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HIV-Co Opportunistic Infections - A Current Picture in Tropical Climatic Eastern Indian Seropositive Population

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1. Introduction

HIV or Human Immunodeficiency Virus, a RNA virus. On exposure to this virus, it directly attacks certain human organs, such as the heart, brain and kidneys. It plays a very significant role in weakening the immune system of its host. The immune system forms the framework in protecting the body from attack by any foreign agent like the bacteria, fungus, virus or any type of infection and even from some cancers by reacting accordingly. The primary cells attacked by HIV are the CD4+ lymphocytes, which are glycoprotein expressed on the surface of T_h cells, macrophages, monocytes, regulatory T cells and dendritic cells and plays a vital role in performing important immune responses in the body. It helps in direct immune function in the body. It is via this CD4 that HIV-1 enters into the host T-cells. A progressive reduction in the number of T cells expressing CD4 occurs on HIV infection. Since CD4+ plays a very important role in maintaining a proper immune system function, progressive loss of CD4+ lymphocytes as destroyed by HIV, the immune system barely works. With more active HIV infection or on prolonged exposure to HIV would deprive the host of its CD4 containing cells and this reduced CD4 count leading to reduced host immunity. Opportunistic infections take advantage of this weak host immune system and manifest their adverse effects. Many people especially during the advanced stage of HIV infection face problems resulting from opportunistic infections (OIs) and cancers.

The HIV/AIDS is a global epidemic and approximately 40 million people are living with HIV/AIDS worldwide (Quinn, 1996). Of all HIV/AIDS infected people, 95% are living in developing countries. Africa is the worst affected of all the continents. It consists of 19 countries worldwide with the highest prevalence of reported infections with more than 24.5 million, and more than 60% of the HIV-infected population. South Africa holds the record of being the country with the largest population living with the disease, at well over 5 million people infected. South Africa is followed by followed by Nigeria in 2nd place and India being the 3rd largest population of HIV infected people. Currently India about 5.134 million HIV infected cases are present in India which comprises of 65% cases of Southeast Asia. In India, HIV/ AIDS pandemic no longer belongs to the high-risk groups but now it is common among the general population (Ran & Hemalatha, 2006; Solomon *et al*.2006). Exponential growth of this epidemic is now at the threshold for India.

2. OIs associated with HIV

As mentioned earlier, taking advantage of this weakened immune system of its host with advanced HIV infection several infections and malignancies called 'opportunistic infections' appear.Opportunistic Infections (OIs) have been recognized as common complications of HIV infection due to immune deficiency which detoriates both the standard of life and life expectancy of the these HIV infected people. One of the main reasons behind hospitalization and substantial morbidity in HIV infected patients due to these OIs. OIs have been recognized as common complications of HIV infection since the beginning of the HIV epidemic (Kanabus *et al*. 2006; CDC, 1982; Selik *et al*.1984). These OIs develop several complicacies which lead to substantial morbidity and hospitalization. Several toxic and expensive therapies are required as a part of the treatment procedure. These ultimately lead to shorten the survival of people with HIV infection OI (Moore & Chassion, 1996; Finkelstein *et al*.1996). The decrease in the CD4 count in these HIV infected people is not doubt partially responsible for these various OIs (Talib *et al*.1993). A dramatic reduction in the incidence of OI among HIV-positive people who have received ART has been observed on introduction of antiretroviral therapy (ART); however, HIV/AIDS patients all around the world cannot afford or are not exposed to ART. Millions of people living with HIV in resource-poor communities/ countries donot get access to ART and in these cases especially the occurrence of OIs is very common (Kanabus *et al*. 2006). Even where ART drugs are available, they do not entirely remove the need for preventing and treating OI. Because of poor adherence, drug resistance or other factors measures to prevent and treat OIs become essential if ART stops working. However, providing prevention and treatment of OIs is of utmost importance to these people as it not only helps HIV-positive persons to live longer, healthier lives, but it can also help to prevent tuberculosis (TB) and other transmissible OIs from spreading to others. At present, the absolute CD4+ count determines the initiation of primary prophylactic therapies for OIs, which is an excellent predictor of the short-term overall risk of developing AIDS among HIV-infected patients (Stein *et al*.1992).

The spectrum and frequency of certain OIs highlight the urgency of studying HIV/AIDS in resource-limited countries like India where locally specific disease patterns may be observed. With the identification of such opportunistic pathogens in these HIV/AIDS patients, the HIV epidemic can be more effectively managed if physicians and health planners are aware of this information. The data may thus serve as a baseline, which can be implemented to the remote district level study as well and may further give an insight into the HIV related opportunistic infections would render help for subsequent HIV/AIDS care and management in a developing country like India.

2.1 Study carried out by our research group

In our study (published as *Current Trends of Opportunistic Infections among HIV- Seropositive patients from Eastern India* published in Jpn.J.Infect.Dis. 61, 49-53, 2008) the HIV-Co Opportunsitic infections from the cases reported from the various HIV-infected patients admitted Calcutta Medical College Hospital, Kolkata West Bengal, and of referred patients from Apex Clinic, Calcutta Medical College Hospital, a referral center for patients of HIV infection or AIDS were included. The patients admitted in the hospital were from different states of eastern India such as Bihar, Orissa, Jharkhand and from West Bengal. Their HIV

status was confirmed by three ERS (Enzyme-linked immunosorbent assay [ELISA], Rapid, Simple), an ELISA (viz., HIV ELISA, Rapid test) and Western blot as recommended by the National AIDS Control Organization (NACO), Ministry of Health and Family Welfare, Government of India (NACO,2000).

For the diagnosis of OIs, routine microbiology smears, cultures and serology should be performed with utmost precaution. Different samples as directed by clinicians were collected depending on patient symptoms and clinical presentation under universal aseptic precautions in suitable sterile containers for the routine diagnosis. For the isolation, culture and identification of species of the pathogen in order to detect the OIs from blood samples, sputum and stool. OIs were diagnosed according to the criteria suggested by the Centers for Disease Control and Prevention (CDC) (CDC,1992). For isolation of *Candida* causing oral candidiasis to the HIV patients, Sabourand's dextrose agar (SDA) was used as transporting media. Pseudohyphae and budding yeast were characteristic findings. The appearance of the lesion and presence of yeast forms on microscopic examination of the oropharynix were sufficient evidence to confirm the diagnosis (Kolmer *et al*.1969). The most prevalent and obtained pure culture of yeast was compared with referral strain *Saccharomyces cerevisiae* ATCC 2601 and that of *Candida albicans* spp. was compared with referral strain *C. albicans* ATCC 10231. Cases of TB were classified as definite if the culture for *Mycobacterium tuberculosis* was positive for acid-fast bacilli. The decontaminated sputum sample from the diagnosed TB patients was further studied for obtaining a pure culture of *M. tuberculosis* growing on prepared LJ slants.The positive pure cultures grew yellow colonies on the slants. The isolated pure culture of *M. tuberculosis* spp. was compared with referral strain *M. tuberculosis* ATCC 25177. Stool specimens from all diarrhea patients (following WHO criteria of watery stool for at last 48 h prior to investigation) were processed (da Silva, & Pieniazek, 2003) and examined microscopically for the presence of *Cryptosporidium parvum*, a zoonotic pathogen that causes chronic watery diarrhea. The staining technique used for staining of *Cryptosporidium* was modified Ziehl-Neelsen (AFB staining). Cryptosporidia and other coccidia stained pink-red. The isolated pure culture of *Cryptosporidium* spp. was compared with a referral strain *Cryptosporidium* (Microbiology QC slides, Himedia SL45-10; Himedia).Enteric bacterial flora from the stool samples of diarrhea patients were isolated using differential selective screening media such as UTI agar (urinary tract infection agar; Himedia) after documenting their clinical manifestations, including intestinal flu, inflammation-associated cramping, abdominal pain, nausea and vomiting. Different enteric pathogens that exhibit a particular colony color facilitate the identity of particular microorganisms such as *Escherichia coli* (pink-magenta), *Proteus mirabilis* (light green), *Enterococcus fecalis* (bluish green), *Staphylococcus aureus* (cream), *Pseudomonas aureginosa* (colorless) and *C. albicans* (pin point white). For isolation of *Vibrio cholerae* and other enteropathogenic *Vibrio*, TCBS agar (thiosulfate citrate bile salt sucrose; SRL, Mumbai, India) was used. Cryptococcal meningitis was confirmed by clinical symptoms and signs as well as the detection of cryptococcal capsular antigen (*Cryptococcus* antigen latex agglutination Test; Remel, Lenexa, Kans., USA). Toxoplasmic encephalitis was diagnosed in the presence of at least two of the following findings: a history of neurological symptoms, neurological signs at admission or suggestive computed tomography scan or magnetic resonance imaging of the brain (Luft, & Remington,1988, 1992). A response to anti-*Toxoplasma* (IgM) antibodies, which was detected by a serological ELISA commercial kit gives a satisfactory result.

Characteristic	No. of Patients: (n=125)	
	Male (%)	Female (%)
No. of HIV-seropositive patients	105 (84)	20 (16)
Age in years (mean ± standard deviation)	(35.6 ± 6.77)	(33.15 ± 6.68)
≤20	1 (0.8)	1 (0.8)
21 – 30	27 (21.6)	7 (5.6)
31 – 40	55 (44)	10(8)
≥41	22 (17.6)	2(1.6)
Mode of transmission of HIV		
Heterosexual transmission	80 (64)	–
Homosexual transmission	6 (4.8)	–
Blood transfusion	3 (2.4)	1 (0.8)
Intravenous drug abuse	20(16)	5(4)
Frequent needle prick	–	–
Vertical transmission	–	–
Unsterilized injection equipments	6 (4.8)	4 (3.2)
CD4+ lymphocyte count/µl (mean ± standard deviation)		
	(439.45 ± 222.11)	(12 ± 93.82)
≤50	18 (14.4)	4 (3.2)
51 – 100	25 (20)	3 (2.4)
101 – 200	38 (30.4)	8 (6.4)
≥201	24 (19.2)	5 (4)

Table 1. Patient Characteristic

In our study, 125 HIV (HIV-1 subtype) patients with OI were studied, of whom, 105 (84%) were male and 20 (16%) were female. The majority of patients (52%) were 31 - 40 years old followed by 27, 19 and 1% for the age groups 21 - 30, ≥41 and ≤20 years old, respectively. Heterosexual mode of transmission was obtained to be the predominant mode of transmission of HIV accounting for 64% of cases, followed by other routes (Table 1).

According to CD4 cell count/cu mm of blood ,the distribution of the study population was a maximum 36% of the population with 101-200 CD4+ cell count, followed by 23, 22 and 17% of patients with ≥201, 51 - 100 and ≤50 CD4 cell count, respectively. A significant finding from an epidemiological point of view was the complete absence of Yeast, HBV and venereal disease in female subjects. The follow-up of the case studies revealed that 7 cases (5.6%) out of 125 HIV-infected patients expired during the later period of their treatment. Ten (8%) of the study patients were receiving ART. Dermatological reactions were found as drug-related complications in patients with HIV infection. The most serious disorder, Steven-Johnson syndrome (SJS), was found to occur in 5 (4%) HIV-infected patients after intake of a combination of rifampicin-isoniazid after beginning treatment for recurrent Pulmonary TB occurring as an OI (Pitche *et al*. 2005).

2.1.1 Prevalence of different OIs

Oral candidiasis (OC) emerged as the most frequent infection to be associated with HIV infection in patients across the total range of CD4+ as studied by us among the spectrum of OIs observed. OC infection was found to be prevalent among 88% of these patients. Oral yeast (*Saccharomyces*)-infection was found in 5.6% of patients. TB emerged as the second most prevalent infection amongst the population as studied by us, developing in 57% of subjects. The diagnosis of TB was definite for all the suspected patients. Both pulmonary (69.4%) and extra pulmonary (16.6%) types were found to be prevalent. Amongst the HIV positive patients extra pulmonary TB was found to be prevalent amongst patients with lower median CD4+ counts (46/µl blood). But amongst the HIV/AIDS patients pulmonary TB was found amongst the patients having median CD4+ of 105/µl blood -which are the most common location of the disease.

HIV is driving the tuberculosis (TB) epidemic in many developing countries including India. During our study to determine the drug resistance pattern of pulmonary TB among HIV seropositive and HIV negative hospitalized patients from different states of Eastern India, (published as *Drug susceptibility profile of Mycobacterium tuberculosis isolated from HIV infected and uninfected pulmonary tuberculosis patients in Eastern India* in Transactions of the Royal Society of Tropical Medicine and Hygiene 104 (2010) 195–201) the TB positive isolates were screened and characterized by conventional laboratory methods followed by first- and second-line drug susceptibility testing on Lowenstein-Jensen medium by the proportion method. The drug susceptibility testing showed 17.7% and 6.6% multidrug-resistant (MDR) TB for the HIV positive and HIV negative patients, respectively. 22.2% of the isolated MDR-TB cases could be classified as extensively drug-resistant (XDR) TB isolates. 88.8% of all the MDR-TB isolates and all XDR-TB isolates were screened from HIV patients. 27.7% of the MDR-TB isolates showed resistance to all the first-line drugs. Mortality rate among the XDR-TB isolates was as high as 75%. Patients with interrupted anti-TB drug treatment were the ones most affected. These findings are critical and the risk to public health is high, particularly with HIV infected patients.

The pathogen most frequently isolated from the diarrheic patients was *C. parvum* (43.1%). In about 47% of the immunocompromised patients, various enteropathogenic species of *Vibrio* were found, while simultaneously the presence of bacterial pathogens from *Enterobacteriacae* was 40% and *E. coli* was found in 42% of cases.

Among the viral OIs, CMV infection was the most predominant; 45% of subjects were positive for CMV infection among 125 HIV-seropositive study subjects. The other viral infections found in the study population were HSV (7.2%) and HBV (5.6%) which were much less in comparison to the prevalence of CMV infection. The absence of any specific clinical symptoms of CMV amongst the patients was an important characteristic of CMV infection and was often indistinguishable from other types of infection. The common unifying feature of CMV disease in the immunocompromised patient was the presence of fever, and approximately 65% of cases developed hearing defects and perceptual organ damage such as optic atrophy and blindness.

The most common form of disseminated cryptococcosis was Meningitis, and it developed in 4% of the study patients. All cases were diagnosed by clinical and neurological symptoms with confirmation by laboratory investigations.

Very few other OIs were found, viz., herpes zoster virus (HZV) infection, syphilis from *T.pallidum*, etc., among the patients investigated. Interestingly, not even a single case of malignancy was found to occur among the investigated patients.

2.1.2 Highlights of our study

Our study highlights that candidial infection is the most common OI, followed by TB and diarrhea, all of which are presumed to result from our geographic, climatic and socio-economic conditions. Early diagnosis of OIs and prompt treatment definitely contributes to increased life expectancy among infected patients, delaying the progression to AIDS. Despite the moderate (n = 125) number of patients included in our study, we believe the data obtained here provide some important background information that can form the basis of future, more elaborative and systematic studies. Furthermore, the data shown can be a valuable means of determining the range and relative frequency of infectious diseases, and this can potentially have an immediate impact on patient care by suggesting appropriate interventions based on the results.

The following table (2) represents the cases of dual infection in these HIV infected patients:

Co-infection with Oral Candiditis	Number of cases	Percentage of Cases
Enteropathogenic *Vibrio*	47	37.6
Tuberculosis	50	40.0
Escherichia coli infection	42	33.6
Cryptosporidial diarrhea	40	32.0

Table 2. Represents the cases of dual infection in these HIV infected patients

As a part of our investigation, we also studied co-infection of Oral Candidiasis with other OIs among the different HIV/AIDS population:

The figures below demonstrate:

The Venn Diagrams below demonstrate the co-infections:

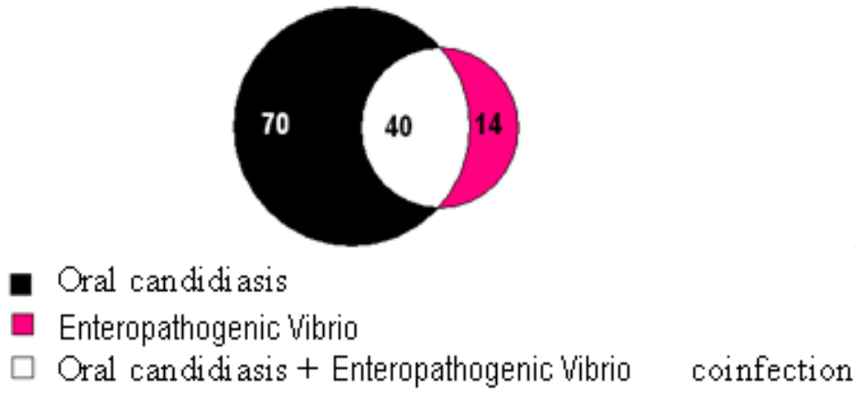


Fig. 1. Co-infection of Oral candidiasis with Enteropathogenic Vibrio

Oral candidiasis was found to be prevalent amongst 110 of the 125 HIV/AIDS infected patients. Enteropathogenic *Vibrio* was found to be prevalent amongst 54 of the AIDS/HIV infected patients. Amongst them, 40 developed co-infection of these two OIs. Thus, only 14 of the 54 patients infected with Enteropathogenic *Vibrio* did not develop any infection from Oral candidiasis.

From our study, it again becomes very prominent that HIV/AIDS patients suffering from Enteropathogenic *Vibrio* have high possibility of developing infection from Oral candidiasis.

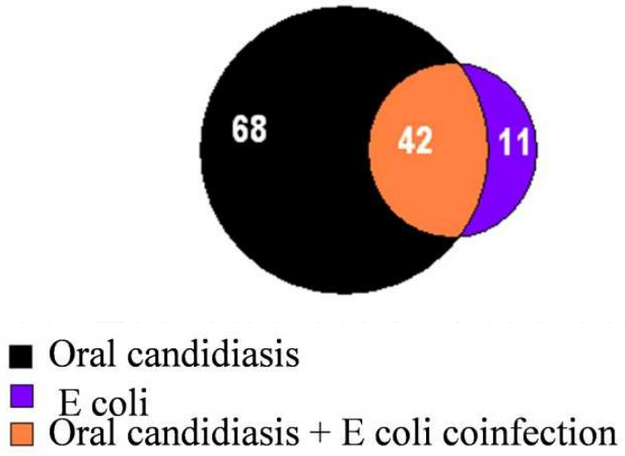


Fig. 2. Co-infection of Oral candidiasis with E coli

Oral candidiasis was found to be prevalent amongst 110 of the 125 HIV/AIDS infected patients as mentioned previously. E coli infection was found to be prevalent amongst 53 of the AIDS/HIV infected patients. Amongst them, 42 developed co-infection of these two OIs. Thus, only 11of the 53 patients infected with E coli did not develop any infection from Oral candidiasis.

From our study, it again becomes very prominent that HIV/AIDS patients suffering from E Coli develop high possibility of developing infection from Oral candidiasis.

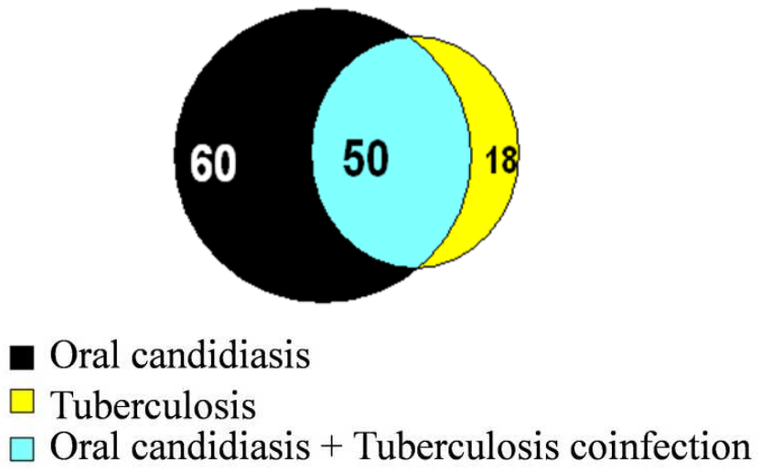


Fig. 3. Co-infection of Oral candidiasis with E coli

Oral candidiasis was found to be prevalent amongst 110 of the 125 HIV/AIDS infected patients as mentioned previously. TB infection was found to be prevalent amongst 68 of the AIDS/HIV infected patients. Amongst them, 50 developed co-infection of these two OIs. Thus, only 18of the 58 patients infected with TB did not develop any infection from Oral candidiasis.

From our study, it again becomes very prominent that HIV/AIDS patients suffering from TB develop high possibility of developing infection from Oral candidiasis.

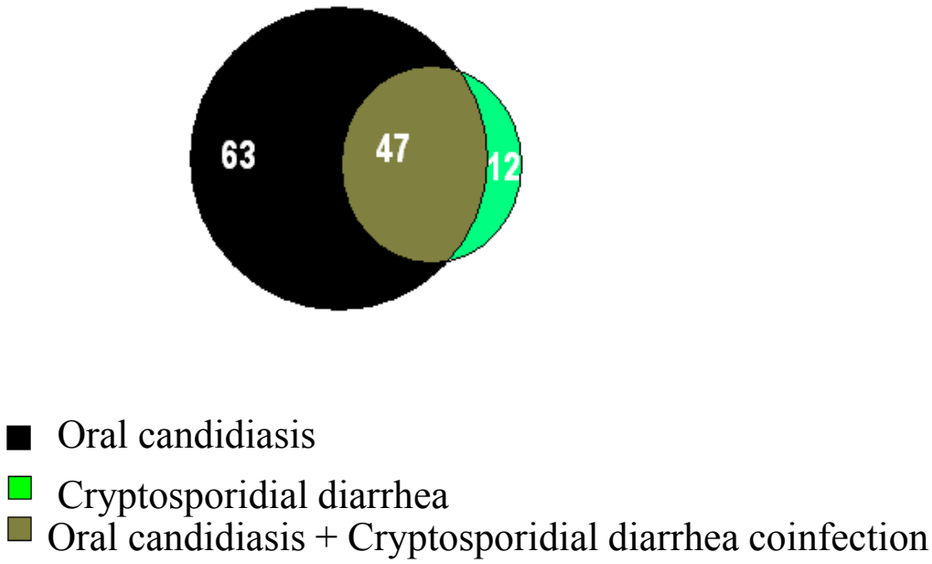


Fig. 4. Co-infection of Oral candidiasis with Cryptosporal diahorrhea

Oral candidiasis was found to be prevalent amongst 110 of the 125 HIV/AIDS infected patients as mentioned previously. Cryptosporal diahorrheal infection was found to be prevalent amongst 59 of the AIDS/HIV infected patients. Amongst them, 47 developed co-infection of these two OIs. Thus, only 12 of the 59 patients infected with TB did not develop any infection from Oral candidiasis.

From our study, it again becomes very prominent that HIV/AIDS patients suffering from Cryptosporal diahorrhea develop high possibility of developing infection from Oral candidiasis.

In another different study undertaken by our research group, (published as *Incidence of multiple herpesvirus infection in HIV seropositive patients, a big concern for Eastern Indian scenario* published in Virology Journal 2010, **7**:147) we were also eager to study the spread of the different *betaherpes* virus infection amongst these HIV infected patients. All herpes viruses share a characteristic ability to remain latent within the body over long periods. These herpes viruses play a very important role in further worsening the scenario in case of the HIV infected patients. For this purpose, in order to investigate the incidence of the different herpes viruses amongst the HIV/AIDS patients, we reviewed 200 HIV/AIDS patients, admitted between January 2006 to November 2008 at Calcutta Medical College Hospital, Kolkata, West Bengal, Apex Clinic, Calcutta Medical College Hospital- and ART Center, School of Tropical Medicine, for the detection of viral opportunistic infections. Their HIV status was confirmed as before by three ERS (Enzyme Linked Immunosorbent Assay [ELISA], Rapid, Simple) as before, an ELISA (HIV ELISA, Rapid test)and Western Blot as recommended by the National Aids Control Organization (NACO), Ministry of Health and Family Welfare, Government of India. The admitted patients were referred to us because they presented symptoms related to HIV infection or symptoms of unknown origin such as prolonged fever. The study group comprised of 140 (70%) males and 60 (30%) females, with

mean ages of 36 ± 16 and 35 ± 12 years respectively. The patients included in the study were from different states of Eastern India.
The viral OIs were primarily diagnosed by the common clinical manifestations as diagnosed by the clinicians.

2.1.3 Primary clinical symptoms for CMV infection (As confirmed by the clinicians)

For the diagnosis of active CMV infection, the primary clinical symptoms were retinitis (an infection of the eyes), pneumonia, blindness and gastrointestinal disease. The common clinical feature of CMV disease is retinitis. Retinitis is charecterised by painless, gradual loss of vision, floaters etc. Often, retinitis begins in one eye, but then progresses gradually to the other eye. If kept without treatment, progressive damage to the retina can lead to blindness in 4-6 months or less. Even with regular treatment, the disease can worsen to blindness. This may be because CMV may become resistant to the drugs so the drugs can no longer kill the virus, or because the patient's immune system has deteriorated further. Patients with CMV retinitis also have a chance of developing retinal detachment, in which the retina detaches from the nerves of the eye, causing blindness.
Other symptoms following active CMV infection include oesophagitis. Cytomegalovirus (CMV) esophagitis is a viral infection of the esophagus, which is the muscular tube through which food travels from the mouth to the stomach. It is charecterised by dysphagia - difficulty in swallowing or Odynophagia - painful swallowing,low grade fever, mouth sores.
Colitis is another clinical symptom due to active CMV infection. The clinical presentation ae as follows: pain abdomen, bloody diarrhea, fever, anorexia, malaise,dehydeation, weight loss, chronic watery diahorrea. HIV infected patients suffering from CMV colitis usually benefit from antiviral treatment.
CMV Pneumonitis is charecterised by cough, breathlessness. Pneumonitis is a common manifestation of CMV infection. It is highily associated with immunocompromised patients with fever and dyspnea.
Encephalitis caused by CMV is characterized by altered mental status, convulsion and headache.
Radiculoneuropathy is characterized by weakness/paralysis of lower limbs, pain lower back, urinary retention etc.

2.1.4 Primary clinical symptoms for HSV infection (As confirmed by the clinicians)

Among HIV-1 infected individuals, HSV-1 and HSV-2 infections are common, with prevalences that approximate or exceed those in the general population. Primary symptoms of HSV included persistent vesicular and ulcerative lesions of the oral and anogenital areas, often with extensive or deep ulcerations and blisters on or around the genitals or rectum. The blisters left tender ulcers (sores) that took two to four weeks to heal the first time they occurred. Other symptoms included tender tonsils covered with a whitish substance that made swallowing difficult or blisters present in the mouth.

2.1.5 Primary clinical symptoms for EBV infection

EBV+ and HIVincreases by many fold the risk of non-Hodgkins lymphoma (NHL) over general population, though overall risk remains small. In HIV, EBV most highly

associated with Lymphoma, Primary CNS (PCNSL). Primary diagnosis of EBV was based on the clinical symptoms of fever, sore throat and swollen lymph glands. The commonestclinical presentation of EBV disease in HIV positives is Oral hairy Leukoplakia (OHL).

2.1.6 Primary clinical symptoms for HSV infection

Patients with HIV disease are at risk for developing severe illness from either varicella or zoster. Progressive primary varicella, a syndrome with persistent new lesion formation and visceral dissemination, may occur in HIV-infected patients and may be life-threatening. Zoster eruptions in HIV-infected patients can be extensive and locally destructive, and can become secondarily infected. Zoster may also disseminate cutaneously, and has been reported as the cause of encephalitis in patients with HIV disease (Quinnan et al. 1984;
Cone & Schiffman, 1984 ;Sandor *et al*. 1984 ;Ryder *et al*.1986; Friedman-Kien *et al*.1986; Cohen *et al*.1988; Colebunders *et al*.1988; Cohen, & Grossman, 1989 ; Gilson *et al*. 1989;
Eidelberg *et al*.1986) was primarily diagnosed based on the clinical manifestations of severe headaches, backache, general malaise and fever accompanied by the typical exanthem (rash) of chickenpox. Other symptoms of VZV included painful oral lesions, vesicular rash, facial numbness and loss of hearing/ ear pain.
All the clinical manifestations were confirmed by ELISA test. The following diagnostic test kits were used for the assay of the opportunistic viruses:

Anti- CMV

Serum anti-CMV was determined by a commercially available test kit, CMV IgM, IgG ELISA Test kit was used to detect antibodies against the CMV.

Anti - EBV 1

Serum anti-EBV was determined by a commercially available test kit, EBV IgG, IgM ELISA Test kit was used to detect antibodies against the EBV 1.

Anti- HSV 2

Serum anti- HSVwas determined by a commercially available test kit, HSV type1 IgM ELISA Test kit supplied was used to detect antibodies against the affinity chromatographically purified recombinant antigen HSV-2.

Anti - VZV

Serum anti-VZV was determined by a commercially available test kit, VZV IgM, IgG, IgA
Was used to detect antibodies against the Ellen Strain antigen (ATCC).
Of these herpes viruses studied, our study within the studied population suggests that, the occurrence of CMV is the highest. It accounts to 49% of the total population studied across the range of CD4+.
From the different tests performed, the results were as follows:
The following table (3) represents the cases of viral OIs in these HIV infected patients:
Study population= 200
We were also interested to study the trend of co-infection with CMV amongst these HIV patients.

Type of Viral infection	No. of positive cases	%
CMV	98	49
HSV	94	47
VZV	52	26
EBV	65	32.5

Table 3. Represents the cases of viral OIs in these HIV infected patients.

CMV was found to be associated predominantly with HSV followed by EBV and VZV.
Presence of CMV associated viral OIs in HIV infected population
The following table (4) represents the cases of dual infection with CMV in these HIV infected patients:
Study population= 200

Viral Co-infections	No. of positive cases	%
CMV+HSV	71	35.5
CMV+VZV	32	16
CMV+EBV	41	20.5

Table 4. Represents the cases of dual infection with CMV in these HIV infected patient

The Venn diagrams below to demonstrate the actual distribution of these viral infections amongst the immunocompromised patients under our study:

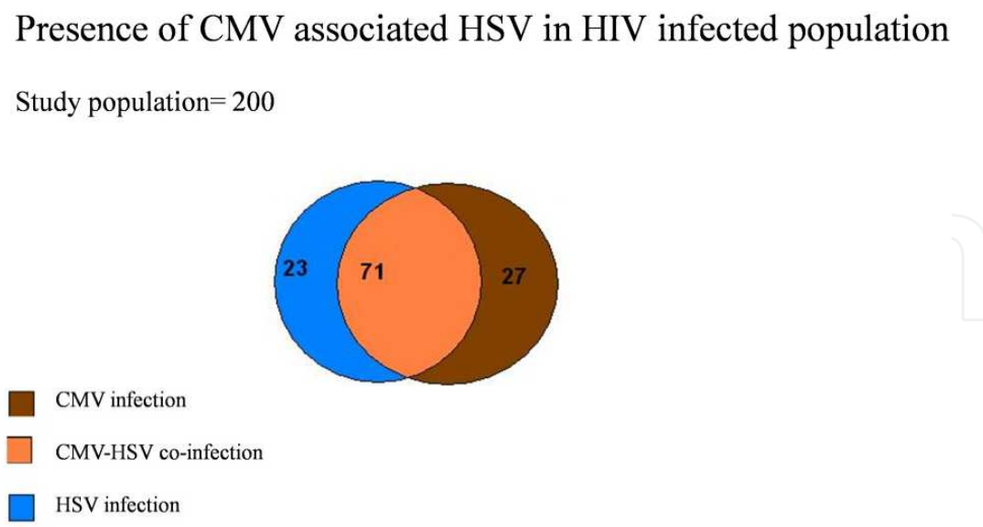


Fig. 5. Co-infection of CMV with HSV

CMV was found to be prevalent amongst 98 of the 200 HIV/AIDS infected patients as mentioned previously. HSV infection was found to be prevalent amongst 94 of the AIDS/HIV infected patients. Amongst them, 71 developed co-infection of these two OIs.

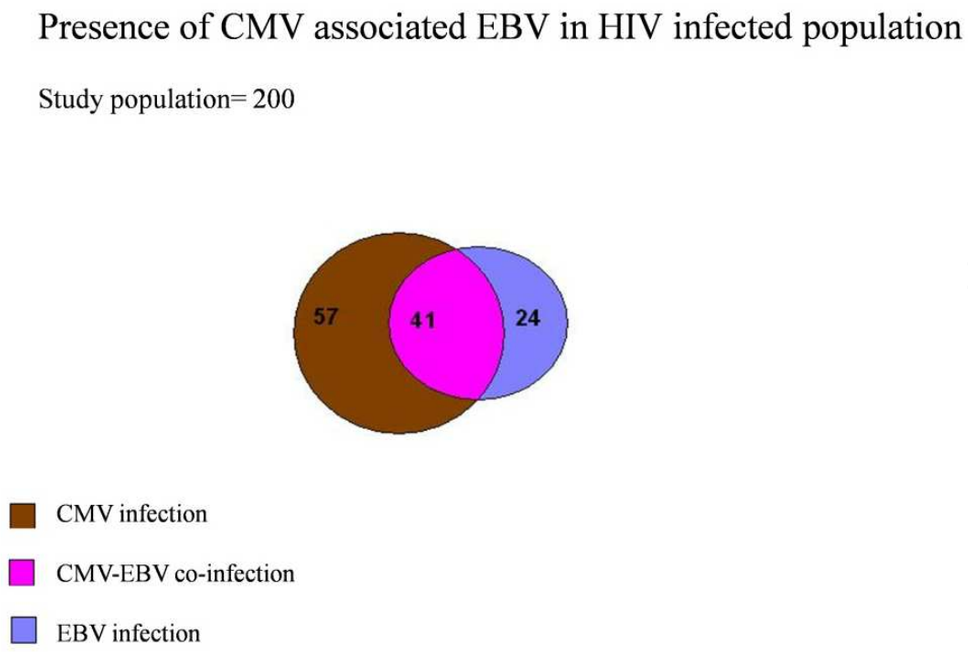


Fig. 6. Co-infection of CMV with EBV

CMV was found to be prevalent amongst 98 of the 200 HIV/AIDS infected patients as mentioned previously. HSV infection was found to be prevalent amongst 65 of the AIDS/HIV infected patients. Amongst them, 41 developed co-infection of these two OIs.

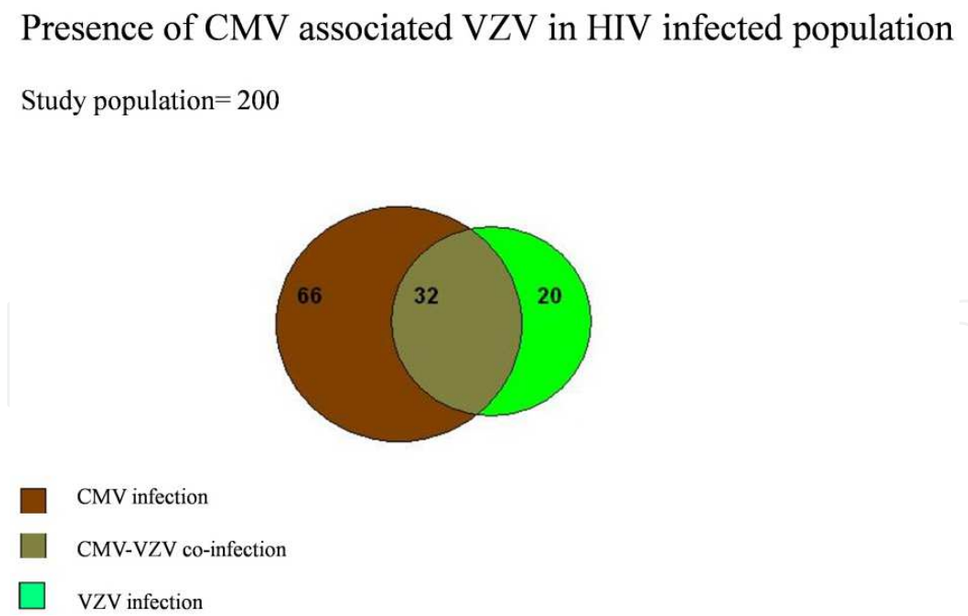


Fig. 7. Co-infection of CMV with EBV

CMV was found to be prevalent amongst 98 of the 200 HIV/AIDS infected patients as mentioned previously. VZV infection was found to be prevalent amongst 52 of the AIDS/HIV infected patients. Amongst them, 45 developed co-infection of these two OIs.

The incidence of CMV was higher among males than females 59/39. HSV was also found to be more predominant in the males 63/ 31. The incidence of VZV and EBV was also found to be dominant in the male population, the dominancy being 46/19 and 31/21 respectively.
HSV infection is found to be dominating in the heterosexual individuals among the study group. There are no significant variations among the homophiles, the drug users and the blood transfusion patients.The incidence of the different viral OIs was also assessed with respect to the CD4+ cell count/µl of blood and patients with mean CD4+ cell count of 51-100 showed the highest prevalence of opportunistic viral antibodies. This was followed by the group with CD4+ count of 101-150, 51-100, 151-200 and >200.
Age related prevalence of opportunistic viral antibodies in the serum of 200 HIV infected patient cohorts was assessed and results showed that individuals in the age group of 21- 40 years had the highest incidence of viral opportunistic infections as evident from the Table below.
The following table (5) represents the HIV-seropositive patient groups in various risk factors:

Risk Behavior	**Male**	**Female**
Blood transfusion	13	6
IVD abuse	25	3
Heterosexual	82	39
Homophiles	20	12
Occupation		
Unemployed	12	46
Government Service	13	-
Non Government Service	115	14
Deaths	3	2

Table 5. Represents the HIV-seropositive patient groups in various risk factors.

Viral opportunistic infections and HIV/AIDS having become so intertwined have constituted a major public health problem in the country. The opportunistic infections, Therefore, play a major role in clinical presentations and remain one of the most frequent causes of death in these patients. The Table below shows the association of the different OIs with the different modes of transmission of HIV amongst the different sexes amongst patients suffering from HIV/AIDS.
The following table (6) represents the different opportunistic viruses which infects HIV/AIDS patients of different age groups

	Risk Factors of HIV transmission							
	Heterosexual		Homophile		IDU		Blood transfusion	
Opportunistic Viruses	Male	Female	Male	Female	Male	Female	Male	Female
CMV	27	19	13	8	13	2	9	3
EBV	23	13	5	2	7	-	2	-
HSV	43	12	11	6	9	3	7	3
VZV	19	9	13	5	11	-	6	2

Table 6. Represents the different opportunistic viruses which infects HIV/AIDS patients of different age groups

From our study, as mentioned previously, CMV was obtained as the most prevalent amongst the different viral OIs amongst the patients suffering from HIV/AIDS. Infection by cytomegalovirus (CMV) is the major cause of morbidity and mortality in individuals with depressed cell mediated immunity of congenital origin, iatrogenic origin and that associated with acquired immunodeficiency syndrome (AIDS). The clinical diagnosis of AIDS with CMV infection can be difficult in the absence of CMV retinitis, polyradiculopathy and the classical CMV syndrome (Wiley & Nelson ,1988; Santosh *et al*.1998). The diagnosis poses difficulties because a 2-3 week period is mandatory for virus isolation. While IgM antibodies as detected by ELISA correlate poorly with the clinical status of CMV infection and facilities for culture are usually not available in most centers (Lanjewar *et al*. 1996). There are a few reports available of CMV infection in Indian patients with HIV/AIDS, which are based primarily on clinical or autopsy evaluation (Lanjewar *et al*. 1988; Becker *et al*. 1996; Nebuloni *et al*. 1998). We found CMV as the most incidental co infection in HIV/ AIDS patient with the overall incidence of 49%. Human immunodeficiency virus (HIV) infection is associated with an increased risk for human herpesviruses (HHVs) and their related diseases. The incidence of HSV in human immunodeficiency virus (HIV)-seropositive patients has not been focused, with reports generally focusing on individual infection (Mcclain *et al*. 1995). In this report, the serum prevalence of HSV is found to be higher in HIV seropositive patients; the overall incidence is around 47%. VZV infection, the overall incidence being 32.5% is the third most incidental coinfection in HIV seropositive patients. VZV is one of the common aetiological agents of viral retinitis. Neurological complications of the reactivation of VZV occur most frequently in elderly persons and immunocompromised patients (Sixbey *et al*. 1989). Gray *et al*.(1994) reported VZV infection of the CNS in more than 4% of patients with AIDS examined at autopsy. In AIDS patients, VZV tends to reactivate from multiple dorsal root ganglia levels, and the disease is often disseminated.

EBV is the least prevalent among the four HHVs studied in our work which is 26% of the total. EBV has been identified as a co-factor in the pathogenesis of a significant proportion of HIV related lymphoproliferative disorders and in oral hairy leukoplakia (Sculley *et al*. 1988). However, only limited information exists on the status of EBV in the course of HIV infection and the extent of its interaction with HIV. There is also growing interest in the biological properties and pathogenic potential of the different EBV subtypes, EBV-1 and EBV-2. Serological findings and studies in saliva and blood have indicated a high incidence of EBV-

2 infection in the course of HIV disease, but there is limited information regarding its significance (Sixbey *et al*. 1989; Sculley *et al*. 1988).

The analysis of the association of immunological status and the presence of viral OIs revealed that the CD4 count was significantly associated with the presence of viral OIs. An increasing CD4 count significantly protected patients from expressing HHVs in our patient cohorts as indicated by the correlation as in Figure 2. It has been detected clinically that more frequently virus infections are associated with the compromised immunity in HIVinfected patients (Kyaw et al.1992). We found that, HIV-infected patients with CD4+ cell counts of around 200 cells/mm3 are less likely to be infected with any virus examined here suggesting that a higherCD4+ cell count does play a role in immunity against virus infection. This clinical outcome is consistent with our finding of significantly lower CD4 cell count in HIV patients with viral OIs, indicating that the diagnosis of viral opportunistic

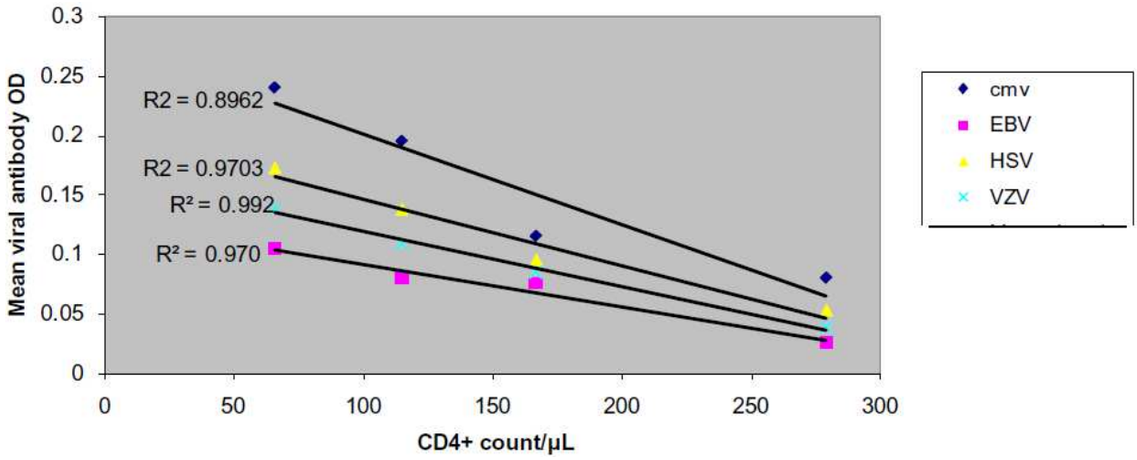


Fig. 7. CD4+ counts/µL of blood versus the antibody titres against the different opportunistic viruses in the patients. The CD4+ count ranges between 50/µL to 300/µL and the antibody titres showing the mean OD of the triplicate ELISA reading.

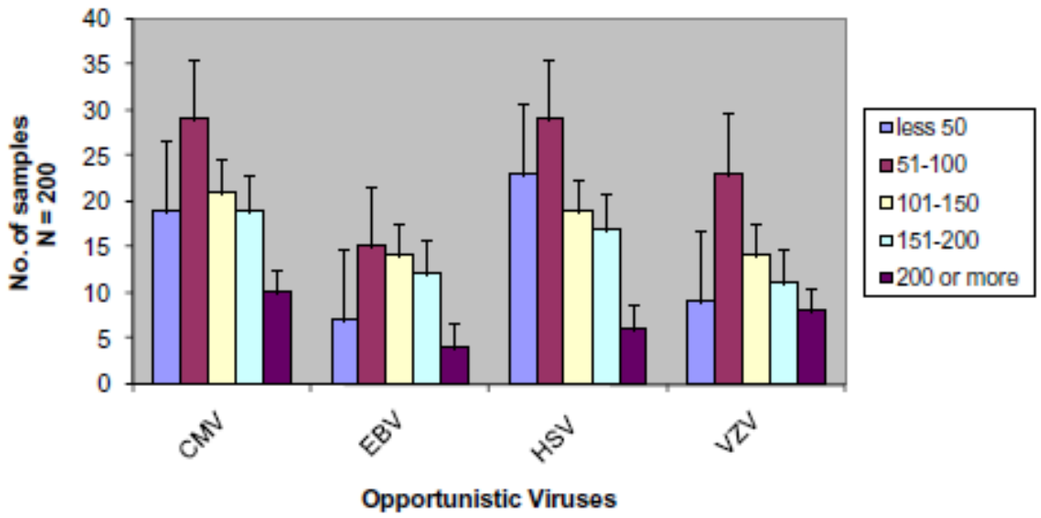


Fig. 8. Antibody prevalence of the corresponding viruses in different age groups of our patients samples.

infections can indeed be correlated with the clinical manifestation and thus is helpful in predicting disease progression. Figure 3 clearly shows that the patient group with CD4+ counts between 51 and 100 cells/µl is most susceptible to viral OI in HIV/AIDS patient.
The groups with CD4+ count less than 50 cells/µl are showing least opportunistic viruses which could be due to the advanced HAART treatment. This study is aimed at providing baseline data on viral opportunistic infections in HIV seropositive population as part of the preliminary investigation on the dynamics of viral opportunistic infections in immunocompromised population of India. One of the major problems is the lack of specific investigations that can provide rapid and reliable confirmation of a clinical diagnosis. A high level of alertness is needed at both clinical and laboratory level and routine surveillance studies need to be undertaken. Institutions in India and other developing countries need to be equipped to face the emerging challenge, in the form of updating the present knowledge, by way of education and training of the personnel, acquisition of skills of improved procedures, and their implementation in appropriate settings with adequate administrative support.

3. Conclusion

This study is aimed at providing baseline data for different pathogenic opportunistic infections in HIV seropositive population as part of the preliminary investigation on the dynamics of viral opportunistic infections in immunocompromised population of Eastern India. As many HIV/AIDS patients in India cannot afford ART, so the detection and awareness towards OIs related to HIV is of immense importance especially in Indian perspective or with respect to other developing countries also. These data may also be of immense importance especially to those countries of the tropical region as the spread of OIs might be comparable to that of our study. A high level of alertness is needed at both laboratory and clinical level and routine surveillance studies need to be undertaken. Institutions in India and other developing countries need to be equipped to face the emerging challenge, in the form of updating the present knowledge, by way of education and training of the personnel, acquisition of skills of improved procedures, and their implementation in appropriate settings with adequate administrative support. Further investigations have to be undertaken with matched control samples as case control analysis with respect to all OIs in HIV seropositive individuals.

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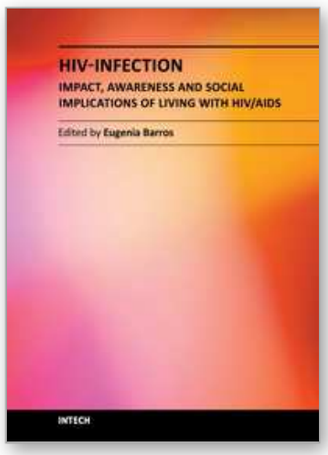
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HIV-infection - Impact, Awareness and Social Implications of living with HIV/AIDS

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The past few decades have seen the escalation of HIV-infections and the 'frantic' search for new drugs to treat the millions of people that live with HIV-AIDS. However because HIV-AIDS cannot be cured, but only controlled with drugs, and the Antiretroviral (ARV) treatment itself results in some undesirable conditions, it is important to generate wider awareness of the plight of people living with this condition. This book attempts to provide information of the initiatives that have been used, successfully or unsuccessfully, to both prevent and combat this 'pandemic' taking into consideration the social, economic, cultural and educational aspects that involve individuals, communities and the countries affected.

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