Recent trends in the spectrum of opportunistic infections in human immunodeficiency virus infected individuals on antiretroviral therapy in South India

Praveen R. Shahapur, Rajendra C. Bidri[1]

Departments of Microbiology, and [1]Medicine, BLDE University's Shri B.M. Patil Medical College, Bijapur, Karnataka, India

Address for correspondence:
Dr. Praveen R. Shahapur, Opposite ITI College, Chalukya Nagar, Solapur Road, Bijapur - 586 103, Karnataka, India. E-mail: drprshahapur@yahoo.co.in

Abstract

Background: Opportunistic infections (OI) are the major cause of morbidity and mortality among human immunodeficiency virus (HIV) infected individuals. The pattern of OIs differs widely, hence it is necessary to correlate spectrum of OIs and CD4 counts among HIV infected individuals in specific localities. **Materials and Methods:** The present study describes the clinical and laboratory profiles of different OIs among 55 HIV seropositive patients. CD4 count was estimated and antiretroviral therapy (ART) was started in 27 patients as per National Acquired Immunodeficiency Syndrome Control Organization guidelines. These 27 patients were classified into stage 1, stage 2 and stage 3 based on CD4 counts of >500 cells/μl, 200-499 cells/μl and <200 cells/μl respectively. The OIs presented by respective groups were documented. **Results:** Pulmonary tuberculosis was found to be the most common OI constituting 43.6% of all cases followed by candidiasis (30.9%), cryptosporidial diarrhea (21.8%), herpes zoster (16.3%), cryptococcal meningitis (3.63%), *Pneumocystis jirovecii* pneumonia (1.81%), and other miscellaneous infections (23.6%). Only 1 patient was found in stage I while 13 patients each were grouped in stage II or stage III. The mean CD4 count in our study population who were on ART was 230 ± 150 cells/μl. **Conclusion:** The pattern of OIs among our study group did not differ significantly from patients not receiving ART. The effect of ART on CD4 count differs from patient to patient based on the degree of depletion of CD4 count before the initiation of ART, drug adherence, concomitant OIs and their treatment.

Key words: Antiretroviral therapy, CD4 count, Human immunodeficiency virus, opportunistic infections, south India

INTRODUCTION

Opportunistic infections (OIs) are the most common complication of human immunodeficiency virus (HIV) infection.[1-3] OI cause significant morbidity and mortality in people with HIV infection.[4,5] The identification of pathogens responsible for OI is very important in managing the HIV infected individual. The spectrum of OI of a particular locality should be known to prevent these infections by giving adequate prophylaxis. The antiretroviral therapy (ART) has reduced the incidence of OI among HIV infected individuals; however the efficacy of the ART depends on the patients adherence to the regimen of drugs, stage at which treatment was started, drug resistance and other factors.[6] At present the initiation of prophylactic therapies against opportunistic pathogens is mainly based on the absolute CD4 count, as it is generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection.[7]

The relative frequencies of specific OIs may vary in different countries and even in different areas within the same country.[8-10] Knowledge of the most common OI of that geographical area will help in implementing the preventive measures against that pathogen. Tuberculosis is the most common OI among HIV infected individuals of Guatemala, Sub-Saharan Africa [11] and Bangladesh. [12] *Pneumocystis carinii* pneumonia is most common cause of OI

in Malaysia,[13] Hong Kong,[14] China.[15] *Penicillium marneffei* is the commonest cause of OI in Thailand.[11] There are many reports available regarding the pattern of OIs in HIV infected individuals, but very few reports regarding the OIs with their CD4 count and ART. Hence we are reporting the recent trends in the spectrum of OIs and their respective CD4 count among patients on ART.

MATERIALS AND METHODS

The present study was carried out in the Shri B. M. Patil Medical College Hospital and Research Centre Bijapur, Karnataka, India, which is a tertiary care center with undergraduate, post-graduate and super specialty teaching hospital. Study period was for 6 months from July 2009 to December 2009. A total of 3557 patients attending Shri B. M. Patil Medical College Hospital and Research Center Bijapur, with different diseases were screened for HIV infection and out of which 55 HIV seropositive individuals were included in the study to note the pattern of OIs. The HIV infected individuals were interviewed in detail and their socio-demographic data was collected with the help of a proforma. These patients were referred to ART Centre District Hospital for CD4 cells estimation and if necessary ART. In ART center free ART is issued based on their CD4 count and National Acquired Immunodeficiency Syndrome (AIDS) Control Organization (NACO) Guidelines. These patients were monitored in our hospital for initiation of therapy and any complications thereafter.

Inclusion criteria
All adult patients admitted with diagnosis of HIV/ AIDS, in medicine wards and referrals from other departments during July to December 2009 were included in this study.

Exclusion criteria
Patients admitted to Pediatric wards, patients with all other immune compromised states such as malignancies, organ transplant, patients on steroids therapy or immunosuppressive therapy and diabetes mellitus were excluded.

Ethical consideration
HIV testing was done with pre and post-test counseling after informed consent. Data collected was strictly confidential. Institutional ethical committee of BLDE University's Shri. B. M. Patil Medical College approved the study design.

All the 55 patients were investigated for various opportunistic pathogens. Their HIV status was confirmed as per NACO guidelines[16] by HIV rapid test and enzyme-linked immunosorbent assay (ELISA). Evaluation of whole blood CD4 count of the HIV seropositive patients was done as per the NACO guidelines,[17] using 5 fluorescence-activated cell sorting count flowcytometer (Becton Dickenson, Sanjose, Calif., USA). As per NACO guidelines, only 27 patients out of 55 had estimated CD4 count and ART.[18] These 27 patients were classified as per Centers for Disease Control (CDC) guide lines[19] into stage 1, stage 2 and stage 3 based on CD4 counts of >500 cells/µl, 200-499 cells/µl and <200 cells/µl respectively. Though the viral load of the patient is an important indicator for commencement and monitoring of ART, in our study viral load estimation was not done because of its high cost. All 27 patients were receiving ART as per NACO guidelines, most common ART was non-nucleoside reverse transcriptase inhibitor based (nevirapine) triple drug regime. Patients with tuberculosis were received efavirenz (600 mg) based regimen. The OIs presented by the respective group were documented. Various samples e.g.: Sputum, oral swab, blood, stool, urine, cerebrospinal fluid (CSF), lymph node aspirate were collected as per symptoms and clinical presentations under universal aseptic precautions in suitable sterile containers. Specimens were stained using appropriate stains e.g.: Gram, Ziehl-Neelsen, Kenyon's staining, silver methenamine and examined under the microscope. Sputum samples were stained after concentration technique. CSF samples were examined for *Cryptococcus* by Indian ink wet mount. Appropriate media like blood agar, MacConkey agar, chocolate agar, sabourauds dextrose agar and Lowenstein Jensen were used for isolation of microbial pathogens. The pathogens isolated were further identified following standard protocol. The sera were examined for syphilis (rapid plasma reagin test-Tulip diagnostics, *Treponema pallidum* hemagglutination assay [TPHA] test — Immutrep TPHA Omega diagnostics Ltd, Scotland, UK), hepatitis B (SD Bioline ELISA — hepatitis B surface antigen), herpes simplex virus 1 and 2 (immunoglobulin M — Equip — R Glaxo), malaria (SD Bioline Malaria Ag Pf/Pan rapid test), rickettsial fever (Weil-felix test-Tulip diagnostics). OIs among these patients were treated as per NACO guidelines in our hospital. The statistical analysis was performed using Microsoft office excel 2007.

RESULTS

Out of 55 HIV patients 36 (65.5%) were males and 19 (34.5) females. Among male patients maximum (15) were in the age group of 31-40, whereas among female patients maximum were in 21-30 age group. The mode of transmission of HIV in all patients of the study group was by heterosexual transmission.

Pulmonary tuberculosis was found to be the most common OI constituting 43.6% of the cases followed by candidiasis with 30.9% cases. The majority of cases were only with oral candidiasis although two cases had esophageal candidiasis. Other OI were cryptosporidial diarrhea (21.8%), herpes zoster (16.3%), cryptococcal meningitis (3.63%) and *Pneumocystis jirovecii* pneumonia (1.81%), while 23.6% cases were with miscellaneous infections. Among miscellaneous patients, 4 (7.27%) patients presented only with lymphadenopathy, 2 (3.63%) patients had malaria, 2 (3.63%) patients had hepatitis (Non hepatitis B), 2 (3.63%) patients had bacterial meningitis and 1 (1.81%) patient had Rickettsial fever and syphilis. All the patients were presented with one or the other associated diseases like, hepatitis, lymphadenopathy, apart from AIDS defining OIs. Apart from 24 cases of pulmonary tuberculosis, 2 patients had tubercular meningitis. In diarrheal disease patients, 41.6% cases were presented with mixed infection of *Escherichia coli* and *Cryptosporidium parvum*. Among viral OIs Herpes zoster was most predominant with 16.3% patients while other viral infection to be reported was Hepatitis B (3.6% patients). Among fungal OIs majority of the patients were infected with *Candida albicans*, 30.3%, *P. jirovecii* pneumonia (1.81%) and cryptococcal meningitis (3.63%). Unlike previous reports on OI, Kaposi's sarcoma, atypical mycobacterial infection and disseminated cytomegalovirus disease were not observed in our study population.[20] Although few other infections such as pyogenic meningitis, syphilis, malaria, rickettsial fever were found among patients investigated.

Statistical analysis of the whole study group patients who were on ART, had mean CD4 count of 230 ± 152 cells/μl, stage II patients had 340 ± 87 cells/μl and stage III patients had 96 ± 38 cells/μl. The median duration of ART among the study population was 6 months. The distribution of the study populations based on CD4 cells/μl of blood, in stage I only one patient had CD4 count >500 cells/μl who was asymptomatic. In stage II, 13 patients presented CD4 counts between 200 and 499 cells/μl, who had one or two OIs with some non-opportunistic diseases [Table 1]. Another 13 patients with stage III were presented their CD4 count <200 cells/μl, with multiple OIs and with multiple organ system involvement [Table 2].

DISCUSSION

OIs are the major cause of morbidity and mortality in immune-compromised individuals as there will be lowered cellular and humoral defenses in these patients. In our study, all the patients presented with most of constitutional symptoms of the disease. The 31-40 years age group was found to be most commonly (41.66%)

Table 1: Disease spectrum in stage II patients

CD4 count 200-499/µl	*N* = 13 (%)
P. tuberculosis, herpes, candidiasis	3 (23)
Cryptosporidial diarrhea and candidiasis and P. tuberculosis	2 (15.3)
Cryptosporidial diarrhea and lymphadenopathy	2 (15.3)
P. tuberculosis and herpes zoster	3 (23)
Fever of unknown origin, lymphadenopathy	1 (7.6)
Syphilis	1 (7.6)
Asymptomatic	1 (7.6)

P. tuberculosis: Pulmonary tuberculosis

Table 2: Disease spectrum in stage III patients

CD4 count <200/µl	*N* = 13 (%)
Disseminated tuberculosis, herpes, cryptosporidial diarrhea, oral thrush	1 (7.6)
P. tuberculosis, candidiasis	2 (15.3)
Bacterial pneumonia, herpes, candidiasis	2 (15.3)
P. tuberculosis, malaria	1 (7.6)
Pneumocystis jirovecii pneumonia	1 (7.6)
P. tuberculosis, HIV encephalopathy, candidiasis	1 (7.6)
Cryptosporidial diarrhea, candidiasis, herpes	2 (15.3)
Cryptococcal menigitis, oral thrush, P. tuberculosis	1 (7.6)
Cholecystitis and pancreatitis	1 (7.6)
Disseminated tuberculosis, cryptosporidial diarrhea, candidiasis	1 (7.6)

HIV: Human immunodeficiency virus, P. tuberculosis: Pulmonary tuberculosis

involved among men and 21-30 years age group (26.3%) among women. Heterosexual transmission was the only mode of transmission in our study population. All the female patients in our study group were married monogamous. This observation explains the shift of the epidemic from high risk groups like sexually transmitted diseases and injectable drug users, to low risk groups like married monogamous women.[21] This finding is based on the interview with the study group female patients, but polygamous relation cannot be ruled out. Another study from south and north India also reported that 88-90% of the HIV infected females were monogamous.[22,23] In our study, we observed pulmonary tuberculosis was the most common OI, followed by candidiasis, cryptosporidial diarrhea, herpes zoster, cryptococcal meningitis and *P. jirovecii* pneumonia. Remaining 23.6% patients had conditions other than well-recognized OIs. Various studies show a different pattern of OIs. The study from Tamil Nadu,[24] reported commonest OI as tuberculosis 61% followed by Candidiasis (41%), diarrhea (16%), fungal infections of skin (16%). Study of NACO[25] has also reported tuberculosis as the major OI with 62% incidence followed by candidiasis (57%) and chronic diarrhea (47%). Another study from North India,[26] also reports tuberculosis (TB) as the most common OI (71%) followed by candidiasis (39.3%), *P. jiroveci* pneumonia (PCP) (7.4%), cryptococcal meningitis and cerebral toxoplasmosis (3.7% each). A study from Karnataka[27] reported that the oral

candidiasis with 59% patients as the most common OI, followed by tuberculosis (56.00%), cryptosporidium infection (47.00%) and *P. carinii* (7.00%). Another study from Eastern India[28] also reported Oral candidiasis (88%) as the most common OI, followed by tuberculosis (57%), enteropathogenic *Vibrio* (47%), cytomegalovirus infection (45%), cryptosporidial diarrhea (43%), *E. coli* infection (42%). Our study reports are in accordance with other reports.[26] The most important finding of our study population is the pattern of OIs among our study group did not differ much from patients not receiving ART, this may be because of non-adherence to ART and/or improper treatment of OIs. These observations highlight the importance of knowing the region specific OIs. Most often these OIs will not represent new infection but reactivations of the latent infection.[25] Latent infections are the major cause of immune reconstitution inflammatory syndromes, if the ART is started in such patients.[29] The mean CD4 count in the study population who were on ART was 230 ± 152 cells/μl, stage II patients had 340 ± 87 cells/μl and stage III patients had 96 ± 38 cells/μl. The change in the CD4 T-cell count after ART is based on the degree of CD4 depletion prior to ART initiation.[30] An important finding is none of our study group patients were regular in taking ART because of various reasons. The studies evaluating pattern of OIs in patients with ART are very few and we have classified the patients based on their CD4 count as per CDC guidelines into three stages. Among stage one group, only one patient had >500 CD4 cells/μl and no OIs were observed in this patient. Stage II group with CD4 count between 200 and 499 cells/μl, presented with one or two OIs and some patients presented even non OIs. Stage III group patients with <200 cells/μl CD4 count, presented with multiple OIs with multi system involvement, because of severe immunosuppression. Early diagnosis and prompt treatment of OIs definitely contributes to increased life expectancy among infected patients, delaying the progression to AIDS.[31]

REFERENCES

1. Centers for Disease Control (CDC). Update on acquired immune deficiency syndrome (AIDS) — United States. Morb Mortal Wkly Rep 1982;31:507-8, 513-4.
2. Kaplan JE, Hu DJ, Holmes KK, Jaffe HW, Masur H, De Cock KM. Preventing opportunistic infections in human immunodeficiency virus-infected persons: Implications for the developing world. Am J Trop Med Hyg 1996;55:1-11.
3. Selik RM, Haverkos HW, Curran JW. Acquired immune deficiency syndrome (AIDS) trends in the United States, 1978-1982. Am J Med 1984;76:493-500.
4. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. Ann Intern Med 1996;124:633-42.
5. Finkelstein DM, Williams PL, Molenberghs G, Feinberg J, Powderly WG, Kahn J, et al. Patterns of opportunistic infections in patients with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:38-45.
6. Shahapur PR, Bairy I, Shivananda PG. Effect of "HAART" on CD4+ T lymphocyte counts in HIV seropositive south-Indian individuals — A follow up study. Indian J Pathol Microbiol 2005;48:270-2.
7. Shahapur PR, Bairy I, Shivananda PG. CD4 and CD8 reference counts in normal healthy south-Indian adults. Indian J Med Microbiol 2008;26:280-1.
8. Giri TK, Pande I, Mishra NM, Kailash S, Uppal SS, Kumar A. Spectrum of clinical and laboratory characteristics of HIV infection in northern India. J Commun Dis 1995;27:131-41.
9. Kaur A, Babu PG, Jacob M, Narasimhan C, Ganesh A, Saraswathi NK, et al. Clinical and laboratory profile of AIDS in India. J Acquir Immune Defic Syndr 1992;5:883-9.
10. Ayyagari A, Sharma AK, Prasad KN, Dhole TN, Kishore J, Chaudhary G. Spectrum of opportunistic infections in human immunodeficiency virus (HIV) infected cases in a tertiary care hospital. Indian J Med Microbiol 1999;17:78-80.
11. Kaplan JE, Roselle G, Sepkowitz K. Opportunistic infections in immunodeficient populations. Emerg Infect Dis 1998;4:421-2.
12. Matin N, Shahrin L, Pervez MM, Banu S, Ahmed D, Khatun M, et al. Clinical profile of HIV/AIDS-infected patients admitted to a new specialist unit in Dhaka, Bangladesh — A low-prevalence country for HIV. J Health Popul Nutr 2011;29:14-9.
13. Jamaiah I, Rohela M, Tok EL, Tan CL, Tan WH, Teo WS, et al. Pneumocystis carinii (jirovecii) pneumonia (PCP): The most common opportunistic infection observed in HIV/AIDS cases at the University Malaya Medical Centre, Kuala Lumpur, Malaysia. Southeast Asian J Trop Med Public Health 2012;43:825-31.
14. Wong KH, Lee SS, Lo YC, Li PC, Ho HF, Sitt WH, et al. Profile of opportunistic infections among HIV-1 infected people in Hong Kong. Zhonghua Yi Xue Za Zhi (Taipei) 1995;55:127-36.
15. Huang LF, Tang XP, Cai WP, Chen XJ, Lei CL, Li LH, et al. An analysis of opportunistic infection in 762 inpatients with human immunodeficiency virus infection in Guangdong areas. Zhonghua Nei Ke Za Zhi 2010;49:653-6.
16. National AIDS Control Organization. Guidelines on HIV Testing. NACO: March 2007.
17. National AIDS Control Organization. National Guidelines for the Enumeration of Cd4' T-Lymphocytes with Single Platform Technology for Initiation and Monitoring of Art in HIV Infected Individuals. NACO; March 2007.
18. National AIDS Control Organization. Antiretroviral Therapy Guidelines for HIV Infected Adults and Adolescents Including Post-exposure Prophylaxis. NACO; May 2007.
19. Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years — United States, 2008. MMWR Recomm Rep 2008;57:1-12.
20. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis 2003;36:79-85.
21. Gangakhedkar RR, Bentley ME, Divekar AD, Gadkari D, Mehendale SM, Shepherd ME, et al. Spread of HIV infection in married monogamous women in India. JAMA 1997;278:2090-2.
22. Newmann S, Sarin P, Kumarasamy N, Amalraj E, Rogers M, Madhivanan P, et al. Marriage, monogamy and HIV: A profile of HIV-infected women in south India. Int J STD AIDS 2000;11:250-3.
23. 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.
24. Kumarasamy N, Solomon S, Jayaker Paul SA, Venilla R, Amalraj RE. Spectrum of opportunistic infections among AIDS patients in Tamil Nadu, India. Int J STD AIDS 1995;6:447-9.
25. Misra SN, Sengupta D, Satpathy SK. AIDS in India: Recent trends in opportunistic infections. Southeast Asian J Trop Med Public Health 1998;29:373-6.
26. Sharma SK, Kadhiravan T, Banga A, Goyal T, Bhatia I, Saha PK. Spectrum of clinical disease in a series of 135 hospitalised HIV-infected patients from north India. BMC Infect Dis 2004;4:52.

27. Singh A, Bairy I, Shivananda PG. Spectrum of opportunistic infections in AIDS cases. Indian J Med Sci 2003;57:16-21.
28. Chakraborty N, Mukherjee A, Santra S, Sarkar RN, Banerjee D, Guha SK, *et al*. Current trends of opportunistic infections among HIV-seropositive patients from Eastern India. Jpn J Infect Dis 2008;61:49-53.
29. Crum-Cianflone NF. Immune reconstitution inflammatory syndromes: What's new? AIDS Read 2006;16:199-206, 213, 216.
30. McKinnon LR, Kimani M, Wachihi C, Nagelkerke NJ, Muriuki FK, Kariri A, *et al*. Effect of baseline HIV disease parameters on CD4+ T cell recovery after antiretroviral therapy initiation in Kenyan women.

PLoS One 2010;5:e11434.
31. Ramana KV, Mohanty SK. Opportunistic intestinal parasites and TCD4+ cell counts in human immunodeficiency virus seropositive patients. J Med Microbiol 2009;58:1664-6.

Staying in touch with the journal

1) **Table of Contents (TOC) email alert**
Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to **www.jnsbm.org/signup.asp.**

2) **RSS feeds**
Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal's website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewzCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add **www.jnsbm.org/rssfeed.asp** as one of the feeds.