Original Article

Profile of Presentation of Human Immunodeficiency Virus Infection in North India, 2003-2007

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ABSTRACT

Background: Clinico-epidemiological profile of the Human immunodeficiency virus (HIV) epidemic in India is varied and depends on multitude of factors including geographic location. We analyzed the characteristics of HIV-infected patients attending our Immunodeficiency Clinic to determine any changes in their profile over five years. **Settings and Design:** A retrospective observational study. **Materials and Methods:** The study sample included all patients with HIV infection from January 1, 2003 to December 31, 2007. Diagnosis of HIV was made according to National AIDS Control Organization guidelines. **Results:** Of 3 067 HIV-infected patients, 1 887 (61.5%) were male and 1 180 (38.5%) were female patients. Mean age of patients was 35.1 ± 9.0 years. Majority (91.8%) of patients were in the age group of 15 to 49 years. Progressively increasing proportion of female patients was noted from year 2004 onward. Median CD4 count at presentation in year 2003 was 197/μl (Interquartile range [IQR] = 82.5-373) while in year 2007 it was 186.5/μl (IQR = 86.3-336.8). Mean CD4 count of male patients was 203.7 ± 169.4/μl, significantly lower as compared with female patients, which was 284.8 ± 223.3/μl (*P* value ≤0.05). Every year, substantial proportions of patients presenting to clinic had CD4 count <200/μl indicating advanced disease. Predominant route of transmission was heterosexual in 2 507 (81.7%) patients. Tuberculosis and oropharyngeal candidiasis were the most common opportunistic infections (OIs). Cryptococcal meningitis was the most common central nervous infection. Our patients had comparatively lower median CD4 counts at the time of presentation with various OIs. **Conclusions:** Patients had advanced stage of HIV infection at the time of presentation throughout five years. Females presented earlier during the course of HIV infection. There is need for early screening and increasing awareness in healthcare providers to make a diagnosis of HIV much sooner.

Keywords: Clinical profile, HIV, time trends

Introduction

Human immunodeficiency virus (HIV) infection is a global pandemic. This infection has reached an important threshold in India. India has about 2.5 million infected individuals, the third highest in the world. The estimated adult prevalence was 0.36% in 2006 and was higher among males (0.43%) than in females (0.29%).[1]

Epidemiology of HIV infection is constantly changing throughout the world. The characteristics of patients reported between 1981 and 1987 from United States of America (USA) differ significantly from those cases reported in late nineteen nineties. The epidemic has become increasingly an epidemic of females and heterosexuals.[2] Clinico-epidemiological profile is changing in India as well. It is spreading from groups with high-risk behaviors to general population and from

Access this article online	
Quick Response Code:	Website: www.ijcm.org.in
	DOI: 10.4103/0970-0218.99914

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Received: 23-04-10, **Accepted:** 03-02-12

urban to rural populations. As a result, more and more antenatal clinic attendees, especially from Northern states, are becoming HIV positive.[1] As the HIV epidemic changes over the time continuously, it is important to monitor the trends regularly. It would provide vital information to plan future control programs. A clinic-based data from a large tertiary care center is presented here.

Materials and Methods

This retrospective observational study was carried out at the HIV clinic of Post Graduate Institute of Medical Education and Research (PGIMER) Chandigarh, a tertiary care referral hospital in Northern India. The hospital caters to patients from Chandigarh and the surrounding areas, which includes Punjab, Haryana, Uttar Pradesh, Uttaranchal, Himachal Pradesh, and Jammu-Kashmir.

All patients presenting to HIV clinic for the first time from January 1, 2003 to December 31, 2007 were included in the study. Diagnosis of HIV was confirmed by ELISA (Enzyme-linked immunosorbent assay) using two different antigens and a rapid test as recommended by National AIDS Control Organization (NACO).[1] Data extraction sheet was developed to obtain necessary information from medical records. Age, sex, marital state, route of transmission, CD4 count, and presence of opportunistic infections (OIs) were used as variables. These were noted at the presentation to the clinic. During the study period, 3212 HIV-positive patients were registered at the clinic and of those, 3067 clinic records were suitable for the final analysis. The following criteria were used to define common concomitant infections: The diagnosis of pulmonary tuberculosis (TB) required clinical syndrome of fever, productive cough and/or hemoptysis, night sweats, and weight loss with suggestive chest X-ray findings. Sputum acid fast bacilli (AFB) smears were routinely sent of all suspected TB patients, yet diagnosis did not require AFB smear positivity. Disseminated TB: clinical features suggestive of TB with concurrent involvement of at least two non-contiguous organs in the presence of bacteriological and/or histopathological evidence of TB and improvement with anti-TB therapy. The diagnosis of TB meningitis required a compatible clinical syndrome (i.e., fever, and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures, and/or focal deficits), cerebrospinal fluid analysis demonstrating pleocytosis with mononuclear predominance, elevated cerebral spinal fluid (CSF) protein, and low CSF glucose, exclusion of bacterial meningitis, and a negative India ink. The diagnosis of TB lymphadenitis required either a lymph node biopsy or fine needle aspiration demonstrating caseating granulomas on histopathology and/or a positive AFB smear. *Pneumocystis jiroveci* pneumonia (PCP): bilateral, diffuse interstitial infiltrates on chest radiograph or high-resolution computed tomography (HRCT), with hypoxemia (PaO_2 <12 kPa) and sputum smears/cultures negative for aerobic bacteria, and AFB and/or demonstration of *Pneumocystis jiroveci* in induced sputum. The diagnosis of cryptococcal meningitis required a compatible clinical syndrome (i.e., fever, and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures, and/or focal deficits), cerebrospinal fluid analysis to rule out other etiologies, and a positive India ink. For the diagnosis of central nervous system (CNS) toxoplasmosis, a compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever, and positive IgG serology was required. Cryptosporidiosis: a compatible clinical syndrome consisting of acute or subacute onset of profuse, non-bloody watery diarrhea and microscopic identification of the oocysts in stool or tissue. Oocysts stain red with varying intensities with a modified acid-fast technique. Histoplasmosis: a compatible clinical syndrome of fever, fatigue, and weight loss, detection of Histoplasma antigen in blood or urine and/or growth of organism in blood, bone marrow, respiratory secretions, or localized lesions sample. Cytomegalovirus (CMV) disease: a compatible clinical syndrome with retinal, gastrointestinal involvement and characteristic retinal changes observed on funduscopic examination, demonstration of mucosal ulcerations on endoscopic examination combined with colonoscopic or rectal biopsy with histopathological demonstration of characteristic intranuclear and intracytoplasmic inclusions and/or CMV viremia detected by PCR (polymerase chain reaction), antigen assays, or blood culture. Oropharyngeal Candidiasis: clinical features showing painless, creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface supported by clinical response to appropriate therapy.

Statistical analysis

Statistical analysis was done using the statistical software 'SPSS version 13.0' (SPPS Corp, Chicago, IL, USA). Descriptive analysis consisted of mean with standard deviation and range for various parameters. Median was used where data had skewed distribution. Frequencies of OIs were expressed as percentage. Continuous variables were analyzed using student's *t*-test, whereas Fisher's exact test was used to compare the ordinal variables. All the statistical tests performed were two tailed; $P<0.05$ was considered as statistically significant.

Results

Of the 3 067 clinic records analyzed, 1887 (61.5%)

were male and 1 180 (38.5%) were female patients. Percentage distribution of 3 067 HIV-infected patients according to sex over a period of five years (2003-2007) has been shown in Figure 1. Mean age of study group was 35.1 ± 9.0 years. 91.8% individuals were in the age group of 15 to 49 years and 7.8% were above the age of 49 years. Median CD4 count of whole group was 187/ µl (Interquartile range [IQR] = 97-319). Median CD4 count at presentation in each year separately in male and female gender has been shown in Figure 2. Mean CD4 count of male patients was 203.7 ± 169.4/µl, which was significantly lower as compared with female patients, which was 284.8 ± 223.3/µl (*P* value ≤0.05). This pattern was consistently seen in all the five years. Progressively increasing proportion of female patients was noted from year 2004 onward. A total of 1244 patients had CD4 count less than 200/µl, while 592 patients had CD4 count in-between 200 to 350/µl. Each year, substantial number of patients presenting to clinic had CD4 count <200/µl with percentage of patients varying from 25.3% in year 2004 to 51.4% in year 2006. There was no significant change in the CD4 count documented at presentation in these patients over the period of five years with median CD4 count at presentation in year 2003 being 197/µl (IQR = 82.5-373), while in year 2007 it was 186.5/µl (IQR = 86.3-336.8). Predominant route of transmission was heterosexual in 2507 (81.7%) patients. This was the main route of transmission during the five years. Second most common mode of transmission in the study group was IV/IM injections seen in 125 (4.1%) patients, which included IV drug abusers, unsafe injections, occupational exposure/surgical mishaps, etc. Number of infections due to blood transfusions showed progressive decline over the years while number of patients acquiring HIV infection through IV/IM injections showed progressive increase from year 2003 till 2007. Further elaboration of various routes of transmission and trends of these various routes over the study period of five years from 2003 to 2007 has been done in Figures 3 and 4, respectively. Majority (89%) of patients were married. Among female patients, substantial number (91%) had spouse who were seropositive.

Eight hundred and thirty one (27.1%) patients had 856 episodes of OIs at the time of presentation which included 408 patients with various forms of TB. Oropharyngeal candidiasis infection was seen in 334 patients. Cryptococcal meningitis was seen in 42 patients with one case of disseminated cryptococcosis. Forty patients had PCP and four patients had cerebral toxoplasmosis. Frequency of other OIs is shown in the Table 1. Among these patients with various OIs, pulmonary TB and cryptococcal meningitis showed progressively increasing trends over the five-year period. Patients with extrapulmonary TB showed progressively decreasing trends over these five years. Patients with PCP showed initial increase till year 2004 then progressively decreasing trends over remaining years while patients

Table 1: Various opportunistic infections detected in 3067 patients with HIV-infection

Type of opportunistic infections	Number (%)
Oropharyngeal candidiasis	334 (39)
Extrapulmonary tuberculosis	248 (28.9)
Pulmonary tuberculosis	160 (18.7)
Cryptococcal meningitis	42 (4.9)
Pneumocystis carinii pneumonia	40 (4.7)
Progressive multifocal leukoencephalopathy	9 (1.1)
Cytomegalovirus (CMV) infection	8 (1.0)
Isosporidium	5 (0.6)
Central nervous system (CNS) toxoplasmosis	4 (0.5)
Cryptosporidium	4 (0.5)
Mycobacterium avium–intracellulare complex disease (MAC)	1 (0.1)
Histoplasmosis	1 (0.1)

HIV: Human immunodeficiency virus

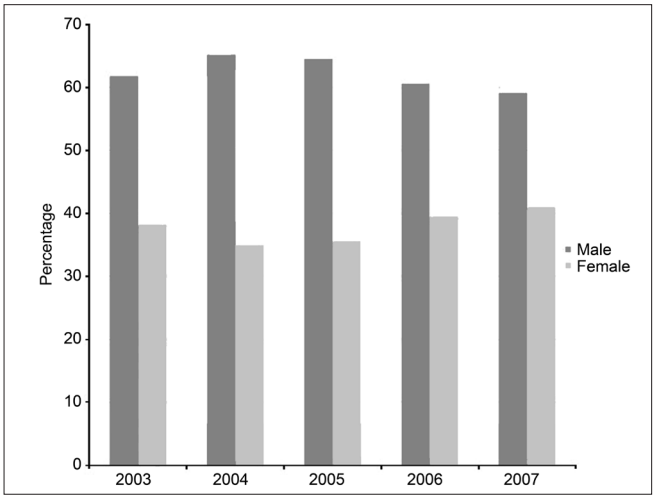

Figure 1: Percentage distribution of 3 067 HIV-infected patients according to sex over a period of 5 years (2003-2007)

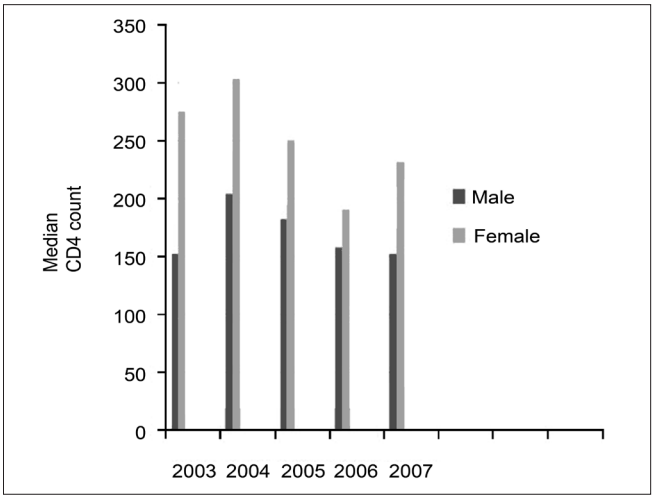

Figure 2: Distribution of CD4 count among male and female gender over a period of 5 years (2003-2007)

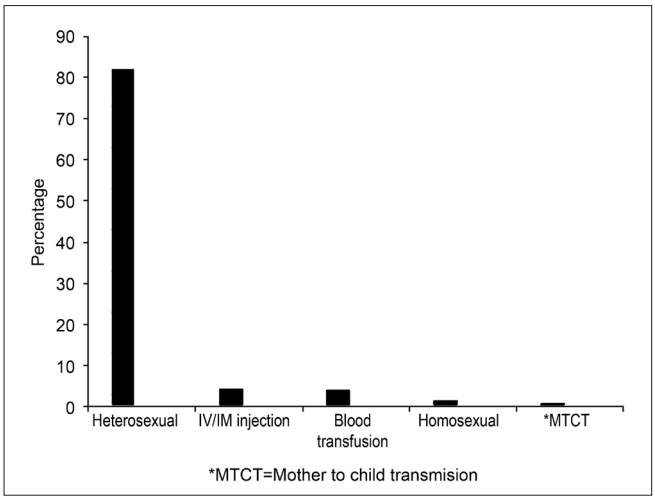

Figure 3: Modes of transmission of HIV infection in study cohort

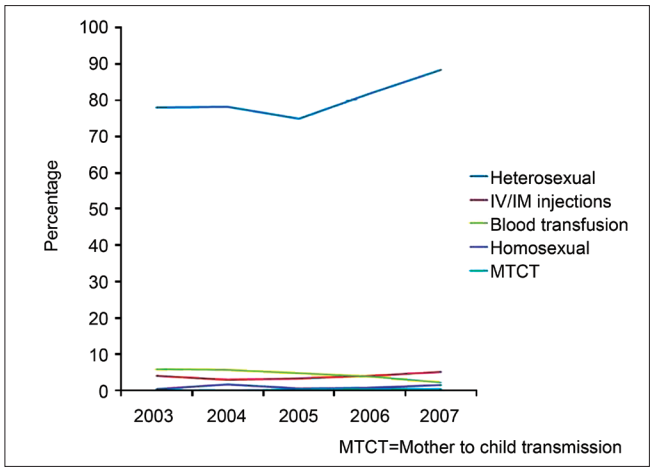

Figure 4: Trends of various HIV transmission routes over a period of 5 years (2003-2007)

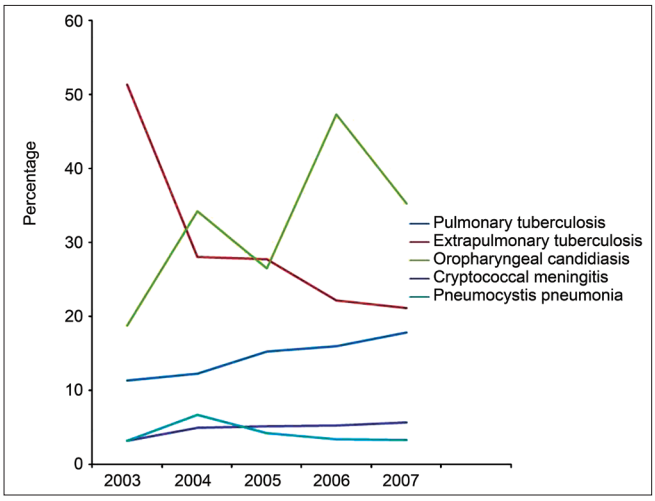

Figure 5: Trends of various opportunistic infections over the study period of five years

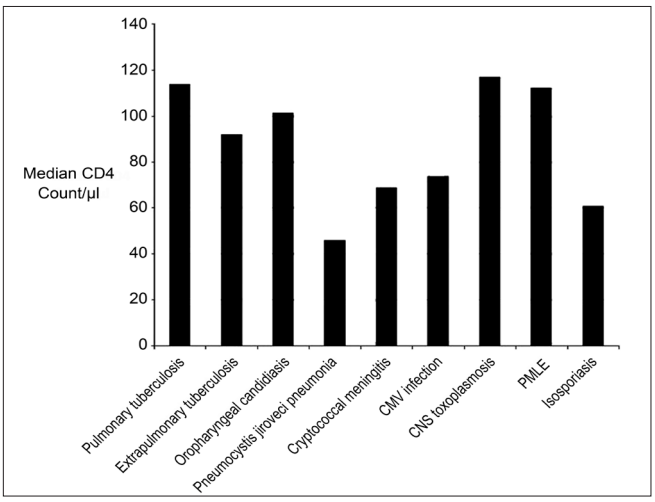

Figure 6: Distribution of CD4 count among HIV-infected patients with various opportunistic infections

with oropharyngeal candidiasis showed fluctuating trends over these five years [Figure 5].

Median CD4 count in patients with TB was 103/µl (IQR = 52-170.8). Median CD4 count was 114/µl (IQR = 51.5- 170.5) with pulmonary TB and 92/µl (IQR = 52-175) in extrapulmonary TB. Median CD4 count of patients with candidiasis was 101.5/µl (IQR = 40.3-181.8) while median CD4 count in cryptococcal meningitis was 69/ µl (IQR = 33-107.5). Patients suffering from PCP had the lowest median CD4 count of 46/µl (IQR = 22.3-100.8). Detailed distribution of CD4 count among HIV-infected patients with various OIs is shown in Figure 6. Patients developing OIs had significantly lower CD4 count (mean CD4 count = 133.9 ± 125.4/µl) compared with those without OIs (mean CD4 count = 272.8 ± 204.6/µl) (*P* value≤0.0005). 713 (85.8%) patients presenting with OIs had CD4 count <200 cells/µl**.**

There was no statistical difference in number, age, sex, and CD4 count at the time of presentation among patients visiting the clinic in year 2003 from those patients visiting the clinic in year 2007.

Discussion

The clinico-epidemiological profile of the HIV epidemic in India is varied and depends on multitude of factors including geographic location. Thus, epidemiological data on HIV/AIDS relevant to a specific region are important in providing vital information to plan future control programs in that specific region. We conducted this clinic-based retrospective observational study to describe the clinico-epidemiological profile at presentation of HIV-infected patients over a period of five years from 2003 to 2007.

Male patients predominated the study group. Majority of patients were in economically productive age group. An observational study done at PGIMER,

Chandigarh, during the period 1987-1996, among 622 HIV-infected patients revealed similar findings.[3] Another retrospective cross-sectional study carried out in zonal referral center at Chandigarh from September 1999 to September 2005 showed male predominance among the study subjects.[4] The findings of index study are also in consonance with the national level statistics provided by NACO-India.[1]

Worldwide, the most common mode of transmission is through heterosexual route, particularly in developing countries.[5] Predominant mode of HIV transmission in this study too was through heterosexual route and it remained the major mode of transmission throughout five years. This is in consonance with the national level statistics provided by NACO.[1] Two other observational studies conducted at Chandigarh also showed similar findings.[3,4]

Transmission through contaminated blood and blood products showed progressive decrease over the years. This was achieved by screening of voluntary donors for HIV and banning the professional blood donors. An observational study conducted during the period of 1987-1996 in similar setting showed progressive drop in percentage of patients acquiring infection through blood, blood products, and hemodialysis.[3]

Another route of HIV transmission was IV/IM injections which showed a progressive increase over the years in index study. Approximately 3% of patients had unsafe medical injections as the only identifiable source of HIV acquisition according to data provided by NACO. In villages and small towns in developing countries, many patients reported receiving injections administered by unqualified medical practitioners without proper sterilization. These injections may contribute to the spread of HIV both within high-risk groups and between high-risk groups and the general population.

Gangakhedlkar *et al.* showed high prevalence of HIV infection among females in general population, who were previously considered as a low-risk group in India.[6] Recent surveillance data indicate that HIV epidemic is increasingly feminizing in India like in many other African countries.[7-9] Most Indian females acquire HIV from their husbands as 90% of infected women reported to be married and monogamous.[10-12] An observational study conducted among 28 139 married women who underwent intimate partner violence showed that physical violence combined with sexual violence by husband was associated with increased prevalence of HIV infection among married women in India.[13] We also noted progressively increasing proportions of female patients from year 2004 onward. A six-year (2002-2007) Integrated Counselling and Testing Centre (ICTC) based study from North-western India showed progressively increasing percentage of HIV-infected female patients among all the attendees of ICTC except in year 2005.[14] In the index study, mean CD4 count of male patients was significantly lower than female patients. This pattern was consistently seen in all the five years. The possible explanation would be that the majority of women acquired infection from their husbands. Men acquire infection due to their risky behaviors and pass it to their marital partners. As they acquire infection earlier than females, they present with advanced disease and lower CD4 counts compared with females. As a protocol, the spouses of these male patients were screened for HIV. Another reason for male predominance with advanced disease would be the disease pattern of HIV in India as HIV epidemic in Indian women is younger than that in men.

Several OIs occur in patients infected with HIV. The probability of HIV-infected individual developing an OI is influenced by level of immunosuppression, relative virulence of the potential pathogen, and exposure to the potential pathogen. An accurate estimate of type and burden of OIs among these patients will help us to plan and implement appropriate management strategies. Study done at the Royal Free Hospitals in London, England (1982-1995) reported 1 713 AIDS patients among 3 875 HIV-positive patients. The five most common AIDS-defining illnesses were Pneumocystis pneumonia (16.7%), esophageal candidiasis (15.2%), Kaposi sarcoma (13.2%), *Mycobacterium avium–intracellulare complex* (9.6%), and CMV retinitis (9.5%).[15] A retrospective observational cohort study from Singapore reported 834 cases having one or more AIDS-defining diseases among 1 504 patients studied. The most frequent causes were Pneumocystis pneumonia (35.7%), *Mycobacterium tuberculosis* (22.7%), and herpes simplex (7.4%).[16] In a study from tertiary care hospital, from Kolkata, oral candidiasis and Herpes Simplex Virus (HSV)-2 were the most common OIs.[17] TB and Oropharyngeal candidiasis were the most common OIs reported in few other studies reported from India.[18-21] Various forms of TB and Oropharyngeal candidiasis were the two main OIs observed in the present study. Patients developing OIs had lower CD4 counts as compared with previous studies reported from this subcontinent. One study from western India noted median CD4 count of 195/µl in patients with pulmonary TB while a study from eastern India reported median CD4 count of 137/µl.[17,21] In index study, median CD4 count in these patients at presentation was 114/µl and patients with extrapulmonary TB had much lower median CD4 count of 92/µl. Patients with oral candidiasis have been reported to be having lower CD4 counts. It has been reported as a marker of immunosuppression. One study from Pune, India, documented CD4 count of 151/µl

while another study from southern India reported CD4 count of 107/µl in these patients.[18,21] Our index study showed median CD4 count of 101.5/µl in these patients. Substantial proportions of patients had CD4 count<200 at presentation with 51.4% of patients in year 2006 with this level of CD4 count. An observational study done at PGIMER, Chandigarh, during the period of 1987-1996 among 622 HIV-infected patients reported much lower percentage (29%) of patients with full-blown HIV disease.[3] Importantly, index study has shown for the first time from this part of subcontinent that the CD4 count has not changed much at presentation to immunodeficiency clinic over the period of five consecutive years. This important finding calls for strengthening of various aspects of control program to detect HIV infection in early stages resulting decrease in morbidity and mortality.

Among the different infections affecting the CNS, cryptococcal meningitis is the most common HIV-associated condition both in developed and developing countries, contributing significantly to increased morbidity and mortality.[22-25] Similarly, cryptococcal meningitis was the most common CNS OI found in this study. There was progressive increase in percentage of patients presenting with this OI over the study period of five years. Despite the higher number of pulmonary and extrapulmonary TB, number of TB meningitis was lesser than cryptococcal meningitis. This finding reemphasizes the importance of excluding cryptococcal meningitis in all HIV-infected patients presenting with features of CNS infection. Early diagnosis and effective treatment may considerably reduce the morbidity and mortality associated with this condition.

In conclusion, the majority of HIV patients were male in sexually active and economically productive age group. Most common mode of transmission was heterosexual route. Female patients presented at earlier stage of HIV infection as compared with male patient, throughout the study period of five years. Progressively increasing proportions of female patients were seen from the year 2004 onward. TB and oropharyngeal candidiasis were the most common OIs, whereas cryptococcal meningitis was the most common CNS OI. Among the patients with various OIs, pulmonary TB and cryptococcal meningitis showed progressively increasing trends over the study period of five years. Patients with extrapulmonary TB showed progressively decreasing trends over these five years. Patients developing OIs had lower CD4 counts as compared with previous studies reported from this subcontinent. Most of the patients were in advanced stage of HIV infection at the time of presentation and this has been the pattern in all the five years. These findings call for improving the various aspects of the AIDS control program.

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How to cite this article: Kumar S, Wanchu A, Abeygunasekera N, Sharma A, Singh S, Varma S. Profile of presentation of Human Immunodeficiency Virus infection in North India, 2003-2007. Indian J Community Med 2012;37:158-64.

Source of Support: Nil, **Conflict of Interest:** None declared.