Original Research Article

Spectrum of opportunistic infections in relation to CD4 count in HIV-2 patients

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Abstract

Background: Opportunistic infections (OIs) are the most common complication of human immunodeficiency virus (HIV) infection. OIs cause significant morbidity and mortality in people with HIV infection. There is very little published data available on opportunistic infections in HIV-2 in India. **Aim:** To study the opportunistic infections with respect to CD-4 count in HIV-2 patients. **Material and Methods:** This cross-sectional study included HIV-2 patients who visited ART centre in tertiary care hospital through SACEP and / or HIV-2 patients admitted in the medical wards over a period of 19 months and who were documented HIV-2 reactive with western blot confirmation. Every 6 monthly CD4 counts of all patients were noted and occurrence of opportunistic infections with respect to CD4 count was evaluated. **Results:** The OI spectrum observed in our study was Tuberculosis (28.72%) being most common followed by Candidiasis (9.34%), Diarrhoea (7.96%), Herpes (6.23%), Lymphoma (1.73%), CMV retinitis (1.38%), PCP (1.38%), CNS Toxoplasmosis (1.04%), PML (0.69%) and Cryptococcal meningitis (0.69%). Tuberculosis, oral candidiasis, diarrhoea and herpes infections manifests at comparatively higher CD4 count as compared to cryptococcal meningitis, CMV retinitis and PCP. **Conclusion:** HIV-2 infection has long asymptomatic period, is less virulent but causes immunosuppression, as well as AIDS characterized by the opportunistic infections at lower CD4 counts.

Key words: HIV-2 infection, CD4 count, opportunistic infections, tuberculosis, candidiasis

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INTRODUCTION

Human Immunodeficiency Virus (HIV) pandemic is among the greatest health crises ever faced by humanity. The prolonged course of human immunodeficiency virus (HIV) infection is marked by a decrease in the number of circulating CD4+T helper cells and persistent viral replication, resulting in immunologic decline and death from opportunistic infections and neoplasm.[1,2] Opportunistic infections (OIs) are the most common complication of human immunodeficiency virus (HIV) infection.[3-5] OIs cause significant morbidity and mortality in people with HIV infection.[6,7] The infective organisms responsible for OIs differ in characteristics from that of conventional communicable disease, and are mainly low or non-virulent. Hence, these could be, non-pathogenic in an individuals with intact immune system (Candida albicans) or known pathogens presenting in a different way than usual in immunocompetent individuals (Cryptococcus neoformans) or in the form of increased virulence, recurrence, multi-drug resistance (Mycobacterium tuberculosis) or atypical presentation (dermatophytosis).[8-10] HIV-1 and HIV-2 are closely related retroviruses of the same genus (Lentiviridae) and share the same modes of transmission. However, HIV-2 differs from HIV-1 as it is associated with lower viral load levels and slower rates of CD4 decline and clinical progression compared with HIV-1;11,12 86% to 95% of people infected with HIV-2 are long-term nonprogressors.[13,14] There is very little published data available on opportunistic infections in HIV-2 in India. Our institution has an ART centre which is one of the largest in the country and has a centre of excellence which caters to special situations like HIV-2 patients, first line ART failure and patients with adverse reaction to ART. Hence, we sought to study the opportunistic infections with respect to CD-4 count as our centre had

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significant number of HIV-2 patients over last many years.

MATERIAL AND METHODS

This cross sectional study was conducted at a tertiary teaching hospital. The study protocol was reviewed and approved by the Institute Ethics Committee.

Study design

This cross-sectional study included HIV-2 patients who visited ART centre in tertiary care hospital through SACEP and / or HIV-2 patients admitted in the medical wards over a period of 19 months and who were documented HIV-2 reactive with western blot confirmation. Western blot confirmation was obtained by sending samples to NARI, Pune.

Patient definition

Any HIV-2 reactive with western blot confirmation patient registered at ART centre or admitted in medical wards and who fulfilled the inclusion criteria.

Inclusion criteria

- All HIV-2 reactive patients with western blot confirmation enrolled at ART centre.
- HIV-1 and HIV-2 co-infected patients.
- All above patients who gave written informed consent were included in study.

Exclusion criteria

- All HIV-1 reactive patients who were non-reactive for HIV-2 infection.
- Patients who did not give written informed consent.

Data collection

Sociodemographic data, WHO clinical staging of study population at the time of initial visit, 6 monthly CD4 counts, ART data were obtained from patient admitted in medicine wards, from ART centre, from white cards available at ART centre, from green book (ART registration book), from SACEP records with NACO permission and from previous case paper records if any available.

Clinical evaluation

Detailed history and clinical examination were done on every ART visit days starting from the day of inclusion into study. All the patients were evaluated at the time of each visit at ART centre for associated symptoms, opportunistic infections. Every 6 monthly CD4 counts of all patients were noted and occurrence of opportunistic infections with respect to CD4 count was evaluated. For the patients who were admitted in medical wards, detailed history and clinical examination were done and details of opportunistic infections, clinical profile and 6 monthly CD4 were taken. Basic lab investigations like complete blood count, liver function test, renal function test, chest x-ray, sputum routine microscopy and for acid fast bacilli, ultrasonography of abdomen and specific investigations for diagnosis of OI like CT brain, CT thorax, CT abdomen, CSF study, pleural fluid study, ascetic fluid study, lymph node FNAC and biopsy, OGD scopy, fundoscopy, etc. were done.

Statistical analysis

Stata SE 13.1 was used to analyse data. Mean, Standard deviation, Standard error, 95% Confidence intervals were calculated. If the variable is not normally distributed, Median and Interquartile range were used. Normality was assessed by the Shapiro-Wilk procedure. Mann Whitney U test was used to test variables that were not normally distributed with 2 groups. Spearman`s correlation coefficient (rho) was used to correlate 2 quantitative variables. A p value (significance) of < 0.05 (Sig.) was deemed statistically significant, $p < 0.01$ as highly significant (HS) and $p < 0.0001$ as very highly significant (VHS).

RESULTS

In our study, total 289 patients of HIV-2 were enrolled. A majority of them 158 (54.7%) belonged to the age group of 41 to 50 years and the median (IQR 25%-75%) age was 46 (42-51) years. Of the 289 individuals analyzed, 203 (70.24%) were males and 86 (29.76%) were females. Male to female ratio was 2.4:1. Thus, in our study prevalence of HIV-2 was more in male as compared with female. This may be due to high risk behaviour in male individuals. Median baseline CD4 count of study population was 211 (123.7-303.2 cells /µl).

Table 1: Distribution of study population according to baseline CD4 count

Baseline CD4 (cells /µl)	No. of cases		Percentage (%)	
≤50	11		3.81%	
51-200	122	238	42.21%	82.35%
201-350	116		40.14%	
>350	40		13.84%	
Total	289		100%	

In the present study, we evaluated the study population according to baseline CD4 categories and we observed that, maximum cases (238, 82.35%) had baseline CD4 count in between 51 to 350 cells /µl. 40 (13.84%) cases had CD4 count >350 cells /µl and 11 (3.81%) cases had CD4 count ≤50 cells /µl.

Table 2: Distribution of study population according to WHO clinical staging

WHO clinical stage	No. of cases	Percentage (%)
I	141	48.79
II	35	12.11
III	60	20.76
IV	53	18.34
Total	**289**	**100**

In our study, 141 (48.79%) cases belonged to WHO stage I while 35 (12.11%) cases belonged to WHO stage II, 60 (20.76%) cases belonged to WHO stage III and 53 (18.34%) cases belonged to WHO stage IV indicating slower progression of HIV-2 infection as maximum cases were had WHO stage I category.

Table 3: Median baseline CD4 count according to WHO clinical staging

Categories	No. of cases	Median baseline CD4 (cells /µl)	IQR (25%-75%)
WHO stage I	141	249	160.750 to 317.500
WHO stage II	35	248	113.250 to 284.750
WHO stage III	60	196.5	108.000 to 310.500
WHO stage IV	53	139	85.000 to 231.750
Total	289	211	123.750 to 303.250

Spearman's correlation coefficient (rho) = -0.258; p <0.0001 (VHS);

95% confidence interval for (rho) = - 0.363 to -0.147 In the present study, median baseline CD4 count in WHO stage I was 249 cells /µl (IQR 25%-75%=160.750 to 317.500) and in WHO stage IV was 139 cells /µl (IQR 25%-75% =85.000 to 231.750). This indicates fall in CD4 count from WHO stage I to WHO stage IV. WHO clinical staging of 289 HIV-2 patients was statistically analyzed by using Spearman's correlation coefficient (rho) with baseline CD4 counts. Results suggest negative linear relationship between WHO clinical staging and CD4 count; rho= -0.258, p <0.0001, 95% CI for rho = - 0.363 to -0.147). In the present study, we observed 13 (4.50%) cases with HIV-1 and HIV-2 dual infection. Out of 289 cases, 117 (40.48%) cases had opportunistic infections.

Table 4: Different types of OIs in study population

OIs	No. of cases	Percentage (%)	Median CD4 (cells /µl)	CD4 IQR (25% - 75%)
Tuberculosis	83	28.72	173	97.500 to 264.750
Candidiasis	27	9.34	198	121.750 to 325.250
Diarrhoea	23	7.96	144	59.250 to 274.250
Cryptococcal meningitis	2	0.69	65.5	38.000 to 93.000
Lymphoma	5	1.73	117	86.750 to 181.500
Toxoplasmosis	3	1.04	139	103.750 to 378.250
PML	2	0.69	112	92.000 to 132.000
CMV retinitis	4	1.38	37	26.000 to 56.500
PCP	4	1.38	80	49.500 to 99.500
Herpes	18	6.23	136.5	89.000 to 209.000

In the present study, we analyzed the presence of different OIs in study population and their occurrence with respect to median CD4 count. We observed, tuberculosis was the most common opportunistic infection in study population (HIV-2). 83 (28.72%) cases had TB (either pulmonary or extrapulmonary TB). Median CD4 count for TB was 173 cells /µl (IQR 25%-75% - 97.50 to 264.75).

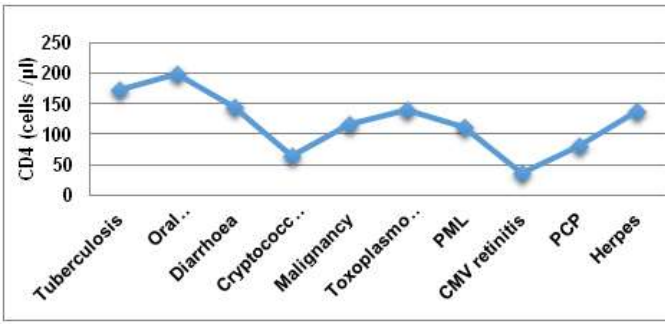

Figure 1: Median CD4 in different OIs

Line chart represents the median CD4 count on which different OIs manifests. Thus, it was observed that tuberculosis, oral candidiasis, diarrhoea and herpes infections manifests at comparatively higher CD4 count as compared to cryptococcal meningitis, CMV retinitis and PCP.

DISCUSSION

In spite of various HIV testing opportunities available, earlier a majority of infected individuals became aware of their status only after they developed opportunistic infections in the late stages.[15,16] This picture was due to the lack of awareness about HIV/ acquired immune-deficiency syndrome (AIDS) in individuals with high-risk behaviour such as men having sex with men, sex workers, and injecting drug users. Clinical course and pattern of opportunistic infections varies from patient to patient and from country to country.[17,18] For example, TB is the most common OI in HIV patients in India,[19] whereas OIs like Mycobacterium avium complex (MAC) and Kaposi's sarcoma, frequently reported in the developed world, are not as commonly reported in India.[20-23] The progression and outcome of HIV/ AIDS is influenced by factors such as baseline health and nutritional status, environment, endemic diseases, and access to therapy. It is important to understand the presentation of HIV disease in the local context. In the present study, out of 289 HIV-2 patients OIs were seen in 117 (40.48%) cases. Pulmonary tuberculosis (18.33%) was the most common AIDS-defining illness observed in this study, and the median CD4 lymphocyte count at the time of diagnosis was 173 cells/µl. The other prevalent AIDS-defining infections are as follows: extrapulmonary tuberculosis (13.84% of patients; median CD4 cell count, 164 cells/µl), candidiasis (9.34% of patients; median CD4 cell count,198 cells/µl), Diarrhoea (7.96%; median CD4 cell count 194 cells/µl), Herpes (6.23% of patients; median CD4 cell count, 136.5 cells/µl), *P. carinii pneumonia* (1.38% of patients; median CD4 cell count, 80 cells/ µl), cytomegalovirus retinitis (1.38% of patients; median CD4 cell count, 37 cells/µl). CNS toxoplasmosis (1.04% of patients; median CD4 cell count, 139 cells/µl), Lymphoma (1.735 of patients; median CD4 cell count, 117 cells/ µl), Cryptococcal meningitis (0.69% of patients; median CD4 cell count, 65.5 cells/ mL) and PML (0.69% of patients; median CD4 cell count, 112 cells/ µl).

Table 5: Comparison of an incidence of occurrence of all OIs with other studies

OIs	Present study (%) HIV-2		Kumarasamy N *et al*.[18] (%) HIV-1	
	No. of cases (%)	Median CD4 (cells /µl)	No. of cases (%)	Median CD4 (cells /µl)
Pulmonary TB	18.33	173	49.3	111
Extrapulmonary TB	13.84	164	11.1	122
Candidiasis	9.34	198	54.5	107
Diarrhoea	7.96	144	4.7	133
Cryptococcal meningitis	0.69	65.5	4.7	91
Lymphoma	1.73	117	-	-
CNS Toxoplasmosis	1.04	139	3.4	135
PML	0.69	112	-	-
CMV retinitis	1.38	37	3.2	51
PCP	1.38	80	6.1	87
Herpes	6.23	136.5	8.6	105

The OI profile spectrum observed in the present study of HIV-2 infection is similar to that seen in HIV-1 with comparable CD4 cell counts. Thus, though HIV-2 is considered to be a more benign virus, it is seen that at low CD4 counts (<200 cells /µl) the patients have all the opportunistic infections which are AIDS defining illnesses. Thus, patients of HIV-2 with low CD4 counts do have serious opportunistic infections. Similar results were obtained while comparing with Kumarasamy N *et al*.[19] However, comparing the percentage incidence of occurrence of all OIs in this spectrum in our study with the study of Kumarasamy N *et al*,[19] it is noted that our study had much lower incidence of OIs particularly comparing TB, candida and PCP infections. As we could not find any study on spectrum of OIs in HIV-2, we compared the spectrum of OIs in our study with spectrum

of OIs in a study on HIV-1. Recent data show that survival of persons with undetectable HIV-2 viral load is similar to that of the general population.[24] However, HIV-2 can cause immune-suppression, as well as AIDS characterized by the same signs, symptoms, and opportunistic infections that are seen in HIV-1. HIV-2-associated AIDS may often be associated with lower viral load levels than HIV-1 (>10,000 copies/mL in HIV-2 versus sometimes millions of copies/mL in HIV-1).[24]

CONCLUSION

HIV-2 infection has long asymptomatic period, is less virulent but causes immunosuppression, as well as AIDS characterized by the opportunistic infections at lower CD4 counts. The response to ART and the pattern of resistance to ART is unique; and further studies should be carried out for the same.

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