ORIGINAL ARTICLE

Socioepidemiological Determinants of Human Immunodeficiency Virus associated Tuberculosis Coinfection in Northern India: A 1:2 Matched Case Control Study

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Abstract

Aims: Our study was designed to assess the sociodemographic correlates of human immunodeficiency virus infection-associated tuberculosis (HIV-TB) coinfection and elucidate its risk factors among patients attending a tertiary healthcare facility in Northern India.

Materials and methods: A 1:2 case–control study, wherein the case group (patients with HIV-TB) was compared with two control groups: I group comprising patients with active tuberculosis (TB) [but without human immunodeficiency virus (HIV)] and II group comprising HIV patients (who did not develop active TB during follow-up). Our questionnaire was designed to obtain data based on sociodemographic and detailed medical history.

Results: Significant differences were observed on comparing gender, age, educational level, per capita income, place of residence, and occupational profile between case group and control group I. Case group was more likely to reside in urban areas ($p = 0.001$) and had a lower average level of formal education ($p = 0.009$) as compared to control group II.

Conclusion: We found patients in the coinfected group to differ significantly from patients with active TB alone, but the trends were similar to the control group I. The most frequent high-risk behavior was observed to be unprotected sexual activity, which is in concordance with the national estimates by National AIDS Control Organization (NACO) and World Health Organization (WHO).

Clinical significance: To minimize the prevalence of HIV-TB, controlling HIV transmission and disease progression in people living with HIV-AIDS (PLHAs) is crucial. Moreover, if the life expectancy of PLHAs is to be improved, HIV should be diagnosed early in the natural history of infection.

Keywords: Antiretroviral therapy, Human immunodeficiency virus, Human immunodeficiency virus infection-associated tuberculosis coinfection, people living with HIV-AIDS, Tuberculosis.

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Introduction

Human immunodeficiency virus infection-associated tuberculosis (HIV-TB) poses an imperative and severe threat to healthcare system globally.[1] Tuberculosis (TB) is one of the first opportunistic infections to appear in HIV-infected people and indeed, one of the key manifestations of HIV. The burden of HIV-TB poses unprecedented challenges on the public health systems, with India bearing the third highest burden in the world.[2]

Globally, 30% of HIV-infected persons are estimated to have concomitant infection caused by *Mycobacterium tuberculosis* with prevalence rates varying from 14% in Europe to 46% in the Southeast Asian region.[3] There are 2.1 million people living with HIV-AIDS (PLHAs) in India, with an estimated adult HIV prevalence of 0.27%.[4] Although only 5% of incident TB patients are HIV-infected, India bears about 10% of the global burden of HIV-TB.[5] Tuberculosis, indeed, causes more than 25% mortality in PLHAs and hence is the leading preventable cause of death among the latter.[6,7]

The HIV-TB coinfection is further complicated by complex socioeconomic factors such as unemployment, poverty, malnutrition, overcrowding, and poor living conditions.[8] Moreover, it has also been found to be intricately linked to male gender, smoking, alcoholism, and drug abuse.[9,10] The prevalence of TB shows a bimodal distribution at the extremes of age.[9] While active TB is more frequent in immune-compromised people, the odds of TB increases as the CD4 cell count decreases in PLHAs.[9–11] The direct and indirect costs of illness due to HIV-TB have been observed to be more than 30% of the annual household income in developing countries and can have an appalling impact on the economy of the developing world. Thus, HIV-TB is not only a medical woe but a grave socioeconomic disaster, being aptly described as the "cursed duo."[12,13]

In a resource-limited setting like India, HIV seropositivity among TB patients varies from 9.4% in New Delhi to 30% in Mumbai.[13,14] Moreover, the importance of concurrent treatment of HIV-TB cannot

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be undermined, since up to 50% of patients with HIV (without treatment) and concurrent TB would die prior to completion of antitubercular therapy (ATT). With the emergence of TB as a fatal complement in HIV-AIDS epidemiology, there is an urgent need to explore the probable multifactorial associations of HIV-TB coinfection.[15]

Our study attempts to do that by unfolding the underlying correlates of HIV-TB. It has been designed to assess the sociodemographic correlates of HIV-TB and elucidate its risk factors among patients attending a tertiary care health facility in Northern India.

Materials and Methods

Study Design

A follow-up 1:2 case–control study.

Study Area

The study was undertaken at the antiretroviral therapy (ART) clinic and TB [directly observed treatment short-course (DOTS)] center of large tertiary care health facility (Lok Nayak Hospital, LNH) located in the central district of New Delhi, India. The ART clinic has been functioning under the aegis of National AIDS Control Organization (NACO) and caters to a large population of Delhi and neighboring states. The study is a part of an ongoing project being undertaken at the ART clinic, LNH.

Study Subjects (Inclusion and Exclusion Criteria)

The study cases comprised HIV-TB coinfected patients who were registered in ART clinic and were on TB treatment (ATT) between October 01, 2016 and October 31, 2018. The controls comprised two control groups, i.e., control I (CGI) were TB patients without HIV who were registered in DOTS center of Lok Nayak hospital, New Delhi and had TB treatment card, while control II (CGII) were HIV patients without TB infection who were registered in ART clinic and did not develop active TB in the follow-up period. The CGI (TB only) was actively screened for HIV to rule out HIV and similarly, CGII (HIV only) was screened for TB to exclude it. Patients who were referred from other hospitals with incomplete baseline data or transferred out before complete evaluation were excluded from the study. Also patients who were severely ill, with psychiatric illness, under 15 years of age, on antimalignant drugs, or not willing to participate were excluded from the study. All patients were followed up till the end of the study.

Sample Size

The sample size was calculated using the Epi info ver.7 software (on the basis of results of similar study[16]), considering the expected exposure rate for controls as 0.81, and a cumulative exposure rate of 0.62 with an odds ratio (OR) of 2.6 with 10% nonparticipation rate. Our calculation has been based on 90% statistical power with a significance level at 5%. Per the calculated sample size, a total of 420 patients were divided equally into three groups: one case group and two control groups. Hence, the sample size was calculated to be 140 in each group.

Sampling Methods

Of the patients who met our inclusion and exclusion criteria, cases and controls were selected by systematic random sampling. We selected five patients on each study day (by simple random sampling) from the outpatient department list of the ART and TB centers. Case group (HIV-TB) and CGI patients were on ATT and were interviewed, whether in the intensive or in the continuation phase, during and after ATT completion. The CGII (HIV patients without TB) subjects were interviewed once during the study period. Both the control groups were representative of the population of the catchment area, from which HIV-TB coinfected cases had been detected.

Matching

Individual age and gender matching were done for both the cases and the control groups. The confounders such as smoking, alcoholism, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and malignancies were also matched at the time of selection of control groups.

Data Collection and Statistical Analysis

A pretested, in-house questionnaire was designed to obtain data on sociodemographic and detailed medical profile (particularly pertaining to risk factors for HIV, TB, and HIV-TB coinfection) by direct interview. Sociodemographic variables included sex, age, residence, religion, marital status, educational status, occupation, and per capita monthly income (Gupta–Mahajan scale). The medical history comprised mode of detection and duration of HIV, CD4 count, risk factors, and family history of HIV-TB. The data were analyzed using Epi info ver.7 software. Univariate analysis was carried out for the association of clinical, laboratory, and sociodemographic variables. Crude ORs with 95% confidence intervals (CIs) were estimated. The level of significance was set at 0.05.

Ethical Considerations

Ethical clearance was obtained from the Institutional Ethical Committee, Maulana Azad Medical College and associated LNH. All ethical requirements including voluntary, written informed consent, and confidentiality of subject' responses were strictly adhered to throughout the study.

Results

Our ART center had registered a total of 2,947 HIV cases during the study period (2016–2018), of which 1,857 were males, 901 were females, and 35 were transgenders and 154 were less than 15 years. While the total number of patients on ART was 1,456, the total number of HIV-TB patients were 950 (approximately a third of HIV cases).

As per Table 1, of the 420 patients studied, 267 (63.6%) were males, 147 (35.0%) females, and 6 (1.4%) were transgenders. A greater proportion of male patients ($n = 100$, 71.4%) were observed in the case group as compared to CGI ($n = 74$, 52.9%) and CGII ($n = 93$, 66.4%). The mean age of the case group was 34.91 ± 8.57 years, with an age range of 20–65 years. Among the CGI, the mean age was observed to be 29.79 ± 12.65 years (range = 16–70 years), while the mean age in CGII was found to be 35.21 ± 8.71 years (range = 20–65 years). Both age and sex differences were found to be significantly different among case group vs CGI ($p = 0.000$).

As per Table 2, the case group subjects were more likely to be residents of urban areas as compared to CGI and CGII ($p \leq 0.001$) (the majority of whom were slum dwellers). A significant difference was observed in marital status on comparing cases with CGI ($p < 0.001$), with case group individuals being more likely to be married. Among the case group, a relatively higher proportion of individuals ($n = 41$, 29.3%) had attained primary education in comparison to CGI, while CGII comprised maximum number of subjects with complete secondary education. More than 60% of the study subjects were Hindus; however, there was a significantly greater proportion of

Table 1: Sex and age distribution of the study subjects

Age and sex		*Case group (HIV/TB) no (%)*	*Control group I (TB) no (%)*	*Control group II (HIV) no (%)*	*Total no. (%)*	*p value case vs control I*	*p value case vs control II*
Sex	Males	100 (71.4)	74 (52.9)	93 (66.4)	267 (63.6)	0.001	0.58
	Females	39 (27.9)	66 (47.1)	42 (30.0)	147 (35.0)		
	Transgender	1 (0.7)	0 (0.0)	5 (3.6)	6 (1.4)		
Age (years)	15–24	9 (6.4)	62 (44.3)	11 (7.9)	82 (19.5)	0.000	0.78
	25–34	57 (40.7)	34 (24.3)	58 (41.4)	149 (35.5)		
	35–44	59 (42.1)	24 (17.1)	52 (37.1)	135 (32.1)		
	45–54	11 (7.9)	12 (8.6)	16 (11.4)	39 (9.3)		
	≥55	4 (2.9)	8 (5.7)	3 (2.1)	15 (3.6)		

Table 2: Sociodemographic profile of the study subjects

Sociodemographic variables		*Case group (HIV/TB) no (%)*	*Control group I (TB) no (%)*	*Control group II (HIV) no (%)*	*Total no. (%)*	*p value case vs control I*	*p value case vs control II*
Residence	Urban	75 (53.6)	58 (41.4)	51 (36.4)	184 (43.8)	0.000	0.001
	Rural	27 (19.3)	0 (0.0)	50 (35.7)	77 (18.3)		
	Slum	34 (24.3)	82 (58.6)	37 (26.4)	153 (36.4)		
	Homeless	4 (2.9)	0 (0.0)	2 (1.4)	6 (1.4)		
Marital status	Married	98 (70.0)	85 (60.7)	94 (67.1)	277 (66.0)	0.000	0.50
	Single	23 (16.4)	51 (36.4)	20 (14.3)	94 (22.4)		
	Divorced and widow	19 (13.6)	4 (2.8)	26 (18.6)	49 (11.6)		
Educational status	Illiterate	40 (28.6)	53 (37,9)	39 (27.9)	132 (31.4)	0.011	0.009
	Primary	41 (29.3)	27 (19.3)	37 (26.4)	105 (25.0)		
	Secondary	33 (23.6)	35 (25.0)	47 (33.6)	115 (27.1)		
	Higher second-ary	25 (17.9)	16 (11.4)	10 (7.1)	51 (12.1)		
	Graduate and above	1 (0.7)	9 (6.4)	7 (5.0)	17 (4.0)		
Religion	Hindu	102 (72.9)	75 (53.6)	110 (78.6)	287 (68.3)	0.000	0.51
	Muslim	29 (20.7)	63 (45.0)	22 (15.7)	114 (27.1)		
	Sikh	7 (5.0)	0 (0.0)	5 (3.6)	11 (2.6)		
	Christian	1 (0.7)	2 (1.4)	2 (1.4)	5 (1.2)		
	Others	1 (0.7)	0 (0.0)	1 (0.7)	2 (0.5)		

Table 3: Distribution of per capita income of the study subject

Economic profile		*Case group (HIV/TB) no (%)*	*Control group I (TB) no (%)*	*Control group II (HIV) no (%)*	*Total no. (%)*	*p value case vs control I*	*p value case vs control II*
Per capita income (Rs.)*	Lower <500	14 (10.0)	33 (23.6)	22 (15.7)	69 (16.4)		
	Upper lower 500–1,299	74 (52.9)	70 (50.0)	73 (52.1)	217 (51.7)		
	Lower middle 1,300–2,499	32 (22.9)	22 (15.7)	26 (18.6)	80 (19.0)	0.035	0.219
	Upper middle 2,500–3,999	9 (6.4)	7 (5.0)	14 (10.0)	30 (7.1)		
	Upper 4,000	11 (7.9)	8 (5.7)	5 (3.6)	24 (5.7)		

*Monthly per capita income was calculated as per Gupta–Mahajan scale

self-reported Muslims ($p < 0.001$) in CGI. Majority of the subjects in all the three groups were housewives (22.6%) followed by businessmen (16.4%) and skilled workers (15.2%).

As per Table 3, the vast majority of our subjects belonged to the upper lower socioeconomic class (case group = 74, 52.9% and CGI = 70, 50.0% and CGII = 73, 52.1%). The CGI had a significantly

Table 4: Mode or detection of human immunodeficiency virus status among study subjects

Mode of detection	*Case group I (HIV/TB) no. (%)*	*Control group II (HIV) no. (%)*	*p value case vs control II*	*Total no. (%)*
During prolonged illness	60 (42.9)	72 (51.4)	0.15	132 (47.1)
During detection of TB infection	54 (38.6)	18 (12.9)	0.000	72 (25.7)
Voluntary testing	25 (17.9)	39 (27.9)	0.09	64 (22.9)
During antenatal checking	1 (0.7)	5 (3.6)	0.10*	6 (2.1)
While donating blood	0 (0.0)	4 (2.9)	0.06*	4 (1.4)
While seeking employment abroad	0 (0.0)	2 (1.4)	0.24*	2 (0.7)
Total	140 (100.0)	140 (100.0)	–	280 (100.0)

*Fisher exact test

Table 5: Univariate analysis of risk factors among case group and control groups (I and II)

Possible risk factors		*Case group (HIV/TB)*	*Control group I (TB)*	*OR (95% CI)*	*p value*	*Control group II (HIV)*	*OR (95% CI)*	*p value*
Sex	Male	100	74	2.29 (1.35–3.9)	0.001	93	1.16 (0.67–2.01)	0.57
	Female	39	66			24		
Age (years)	<35	66	96	0.43 (0.26–0.71)	0.000	69	1.09 (0.66–1.79)	0.70
	≥35	74	46			71		
Education	≤Primary	81	80	1.03 (0.62–1.70)	0.90	76	1.16 (0.70–1.91)	0.54
	Others	59	60			64		
Residence	Urban	75	58	1.63 (0.99–2.69)	0.041	51	2.01 (1.21–3.34)	0.003
	Others	65	82			89		
Per capita income (Rs)	<500	14	33	0.36 (0.17–0.74)	0.002	22	0.60 (0.27–1.28)	0.15
	>500	126	107			118		
History of TB in family	Yes	32	20	1.64 (0.85–3.17)	0.11	19	1.74 (0.90–3.40)	0.08
	No	117	120			121		
Currently smoking status	Yes	92	69	1.97 (1.19–3.29)	0.005	67	2.09 (1.25–3.48)	0.003
	No	48	71			73		
Duration of HIV infection	≤3 years	108	*	73	3.10 (1.85–5.19)	0.000		
	>3 years	32		67				

*Not applicable

lower per capita income compared to the case group patients ($p = 0.035$).

As per Table 4, HIV testing during the course of prolonged illness was the commonest mode of HIV detection among our study subjects. An appreciable number of case group subjects ($p < 0.001$) were diagnosed with HIV during TB testing, whereas a larger number of CGII were diagnosed either during voluntary testing ($p = 0.09$) or during blood donation ($p = 0.06$). More than 75% of the case group was known to be retrovirus positive for last 3 years, while it was *vice versa* for CGII.

More than 90% of the subjects in the case group reported to have unprotected sexual intercourse followed by CGII (87.9%). An almost equal proportion of subjects mentioned blood transfusion, injury with contaminated materials, and drug abuse as their exposures, with a significant difference ($p < 0.05$) being observed between case group (HIV-TB) and CGII when compared to CGI. The CD4 count of less than 200 was observed in 35.0% subjects belonging to the case group as compared to CGII (27.9%). This difference in CD4 count was statistically nonsignificant ($p = 0.19$).

Table 5, on univariate analysis, the factors found to be associated with HIV-TB coinfection, between case group and CGI were gender (males, OR = 2.29, 95% CI: 1.35–3.9), age (<35 years, OR = 0.43, 95% CI: 0.26–0.71), urban residence (OR = 1.63, 95% CI: 0.99–2.69), and current smoking status (OR = 1.97, 95% CI: 1.19–3.29). The factors found to be positively associated with HIV-TB, between case group and CGII, were urban residence (OR = 2.01, 95% CI: 1.21–3.34), current smoking status (OR = 2.09, 95% CI: 1.25–3.48), and duration of HIV infection (<3 years, OR = 3.10, 95% CI: 1.85–5.19). It was also observed that among the case group and CGI, the difference was highly significant for age (>35 years) and male gender ($p = 0.001$).

Discussion

Our present study seeks to examine the sociodemographic variants and the risk factors for the HIV-TB coinfection.

In a study conducted by Rajasekaran et al., 74.5% of 4,383 HIV-TB patients were males and a statistically significant difference ($p < 0.001$) of the prevalence of coinfection was observed between the genders.[17] Per NACO estimates, HIV prevalence rate for adult females is 0.29%, while for males it is 0.43%.[4] We found that a significantly greater proportion of male patients suffered from coinfection compared to TB alone. However, no difference in sex distribution was found on comparing coinfected patients with HIV-positive individuals. This seems to suggest that the differential sex-wise distribution arises primarily from the greater predilection of males to risk factors for HIV.

National AIDS Control Organization estimates suggest that prevalence of HIV is higher in the age group of 15–49 years (88.7%), indicating that HIV-AIDS still affects the economically productive members of the society.[18] Most of our case group patients were in the age group of 25–44 years, a distribution not much different from CGII but deviated significantly from the age distribution of CGI. This again suggests that it is the population distribution of HIV infection that primarily drives the risk of coinfection.[18–20]

In keeping with the population norms of our study setting, the vast majority of subjects were Hindus followed in frequency by Muslims. Most of the study subjects were married at the time of interview. When questioned about literacy levels, a significantly greater proportion of patients infected with HIV alone had higher literacy level and patients with active TB alone had lower literacy levels, when compared to the coinfected patients. This is, in turn, concordant with a study by Carvalho et al. which found that subjects with a lower educational level had a higher risk of developing TB.[16] In accordance with the trends for active TB, as reported in multiple previous studies, we observed that patients with active TB alone had a significantly lower per capita income as compared to patients with coinfection and patients with HIV infection alone.[16,18,19] This reiterates the fact that HIV infection predisposes to coinfection, irrespective of the demographic profile of active TB. As regards the habitat, majority of CGI resided in urban slums, a finding backed by reports of epidemiological trends for TB.[7,15] When, however, patients acquire a predisposition for TB disease by means of HIV infection, their distribution becomes more uniform among urban areas, rural areas, and slums, mimicking the prevalence rates of HIV infection.

A majority of our coinfected patients had been known to be infected with HIV for a period of less than 3 years at the time of interview. This finding is likely confounded by the fact that a great proportion of these patients were diagnosed to have HIV infection in the course of routine investigation for active TB disease. Patients in the coinfected group had lower average CD4 counts when compared to their counterparts with HIV infection alone, the finding that authenticates the known natural history of HIV infection.[18,21–23]

Our study, indirectly, reflects the success of NACP efforts as evidenced by a higher rate of HIV detection through voluntary testing. However, it reiterates the need for increasing awareness and encouraging voluntary testing, particularly among groups with high-risk social behaviors.[24]

When questioned regarding risk factors for acquiring HIV infection, both coinfected and CGII had similar variants but were found to differ significantly from CGI. The most frequent high-risk behavior by far was unprotected sexual activity, which is in concordance with the national estimates by NACO and World Health Organization (WHO).[4,6,7]

Conclusion

Our study was designed to determine the unique sociodemographic characteristics that distinguish HIV-TB coinfected patients from patients infected with either disease alone.

Our study is the first study conducted in the capital city of India, i.e., Delhi, which highlights the important socioepidemiological determinants of HIV-TB coinfection, in large population of Delhi. With regard to the sociodemographic variables of age, sex, literacy levels, per capita income, and habitation, we found patients in the coinfected group differ significantly from patients with active TB alone but had shown similar trends to that of the patients with only HIV infection. In a region with higher TB endemicity, this seems to suggest that the native distribution of HIV is a stronger driver for coinfection. While TB prevention and treatment is the key to reduce its prevalence in the population, controlling HIV transmission and minimizing the rates of disease progression for PLHAs are indeed the crucial facets.

Both HIV-AIDS and TB are socially driven diseases, and, hence, understanding the social characteristics of each disease individually and of their coexistence is vital to achieving infection control.

Clinical significance

Majority of our patients were tested for HIV status either during the course of a prolonged illness or during evaluations for active TB disease. At the time of interview, most of the patients with HIV and active TB disease had held the diagnosis for less than 3 years. These were all patients in AIDS clinical stage 3, a diagnosis that would warrant immediate initiation of ART. If the life expectancy and quality of PLHAs is to be improved, it is essential that HIV testing should occur earlier in the natural history of infection. This presents a challenge to NACP by highlighting the necessity to enhance voluntary testing, particularly in the high-risk groups.

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