune-suppression tend to pose diagnostic difficulties. HIV co-infection among TB was nearly 50,000 cases leading to an HIV co-infection rate of 3.4%.[3] Also, there is very little information on HIV seropositivity among TB patients from western India, so it is necessary to know the seroprevalence of HIV in TB patients. In line with international guidelines, India too has adopted an integrated model at the primary healthcare level to provide HIV and TB services by the primary healthcare physician at the same center.

So, we conducted the study to determine the prevalence of HIV infection among newly diagnosed TB patients and compare the clinico-radiological spectrum of TB among HIV seropositive and seronegative patients.

Material and Methods

A prospective study was conducted in the tertiary care center in Western India over a period of 1 year after approval by institutional ethics committee. A total of 307 newly diagnosed, untreated cases of pulmonary TB (PTB) and extrapulmonary pulmonary TB (EPTB) between age 15 and 45 years, who agreed to be part of study were enrolled for the study. All patients who were on any immunosuppressive drugs or known case of any immunosuppressive disease including HIV infection/acquired immunodeficiency syndrome (AIDS) at time of presentation were excluded from the study. PTB suspect is subjected for two sputum examinations, using the Ziehl–Neelsen staining technique. All the PTB patients were subjected to a standard chest radiograph P.A. view and other X-ray projections were indicated. All patients had tuberculin skin test and they were noted and any atypical findings were noted.[4] If required chest computed tomography (CT) scan was also done. Diagnosis of TB lymphadenitis was based on fine-needle aspiration cytology (FNAC), biopsy, cytopathological examination, and/or microbiological evidence of TB. Tubercular pleural effusion, meningitis, pericarditis were diagnosed on clinical history and biochemical, microbiological, and cytological characteristics, along with a response to anti-tubercular treatment. Abdominal TB was diagnosed based on clinical features, ascitic fluid evaluation, and ultrasonography findings or abdominal CT findings suggestive of tubercular pathology along with response to anti-tubercular treatment. DOTS (Directly observed treatment, short-course) treatment card was maintained in which socio-demographic information, contact number, unique identity number of patient (NIKSHAY ID), disease information, smear results, weight of patient, treatment information, HIV testing results, counseling and, DOTS provider, etc., was maintained.[5] All the patients were screened for HIV after counseling and written consent was obtained. Serum sample were collected and assayed for antibodies against HIV according to NACO (National Aids Control Organization) guidelines where samples were screened for HIV using a screening rapid test (HIV Tridot, J. Mitra and Co., India) and was confirmed by fourth-generation enzyme-linked immunosorbent assay (ELISA) (J. Mitra and Co.).[6]

Data management and statistical analysis

Editing of data was done after each interview and in the evening of the same day coding was done to simplify the process of data entry. The data was entered in MS Excel 2007 and the database created in statistical package for the social sciences (SPSS) 16.0 for Windows. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis using Shapiro–Wilk test. Results are expressed as mean ± SD, or median (25^{th}–75^{th} percentile), depending on the number and percentage. The Kruskal–Wallis test was used for those variables that were not normally distributed and further comparisons were done using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test. Spearman's correlation was also used to check correlation between various variables like CD 4 count, extent of disease, and duration of illness. For all statistical tests, a *P* value less than 0.05 was taken to indicate a significant difference. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed while preparing this report.

Results

There were 550 cases of patients aged 15 to 45 years diagnosed as a new case of TB in 1 year, 307 patients were willing to participate in the study. In this study, mean age for the study group was 29.24 ± 8.76 years. Mean age for HIV positive patients was 35.23 ± 5.0 years as compared to 28.89 ± 8.79 years seen in HIV negative patients. Out of 307 patients screened, 17 (5.54%) were found to be seropositive [Table 1]. HIV seroprevalence is found significantly (P <.01, χ^2 9.301) more common in age group 26-35 year but no significant correlation was seen with the sex of the patients. More males were co-infected with HIV (6.82%) than females (2.3%). No statistically significant (P >.05) co-relation was found between HIV-TB co-infection and sex of patient. Most common occupational group in TB patients was laborer 35.83% in which 4.5% were found HIV seropositive. In HIV seropositive group, 35.29% (n = 6) patients were truck drivers compared to 5.52% in HIV negative group, this was the most common occupation among the TB-HIV co-infected.

Table 1: Distribution of tuberculosis patients according to age and type of tuberculosis and HIV serostatus

Age Group (In Years)	Pulmonary TB	Extrapulmonary TB	Total
15-25	83 (0)	41 (1)	124 (1)
26-35	69 (4)	46 (7)	115 (11)
36-45	54 (3)	14 (2)	68 (5)
Total	206 (7)	101 (10)	307 (17)

*Number in parenthesis show HIV seropositive patients. HIV: Human immunodeficiency virus; TB: tuberculosis

In HIV seronegative group, 65.17% (n = 189) patients had PTB, 31.38% (n = 91) had EPTB, and 3.45% (n = 10) had mixed TB. As compared to seronegative group, EPTB (58.82%) and mixed TB (11.77%) were found significantly more common in HIV–TB co-infected group ($P < .05$, $\chi^2 = 5.480$). A total of 3.4% seroprevalence was seen in PTB patients and 9.90% in EPTB patients [Table 1].

Cough was the most common presenting symptom in HIV seronegative group (69.65%) followed by fever and anorexia (64.82% and 42.41%, respectively); while fever was most common presenting symptom in seropositive patients (94.12%) followed by anorexia (64.70%) [Figure 1]. On examination pallor (58.82% vs. 15.86%), oral ulcer (35.3% vs. 0.35%) was found more commonly in seropositive patients. Sputum smear for acid-fast bacilli (AFB) and Mantoux test positivity were found significantly ($P < 0.01$) less in HIV seropositive patients when compared to seronegative group. In chest radiology, upper zone were more commonly found to be involved (55.78% vs 14.28%) in HIV seronegative patients as compared to seropositive patients. Atypical presentation like mid-lower lung zone involvement (15.07% vs 28.57%) were found more commonly in HIV seropositive patients. No HIV-TB co-infected patient was found to have cavitary lesion on chest X-ray compared to 41.71% of patients in seronegative group. In HIV seropositive patients, 64.71% (n = 11) had lymphadenopathy in which 3 had peripheral lymphadenopathy (cervical, axillary or inguinal), 3 had abdominal lymphadenopathy, 2 had both peripheral and abdominal lymphadenopathy while 3 had hilar lymphadenopathy. Two (22.22%) patients had pleural effusion and 2 had tubercular meningitis. Hilar lymphadenopathy on chest radiology was found significantly ($P < .05$) more common in HIV-TB co-infected patients than HIV seronegative TB patients [Table 2]. In HIV seropositive patients, CD4 count ranged from 14 to 298 cells per microliter with mean CD4 count of 86.00 ± 55.50. Though there was no correlation when CD4 counts were correlated with extent of disease ($r = 0.24$, $P < 0.05$) and duration of symptoms ($r = 0.3$, $P < 0.05$).

Table 2: Comparison of various variables between HIV seropositive and HIV seronegative patients in newly diagnosed tuberculosis patients

	HIV Seronegative *n*=270	HIV Seropositive *n*=17
Age	28.89 ± 8.79	35.23 + 5.05
%Males	70.69	88.24
Occupation		
Farmer	4.83	0
Labourer	36.21	5 (29.41)
Service	13.79	3 (17.65)
Truck driver	5.52	6 (35.29)
Housewife	20.4	2 (11.76)
Student	19.31	0
Other/unemployed	0.00	1 (5.88)
Type of Tuberculosis		
Pulmonary	189 (65.17)	5 (29.41)
Extrapulmonary	91 (31.38)	10 (58.82)
Mixed	10 (3.45)	2 (11.77)
Lymphadenopathy	56 (19.31)	11 (64.71)
Mantoux <10 mm	65 (22.42)	13 (76.47)
Chest radiology involvement		
Upper zone involvement	111 (55.78)	1 (14.28)
Mid and lower zone involvement	30 (15.07)	2 (28.57)
Whole lung involvement	52 (26.13)	2 (28.57)
Chest radiology findings		
Exudative infiltrates	77 (38.69)	3 (42.86)
Cavitatory lesion	83 (41.71)	0
Miliary pattern	10 (5.02)	1 (14.29)
Interstitial pattern	5 (2.51)	1 (14.29)
Hydropneumothorax	9 (4.52)	0
Hilar lymphadenopathy	15 (7.54)	3 (42.86)

HIV: Human immunodeficiency virus

Discussion

In our country, 2.14 (1.59–2.84) million people are estimated to be living with HIV infection which in third-largest number of people living with HIV/AIDS (PLHIV) in any country in the world. Among the states, Manipur has shown the highest estimated adult HIV prevalence (1.15%), followed by Mizoram (0.80%), Nagaland (0.78%), Andhra Pradesh and Telangana (0.66%), Karnataka (0.45%), and Goa (0.40%). The states of Punjab, Odisha, Rajasthan, and Madhya Pradesh have an estimated 50,000 – 1 lakh PLHIV each and together account for another 12% of PLHIV. These states, despite low HIV prevalence, have large number of PLHIV due to the large population size.[7,8]

As per WHO's Global TB Report of 2019, among all TB cases, 8.6% were people living with HIV, though only 5% of TB patients are HIV infected in India. In the present study, 5.54% HIV seroprevalence was found in TB patients [Table 1]. In 2018, an estimated 0.8 million TB cases were attributed to HIV infection. Additional 251 000 deaths (range, 223 000–281 000) among HIV positive people has been attributed to TB.[2] Prevalence of HIV seropositivity varies in different studies ranging from 0.5% to 20.39% [Table 3].

According to NACO's 2018 annual report, long-distance truckers and single male migrants constitute a significant proportion of clients of sex workers and these sex workers are the primary drivers of HIV epidemic in India which was shown in our study too.[6]

In our study higher seroprevalence was seen in EPTB patients than in PTB patients (9.90% vs 3.4%) corresponding results were seen in the study by Thanasekaran *et al.*[20] and Purohit *et al.*[10] The comparatively lesser number of PTB cases in HIV seropositive patients in our study were may be due to referral bias as only severely ill TB are referred to our center as it is a tertiary care center. Another reason could be the low mean CD4 counts and thus reduced Th1 response in HIV seropositive group, which is responsible for severe immunosuppression and a greater number of EPTB. Similar results were seen in the study by Sharma SK *et al.*[21] Though in a large data from antiretroviral treatment (ART)

Table 3: Depicts a comparison of HIV seropositivity in TB patients in India

Author	Place of Study	Year of Study	TB Patients	HIV Positive cases (%)
Mohanty *et al.*[9]	Mumbai	1989-94	3878	260 (6.7)
Purohit *et al.*[10]	Ajmer	1993-95	2448	18 (0.7)
Banavaliker *et al.*[11]	Delhi	1994-95	1002	5 (0.5)
Gupta PR *et al.*[12]	Udaipur	1995-96	520	40 (7.7)
Kumar *et al.*[13]	New Delhi	1997-2000	301	42 (14)
Ramachandran *et al.*[14]	Tamil Nadu	1997-98	2361	111 (4.7)
Mandal *et al.*[15]	Varanasi	1999	393	26 (6.6)
Tripathy *et al.*[16]	Pune	1995-2000	2800	571 (20.39)
Sharma *et al.*[17]	New Delhi	2000-2002	555	52 (9.4)
Sharma VY *et al.*[18]	Ahmadabad	2006	200	11 (5.5)
Sharma P *et al.*[19]	New Delhi	2014-2015	227	0
Present study	Rajasthan	2017-2018	307	17 (5.54)

HIV: Human immunodeficiency virus; TB: tuberculosis

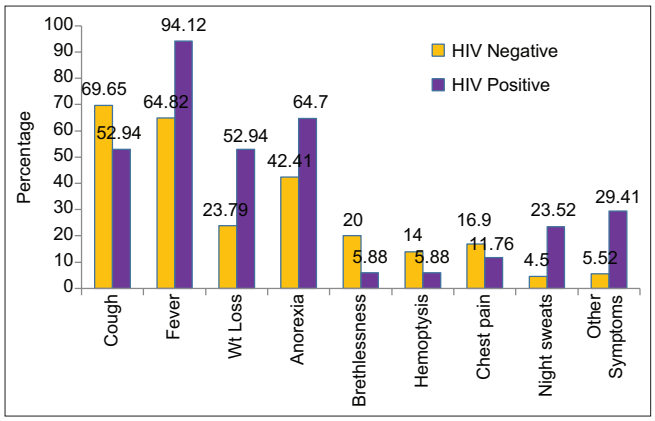

Figure 1: Comparison between presenting symptoms of tuberculosis in HIV seronegative and HIV seropositive patients

center in India, the prevalence of PTB and EPTB was found almost equal.[22] While in a recent study in 137 patients who were seropositive, 58 (42.3%) had TB infection and all those patients had atypical findings. In seropositive TB patient either PTB or EPTB appears to be important opportunistic infection. Fever was the most common presentation similar to our study followed by respiratory symptoms[23] while Kumar *P et al.* reported respiratory symptoms to be predominant.[13]

Statistically, sputum smear positivity for AFB is found significantly ($P < 0.01$) less common in HIV seropositive patients. Comparable results were seen in Indian study of Kumar *et al.*[13] and western data of Richter C *et al.*[22] Lesser patients with sputum positivity for AFB in HIV seropositive patients in this study was may be due to low mean CD4 counts and a smaller number of patients with cavitary lesions. CD4 counts were significantly low in our study population which was similar to the study by Tiewsoh *et al.* and Kapadiya *et al.* However, we could not find any co-relation of severity of illness with CD4 counts[23,24] Among HIV seropositive patients, the typical radiological features of TB, i.e. upper zone infiltrates, were less common, while atypical features such as mid and lower zone infiltrates, exudative lesions, and mediastinal lymphadenopathy were more common. It is evident that the radiological manifestations are mixed and varied in this study. This is because the X-ray findings of TB in HIV infected depend on the level of immunosuppression and most of the patients in this study had CD4 counts < 200 cells/micro l and hence number of atypical findings.

Role of primary care physician

Primary care physicians are the first point of contact for any patient irrespective of disease severity. They are at best position to anticipate and diagnose patients with either HIV or TB or both. By knowing how patients with HIV TB co-infection present coupled with history can easily detect specific cohort. Hence, can guide them for integrated management.

Various atypical presentations of PTB like non-upper lobe lesions, non-cavitary lesions, and predominantly mediastinal lymphadenopathy should raise suspicion. Apart from diagnosing, management could be supervised by serial testing of CD4 counts and follow-up sputum examination during the treatment. Also, complications like a paradoxical response (immune reconstitution inflammatory syndrome [IRIS]) when starting ART can be handled when an integrated approach is followed. Later, patients can be assessed for relapse and drug resistance without any extra effort.[25,26]

Conclusion

Seroprevalence of HIV among TB was found to be 5.54% in our study with the highest rates of seropositivity were between the ages of 26 to 45 years, the most productive age group of population. These patients often present atypically, i.e. non-upper lobe lesions. Primary physicians should be aware of these findings and should actively search for such patients. There is a need to strengthen the existing system, case finding as well as periodic screening of TB among HIV-infected individuals. Efforts should be made for early diagnosis using higher sensitivity diagnostics.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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