Original Research Article

FREQUENCY OF AIDS DEFINING OPPORTUNISTIC INFECTIONS IN HOSPITALIZED HIV INFECTED PATIENTS

BACKGROUND: Human Immunodeficiency virus patients with AIDS defined opportunistic infections with Pneumocystis jiroveci, cryptoccocal, disseminated TB, cytomegalovirus, and cytomegalovirus associated retinitis, and cryptospordiasis.

OBJECTIVE: To determine the frequency of AIDS defining opportunistic infections in hospitalized HIV infected patients.

METHODOLOGY: This cross sectional study was conducted from 21st October 2018 To 20th April 2019 at Department of Medicine, Civil Hospital, Karachi. Total 154 diagnosed patients of HIV were included. For diagnosis of various AIDS defining illness, clinical, radiological and bacteriological evidence of disseminated tuberculosis chronic cough, and weight loss diagnosed by AFB smear/ gene experts. Pneumocystis jiroveci was diagnosed by bronchoalveolar lavage and CD4 counts. Cryptosporidiosis with watery diarrhea and stool sample microscopy, cerebral toxoplasmosis with headache, hemiparesis, vomiting, diagnosed by serology and cytomegalovirus retinitis with blurred vision diplopia, vision impairment and Cryptococcal meningitis with fever >98.6oF. Headache, stiff neck, photophobia diagnosed by microscopy, culture, or antigen was done. Descriptive statistics were calculated and stratification was done. Post stratification chi square test was applied. P value ≤ 0.05 was taken as significant.

RESULTS: There were 71.4% male and 28.6% female patient. The mean HIV duration was 15.25±5.09 months. The overall mean CD4 count was 174.17±12.85/cumm. 18.8% patient were

found with disseminated tuberculosis, 31.2% with pneumocystis pneumonia, 12.3% with cerebral toxoplasmosis, 18.2% with cryptococcal meningitis, 3.9% with cryptospordiasis and 14.9% with cytomegalovirus retinitis.

CONCLUSION: Pneumocystis pneumonia was the most prevalent infection followed by disseminated tuberculosis, cryptococcal meningitis, cytomegalovirus retinitis, cerebral toxoplasmosis, and cryptospordiasis.

KEYWORDS: Frequency, AIDS, Opportunistic Infections, Hospitalized HIV Patients

INTRODUCTION: AIDS (acquired immunodeficiency syndrome) was first recognized in the United States in the summer of 1981, when the U.S. Centers for Disease Control and Prevention reported the unexplained occurrence of Pneumocystis jiroveci pneumonia and or Kaposi's sarcoma in healthy homosexual men in New York and Los Angeles. Months, the disease became recognized in injection drug users (IDUs), in recipients of blood transfusions and in haemophiliacs. As the epidemiologic pattern of the disease unfolded, it became clear that an infectious agent transmissible by sexual (homosexual and heterosexual) contact and blood or blood products was the most likely etiologic cause of the epidemic. In 1983, human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy, and by 1984 it was demonstrated clearly to be the causative agent of AIDS.[1]

HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. At the end of 2007, 33.2 million individuals were living with HIV infection (range: 30.6-36.[1] million) according to joint United Nations program on HIV/AIDS (UNAIDS). More than 95% of people living with HIV/AIDS reside in low and middle income countries, ~ 50% are female, and 2.5 million are children < 15 years.[2] In India HIV was first detected in commercial sex workers (CSW's) in Tamil Nadu in 1986 and since then, the infection is growing quite fast. The 2006 estimates suggest national adult

HIV prevalence in India is approximately 0.36 percent, amounting to between 2 and 3.1 million people, almost half of the previous estimate. Nationally, the prevalence rate for adult females is 0.29 percent, while for males it is 0.43 percent. Prevalence is also high in the 15-49 age group (88.7 percent of all infections), indicating that AIDS still threatens the cream of the society, those in the prime of their working life. While adult HIV prevalence among the general population is

0.36 percent, high-risk groups, inevitably, show higher numbers. Among Injecting Drug Users (IDUs), it is as high as 8.71 percent, while it is 5.69 percent and 5.38 percent among men who have sex with men (MSM) and female sex workers (FSWs), respectively.[3]

The first human immunodeficiency virus (HIV) - positive Pakistani was identified in 1987.[4] Till March 2010, 3325 patients were registered at National AIDS Control Centre, NIH, Islamabad.[5] Human immunodeficiency virus type 1 (HIV-1) specific CD8+ T-cells play a key role in the control of viral replication during HIV-1 infection. The cytotoxic T-lymphocyte (CTL) response is mainly measured at the early stage of infection and its appearance coincides with a rapid fall in plasma viremia during the early stage of infection with HIV-1.[6]

Among all HIV high risk individuals in Pakistan, female sex workers (FSWs) formed the largest group reported, with estimates of 79127 and five different sub-typologies. Injection drug users were the second largest group followed by male sex workers and hijra sex workers with estimates of 31555, 19320 and 14702, respectively.[7]

The rationale behind the study was that in human immunodeficiency virus type-1 (HIV-1) infection there is a decline in viral replication that has been attributed to host immunity, but the components of this response varies among individuals particularly the ability of cytotoxic T-lymphocytes to control viral burden and influence the outcome of the disease. Prior to antiretroviral therapy (ART), opportunistic infections (OIs) were a significant cause of morbidity and mortality in people with HIV infection. Chemoprophylaxis, vaccinations and acute management were all used to some effect to improve outcomes in these patients but only with the upscaling of ART in the mid-1990s was there a significant reduction in OIs and consequent improvement in the prognosis of people with HIV infection.[8,9] The emergence and pandemic

spread of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) constitutes the greatest health challenge in modern times. According to estimates by the World Health Organization and the Joint United Nations Program on HIV/AIDS (UNAIDS), 34 million people were living with HIV at the end of 2010. That same year, some 2.7 million people became newly infected, and 1.8 million died of AIDS.[10]

Infections associated with severe immunodeficiency are known as opportunistic infections (OIs) because they take advantage of a weakened immune system. Some of these OIs are used to mark the stages of HIV/AIDS.[11] Before the widespread use of potent combination antiretroviral therapy (ART), OIs were the principal cause of morbidity and mortality in HIV-infected patients worldwide. In one study, the mortality rate among individuals with a history of preventable OIs was 66.7 per 100 people per year compared with 2.3 per 100 people per year for those without a history of preventable OIs.[12]

.Nevertheless, rates of OIs leading to mortality remain an ongoing cause for concern, with one third of patients presenting late (with depleted immune response), not accessing or having access to HIV therapy and healthcare, and not achieving satisfactory HIV viral load suppression or immune restoration, despite adequate ART.9,[13] The effects of OIs are not only direct: certain OIs can cause progression of HIV itself, causing susceptibility to further infection and higher rates of HIV transmission.[14,15]

Many organisms responsible for OIs in patients with HIV/AIDS have similar clinical presentation and the type of pathogen responsible for morbidity and mortality can vary from region to region. The identification of such pathogens in Pakistan is essential for clinicians providing care for these patients. Hence, the present retrospective study was performed to

evaluate the spectrum of various OIs and determine their relative frequencies in a cohort of hospitalized HIV-infected patients.

PATIENT AND METHODS: The study was performed at the Department of Medicine, Dow University, Civil Hospital Karachi from six months from 21st October 201 to 20th April 2019. Total 154 patients were included as calculated by taking prevalence of cryptosporidiosis HIV hospitalized patient 3%,[121] confidence level 95% and margin of error of 2.7% as calculated by formula $n=[P(1-P)Z \times /2]/e^2$ while the non-probability consecutive sampling technique was used to recruit the population. The inclusion criteria were age over 18- 60 years; both gender and all diagnosed hospitalized cases as per operational definition of HIV while the exclusion criteria patients with other concurrent infection prior to diagnosis of HIV, all outpatient HIV positive patients and those who were not give written consent for inclusion in the study.

HIV Definition: Patients found HIV serology positive and CD4 lymphocyte count <200 cells/mcl or < 14% were labeled as having AIDS.

AIDS Defining Opportunistic Infection: AIDS defining illness included following mentioned below, diagnosed clinically, radiologically and bacteriological evidence.

Pneumocystis Jiroveci: Cough, shortness of breath with respiratory rate >30/min, diagnosed by broncho alveolar lavage sent for histopathologic examination.

Cryptococcal Meningitis: Fever >98.6 oF, headache, stiff neck, photophobia diagnosed by microscopy, culture, or antigen.

Cytomegalovirus Retinitis: Blurred vision, diplopia, vision loss diagnosed by ophthalmoscopy or if required tissue biopsy.

Disseminated Tuberculosis: Defined by having chronic cough >2weeks and weight loss of >5-10kg in 1 month diagnosed by 3 consecutive specimens or gene experts identifying organism.

Cerebral toxoplasmosis: CNS symptoms confirmed by serological evidence of Toxoplasma on PCR.

Cryptosporidiosis: Watery diarrhea, weight loss, dehydration diagnosed by microscopy of stool sample.

Patients were selected on the basis of selection criteria, the risks and benefits of the study were explained to them and after their informed consent, a detailed per approved. Study was conducted after approval from ethical review committee from CPSP. Performa was filled as follows by the candidate only: Patient name, age, gender, admission number and history and physical examination were done and recorded. Patients with HIV diagnostic criteria were enrolled and for diagnosis of various AIDS defining illness clinical, radiological and bacteriological evidence of disseminated tuberculosis chronic cough & weight loss diagnosed by AFB smear/ gene experts, pneumocystis jiroveci with symptoms of cough, shortness of breath, diagnosed by bronchoalveolar lavage and CD4 counts, cryptosporidiosis with watery diarrhea and stool sample microscopy, cerebral toxoplasmosis with headache, hemiparesis, vomiting, diagnosed by serology and cytomegalovirus retinitis with blurred vision diplopia, vision impairment and Cryptococcal meningitis with fever >98.6 F, headache, stiff neck, photophobia diagnosed by microscopy, culture, or antigen were done by experienced doctor with working year of experience at least 4 years.

Data analysis was performed through SPSS Version-20. Descriptive statistics were calculated for quantitative variable like age, BMI, duration of HIV, CD4 count were presented as mean and standard deviation. For quantitative variables like gender, socio-economic status, educational status, opportunistic infection like pneumocystis Jiroveci, Pneumonia, cryptoccocal meningitis, cryptosporidiosis, cytomegalovirus retinitis, disseminated TB and toxoplasmosis were presented as percentages. Effect modifier like age, gender, duration of HIV, CD4 count, socioeconomic

status, and educational status were calculated through stratification. Post stratification chi square test was applied keeping p value < or equal to 0.05 as significant.

RESULTS:

Total 154 patients of either gender with age above 18 years to 60 years meeting inclusion criteria of study were evaluated to determine the frequency of AIDS defining opportunistic infections in hospitalized HIV infected patients. Descriptive statistics were calculated using SPSS version 20. Stratification was done and post stratification Chi square test was applied to observe the effect of modifiers on outcome. P value ≤0.05 was considered as significant.

There were 71.4% male and 28.6% female patient. The overall mean age of patients was 39.56±7.76 years. The age was further stratified in two groups while the overall mean BMI was 20.61±3.88 kg/m2. The overall mean HIV duration was 15.25±5.09 months while the overall mean CD4 count was 174.17±12.85/cumm.

Among 154 patients, 40.3% were from lower class with monthly family income <15,000 PKR, 51.9% were from middle class with monthly family income between 15,000 PKR to 30,000 PKR and 7.8% were from upper class with monthly family income >30,000 PKR.

Among total study subjects, mostly got education till secondary level (49.4%)

In our study, 18.8% patient were found with disseminated tuberculosis, 31.2% with pneumocystis pneumonia, 12.3% with cerebral toxoplasmosis, 18.2% with cryptococcal meningitis, 3.9% with cryptospordiasis and 14.9% with cytomegalovirus retinitis.

The results showed that there was significant association of disseminated tuberculosis with gender (p=0.031) and age group (p=0.006). Cerebral toxoplasmosis was also found significant with educational status (p=0.006).

TABLE I: THE DEMOGRAPHICAL DISTRIBUTION OF THE STUDY POPULATION

GENDER	**FREQUENCY [n = 154 (%)]**
Male	110 (71.4)
Female	44 (28.6)
SOCIO ECONOMIC STATUS	
<15,000 PKR	62 (40.3)
15,000 to 30,000 PKR	80 (51.9)
>30,000 PKR	12 (7.8)
EDUCATIONAL STATUS	
Primary	55 (35.7)
Secondary	76 (49.4)
Inter	23 (14.9)

Table II: FREQUENCY DISTRIBUTION OF DISSEMINATED TUBERCULOSIS, PNEUMOCYSTIS PNEUMONIA, CEREBRAL TOXOPLASMOSIS, CRYPTOCOCCAL MENINGITIS, CRYPTOSPORDIASIS, CYTOMEGALOVIRUS RETINITIS (n=154)

	YES		NO	
	Frequency	**%**	**Frequency**	**%**
Disseminated TB	29	18.8	125	81.2
Pneumocystis pneumonia	48	31.2	106	68.8
Cerebral toxoplasmosis	19	12.3	135	87.7
Cryptococcal meningitis	28	18.2	126	81.8
Cryptospordiasis	6	3.9	148	96.1
Cytomegalovirus retinitis	23	14.9	131	85.1

DISCUSSION: Before the widespread use of potent combination ART, OIs were the principal cause of morbidity and mortality in this population. In the early 1990s, the use of chemoprophylaxis and better strategies for managing acute OIs contributed to improved quality of life and patient survival.[16] However, the widespread use of ART starting in the mid-1990s has had the most profound influence on reducing OI-related mortality in HIV-infected persons in countries where therapies are accessible and affordable.[16-18]

Despite the availability of ART, OIs continue to cause considerable morbidity and mortality for three primary reasons: 1) Many patients are unaware of their HIV infection and seek medical care when an OI becomes the initial indicator of their disease; 2) Certain patients are aware of their HIV infection, but do not take ART, and 3) Some patients are prescribed ART, but fail to attain adequate virologic and immunologic response because of factors related to adherence, pharmacokinetics, or other unexplained biologic factors.[19]

Thus, although hospitalization and death from OIs have decreased in those countries in which ART is accessible and affordable, OIs remain a leading cause of morbidity and mortality in HIV infected persons. Clinicians should be aware of the epidemiology of such infections in order to provide comprehensive high-quality care for these patients. A wide variety of these infections are encountered in the HIV/AIDS population, including bacteria, fungi, viruses, and protozoa. Very often, these represent not new infections but the reactivation of an old infection.

In a study by Balkhair et al,[20] 58% of people who were diagnosed with HIV presented with an AIDS-defining OI and more than half of them 53%) had two or more OIs. The proportion of persons with a CD4+ cell count of <200 cells/μL at the time of HIV infection diagnosis was 77%. This finding was consistent with data from India where 83.4% of patients were late presenters.[21] Data from Europe show that only one-third of patients were defined as late HIV

presenters.[22] The above findings were interesting. Whatever the underlying causes, reducing the number of late-stage diagnoses of HIV infection through earlier and more widespread testing, and promoting early introduction and adherence to ART will substantially reduce the burden of OIs.

PCP was the commonest AIDS-defining OI, accounting for 25% of all diagnosed OI events in a study from Oman.[20] A total of 18 patients 23%) with HIV/ AIDS had PCP as an AIDS-defining OI at their first presentation. A definitive diagnosis of PCP with a demonstration of organisms in induced sputum samples or BAL fluid was made in 11 patients. A presumptive diagnosis of PCP was made in the remaining 7 patients. The prevalence of

PCP in this cohort was higher than that reported in Lebanon 10.9%), and was very much higher than in Europe where only 2–3% of PCP cases were reported among HIV/ AIDS patients.[23] In our study cohort, the reported percentage of patients diagnosed with PCP was 31.2%. Before the widespread use of primary PCP prophylaxis and ART, PCP occurred in 70–80% of patients with AIDS.141 All cases in a study cohort in Nepal occurred among patients with CD4+ counts of <200 cells/μL.[24]

Oral candidiasis was the most common OI 59%) in the cohort comprising of Omani HIV positive patients121 and this finding was similar to that reported in Nepal by Sharma et al.[24] Some investigators from India, have reported oral candidiasis as the second most common infection in AIDS patients, while others have reported very low incidence of candidiasis 27.7%).[25-27] Mycobacterium TB was the commonest isolate reported in a few studies from Hong Kong144 and India.[28] Pulmonary TB was observed in 35% and extra-pulmonary TB in 21% of cases in an Omani study.[20] This is similar to data from Brazil where pulmonary TB was the commonest OI

52.9%).[29] HIV infection is a strong risk factor for active TB in persons with latent M. tuberculosis infection.

In 2008, there were an estimated 1.5 million new cases of tuberculosis among persons with HIV infection, and TB accounted for 26% of AIDS-related deaths.[30] The same year, 1.4 million patients with TB were tested globally for HIV, and 81 countries tested more than half of their patients with TB for HIV. Only 4% of all persons infected with HIV were screened for TB in the same year.[31] TB is endemic in some countries like India, and is the commonest cause of death in AIDS patients.[32] HIV patients are at increased risk of developing active TB because of the high rate of reactivation of latent infection and the high degree of susceptibility to new infection.[33]

A study was conducted in South Korea from 1985 to 1998 at a referral hospital for AIDS to determine the frequency and types of major opportunistic diseases in patients with HIV infection in South Korea in 173 HIV-infected patients and found that 9.8% of the patients developed cytomegalovirus disease.[34]

Another study from Malaysia with the similar purpose of determining the frequency and type of major opportunistic infections in AlDS patients reported the CMV infection was found in 2% o their study cohort.[35] A study from Shanghai by Luo et al. was conducted to estimate the proportion of admissions attributable to specific OIs among people living with HIV

PLWH) and identify the most frequent ones, to characterize the major clinical factors associated with each specific OI.[36] It was reported that CMV was the third most frequent OIs and developed in 20.9% of patients: retinitis, 42 patients; viremia, 148 patients; pneumonia, 1 patient; and colitis, 1 patient.

Cryptosporidium infection was observed in only 3% of the cases in previous study[35] and this was in contrast to data from Ethiopia where 21% of HIV patients had Cryptosporidium.[37] The present

study reported 3.9% of the patients who developed cyrptosporidiosis. Cryptosporidium parvum is an enteric pathogen and a common cause of gastroenteritis in humans. In patients with HIV, cryptosporidiosis may cause potentially fatal complications, including bile duct damage.[38] The rate of infection among individuals with HIV/AIDS in many countries has subsided considerably because of the use of ART.[39]

Cryptococcus neoformans is the most important cause of invasive fungal disease in patients with HIV worldwide. Meningitis is the commonest clinical manifestation of invasive cryptococcosis in patients with HIV. In an Arab study, Cryptococcus meningitis accounted for 22% of OI events 21% of all HIV patients).[40] Indian reports show the incidence of cryptococcal infection including meningitis) to be only 6-8%, whereas it is about 5-11%

in the USA, 33% in Africa, and 28.5% in Thailand.[41] In the present study, 18.2% of the patients developed cryptococcal meningitis. Interestingly, none of the patients in the Lebanese cohort developed cryptococcal meningitis.[22]

Toxoplasmosis, caused by the protozoan Toxoplasma gondii, is one of the major OIs afflicting HIV patients. Serological tests play a crucial role in the diagnosis of toxoplasmosis in immunocompetent persons.[42] The prevalence rate of latent toxoplasmosis in HIV/AIDS vary from 3-97% based on ethnicity and other factors.[43] Cerebral toxoplasmosis is the most common cause of focal neurological disorders in HIV patients. In a study by Balkhair et al.,[20] cerebral toxoplasmosis accounted for 12.5% of all AIDS-defining OIs 12% of all HIV patients). In a study from Lebanon, neurotoxoplasmosis was reported in 21.9% of the HIV-infected patients.[22]

This striking difference probably reflects differences in social behaviour between the two populations. In our cohort, all patients with cerebral toxoplasmosis had positive IgG for

toxoplasmosis, CT/MRI evidence of compatible brain lesions, and clinical and radiological response to therapy for toxoplasmosis.

CONCLUSION: The study results showed pneumocystis pneumonia as the most prevalent infection followed by disseminated tuberculosis, cryptococcal meningitis, cytomegalovirus retinitis, cerebral toxoplasmosis, and cryptospordiasis. These findings showed the necessity of specific measures to prevent OIs. With better knowledge and diagnosis of OIs in HIV patients, clinicians and health planners can tackle the AIDS epidemic in a more effective manner. Early diagnosis of OIs and prompt treatment definitely contributes to increased life expectancy among infected patients, thus delaying the progression to AIDS.

REFERENCES:

1. Fauci AS, Lane HC. Human immunodeficiency virus disease: AIDS and related disorders. Harrison's Principles of Internal Medicine, 17th ed. USA: The McGraw-Hill companies, Inc. 2008; 1137-203.
2. Joint United Nations programme on HIV/AIDS UNAIDS): Reports on global AIDS epidemic, 2006: AIDS epidemic update 2007. Online) Cited 2009 April). Available from URL: http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdfg.
3. National AIDS Control Organization, Ministry of Health and Family welfare, November 2007, Government of India. HIV fact sheets 2003-2006. Online) Cited 2009 April). Available from URL: http://www.nacoonline.org/quick_Linkds/HIV_Data/.
4. National AIDS Control Program. Ministry of Health. United National General Assembly Special Session UNGASS) on HIV/AIDS. Islamabad: Government of Pakistan; 2010.
5. Ilyas M, Asad S, Ali L, Shah M, Badar S, Sarwar MT, et al.Asituational analysis of HIV and AIDS in Pakistan. Virol J 2011; 8:191.

6. Appay V, Papagno L, Spina CA, Hansasuta P, King A, Jones L, et al. Dynamics of T-cell responses in HIV infection. J Immunol 2002; 168:3660-6.

7. Emmanuel F, Blanchard J, Zaheer HA, Reza T, Holte-McKenzie M; The HIV/AIDS Surveillance project mapping approach: an innovative approach for mapping and size estimation for groups at a higher risk of HIV in Pakistan. AIDS 2010; 24:S77-84.

8. Mocroft A, Ledergerber B, Katlama C. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2006;3629377): 22–9

9. Palella FJ, Baker RJ, Moorman AC. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;431): 27–34

10. Joint United Nations Programme on HIV/AIDS UNAIDS). UNAIDS World AIDS Day Report. www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf. Accessed: May2012.

11. Centers for Disease Control. Revised Surveillance Case Definitions for HIV Infection among Adults, Adolescents, and Children aged <18 Months and forHIV Infection and AIDS among Children aged 18 Months to <13 Years—United States, 2008. MMWR 2008; 57:RR-10.

12. Seage GR 3rd, Losina E, Goldie SJ, Paltiel AD, Kimmel AD, Freedberg KA. The relationship of preventable opportunistic infections, HIV-1 RNA, and CD4 cell counts to chronic mortality. J Acquir Immune Defic Syndr 2002; 30:421–8

13. Castilla J, Sobrino P, De La Fuente L, Noguer I, Guerra L, Parras F. Late diagnosis of HIV infection in the era of highly active antiretroviral therapy: consequences for AIDS incidence. AIDS 2002;1614):1945–51

14. Quinn TC, Wawer MJ, Sewankambo N Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project StudyGroup. N Engl J Med 2000;34213):921–9

15. Lawn SD, Butera ST, Folks TM. Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. Clin Microbiol Rev 2001;144): 753–77

16. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998; 352:1725–30.

17. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. AIDS 1999; 13:1687– 95.

18. Al Dhahry SH, Scrimgeour EM, Al Suwaid AR, Al Lawati MR, El Khatim HS, Al Kobaisi MF, et al. Human immunodeficiency virus type 1 infection in Oman: Antiretroviral therapy and frequencies of drug resistance mutations. AIDS Res Hum Retroviruses 2004; 20:1166–72.

19. Bonnet F, Lewden C, May T, Heripret L, Jougla E, Bevilacqua S, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. Scand J Infect Dis 2005; 37:482–7.

20. Braun DL, Kouyos RD, Balmer B, Grube C, Weber R, Günthard HF. Frequency and spectrum of unexpected clinical manifestations of primary HIV-1 infection.Clin Infect Dis. 2015;15:616):1013-21

21. Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: A consensus definition. HIV Med 2011;12:61–4.

22. Naba MR, Kanafani ZA, Awar GN, Kanj SS. Profile of opportunistic infections in HIV-infected patients at a tertiary care center in Lebanon. J Infect Public Health. 2010;3:130–3.

23. Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med 1999; 340:1301–6.

24. Sharma S, Dhungana GP, Pokhrel BM, Rijal BP. Opportunistic infections in relation to CD4 level among HIV seropositive patients from central Nepal. Nepal Med Coll J 2010; 12:1–4.

25. Kaur A, Babu PG, Jacob M, Narasimhan C, Ganesh A, Saraswathi NK, et al. Clinical and laboratory profile of AIDS in India. J Acquir Defic Synd 1992;5:883–9.

26. Ayyagari A, Sharma AK, Prasad KN, Dhole TN, Kishore J, Chaudhary G. Spectrum of opportunisticinfections in HIV infected cases in a tertiary care hospital. Indian J Med Microbiol 1999; 17:78–80.

27. Chan CK, Alvarez Bognar F, Wong KH, Leung CC, Tam CM, Chan KC, et al. The epidemiology and clinical manifestations of human immunodeficiency virus-associated tuberculosis in Hong Kong. Hong Kong Med J 2010; 16:192–8

28. Kumaraswamy N, Solomon S. Spectrum of opportunistic infections among AIDS patient in Tamil Nadu, India. Int J STD AIDS 1995; 6:447–9.

29. Santos Mde L, Ponce MA, Vendramini SH, Villa TC, Santos NS, Wysocki AD, et al. The epidemiological dimension of TB/HIV co-infection. Rev Lat Am Enfermagem 2009; 17:683–8

30. Harrington M. From HIV to tuberculosis and back again: A tale of activism in 2 pandemics. Clin Infect Dis 2010; 50:S260–6.

31. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: The epidemiology and the response. Clin Infect Dis 2010; 50:S201–7.

32. Swaminathan S, Nagendran G. HIV and tuberculosis in India. J Biosci 2008; 33:527–37.

33. Cruciani M, Malena M, Bosco O, Gatti G, Serpelloni G. The impact of human Immunodeficiency virus type 1 on infectiousness of tuberculosis: A meta-analysis. Clin Infect Dis 2001; 33:1922–30

34. Oh MD, Park SW, Kim HB, Kim US, Kim NJ, Choi HJ, et al. Spectrum of opportunistic infections and malignancies in patients with human immunodeficiency virus infection in South Korea. Clinical infectious diseases. 1999 Dec 1;296):1524-8.

35. Nissapatorn V, Lee C, Fatt QK, Abdullah KA. AIDS-related opportunistic infections in Hospital Kuala Lumpur. Japanese journal of infectious diseases. 2003 Oct 1;565/6):187-92.

36. Luo B, Sun J, Cai R, Shen Y, Liu L, Wang J, Zhang R, Shen J, Lu H. Spectrum of opportunistic infections and risk factors for in-hospital mortality of admitted AIDS patients in Shanghai. Medicine. 2016 May;9521).

37. Assefa S, Erko B, Medhin G, Assefa Z, Shimelis T. Intestinal parasitic infections in relation to HIV/ AIDS status, diarrhea and CD4 T-cell count. BMC Infect Dis 2009 9:155.

38. O'Hara SP, Small AJ, Gajdos GB, Badley AD, Chen XM, Larusso NF. HIV-1 Tat protein suppresses cholangiocyte toll-like receptor 4 expression and defense against Cryptosporidium parvum. J Infect Dis 2009; 199:1195–204.

39. Tzipori S, Widmer G. A hundred-year retrospective on cryptosporidiosis. Trends Parasitol 2008; 24:184–9.

40. Fauci AS, Lane HC. Human immunodeficiency virus disease: AIDS and related disorders. Harrison's Principles of Internal Medicine, 17th ed. USA: The McGraw-Hill companies, Inc. 2008; 1137-203

41. Satishchandra P, Nalini A, Gourie-Devi M, Khanna N, Santosh V, Ravi V, et al. Profile of neurological disorders associated with HIV/AIDS from Bangalore, South India 1986-96). Indian J Med Res 2000; 111:14–23

42. Machala L, Maly M, Hrda S, Rozsypal H, Stankova M, Kodym P. Antibody response of HIV-infected patients to latent, cerebral and recently acquired toxoplasmosis. Eur J Clin Microbiol Infect Dis 2009; 28:179–82.

43. Nissapatorn V. Toxoplasmosis in HIV/AIDS: A living legacy. Southeast Asian J Trop Med Public Health 2009; 40:1158–78.