Clinical Profile and Its Relationship with CD4+ Count in Treatment Naive HIV – Infected Subjects

Javaid M.I[1]., Iqbal H.M.N[2]., Ghazanfar M[3]., Haider S[4]., Mazhar S[5]., Natiq M[6]., Ahmad R.[7] and Anwar A.[8]
[1,3-8]*Department of Pathology, Allama Iqbal Medical College, Lahore-Pakistan.*
[2]*Incharge Medical Officer BHU 68/F, Hasilpur, Bahawalpur-Pakistan.*

ABSTRACT

Background and Objective*: The human immunodeficiency virus (HIV) infects, destroys and paralyzes the immune system of human body. There is steady rise in the number of cases having AIDS (acquired immunodeficiency syndrome). Decision regarding when to initiate antiretroviral treatment or chemo-prophylaxis for opportunistic infections and clinical monitoring is done with the help of CD4+ counts. Flowcytometry is very expensive and available at specialized centers. Therefore, clinical indicators are needed to be explored to fore see low CD4+ counts and disease progress.*

Methods: *It was a cross-sectional study and conducted among 106 HIV infected, treatment naive individuals with all genders and age range of 18-65 years. Responses regarding clinical signs and symptoms were entered on pre designed structured proforma by history and clinical examination. Blood samples were taken and base line CD4+lymphocyte count evaluated on flowcytometer. Data was analyzed in software SPSS 23 and P value of < 0.05 was considered statistically significant.*

Results: *Participants in this study commonly reported weight loss, fever and cough in 79.2%, 94. 3% and 34.9% of the subjects respectively. Generalized lymphadenopathy and pallor were predominant signs in 22.6% and 54.7% of the subjects. Tuberculosis and HCV infection were seen in 12.3% and 17% subjects. CD4+ counts were lower in symptomatic patients and those having oral thrush, weight loss and other clinical conditions.*

Conclusion: *Oral thrush and weight loss predicted low CD4+ counts and these may be considered as indicator of disease progression in HIV infection. Systematic studies are required on the natural history of disease on larger scale to identify clinical features or conditions that may have some prognostic significance in HIV infected individuals.*

KEYWORDS: *HIV= Human Immunodeficiency Virus, AIDS = Acquired Immune Deficiency Syndrome, CD4+ count = Cluster of differentiation.*

INTRODUCTION

HIV (human immunodeficiency virus) belongs to retrovirus family that infects, destroys and paralyzes immune system of human body. As the infection advances the immune system is no longer able to resist the infections. It can take years to develop full blown disease called AIDS.[1]

HIV destroys CD4+ cells in lymphoid tissues and peripheral blood.[2] Enumeration of CD4+ count is necessary for staging and monitoring the progression of disease.[3] CD4+ count assesses immune dysfunction. CD4+ count is the number of CD4+ cell/µl of blood. It evaluates the danger of opportunistic diseases, prognosis and helps the health personnel when to initiate the antiretroviral therapy.[4]

HIV infection highly contribute to morbidity and is the 6th foremost basis of mortality in the world. The WHO (World Health Organization) estimated that worldwide, 1.5 million population died due to HIV/AIDS related illnesses and 36.7 million are living with HIV infection in 2015.[5]

Early detection of subjects with HIV (CD4+ count > 350/µl) enhances the efficacy of antiretroviral treatments, and reduces onward transmission. Early diagnosis and treatment also decrease the cost of social care by preventing HIV associated illnesses. On contrary, diagnosis of HIV in later stages (CD4+ < 350/µl) will have poor prognosis due to irreparable damage to immune system and associated troubles.[5] Systematic studies are required on the natural history of disease on larger scale to identify clinical features or conditions that may have some prognostic significance in HIV infected individuals.[6]

However, HIV infection has many nonspecific symptoms and signs for example weight loss, rashes and respiratory infections which present as a challenge to health practitioner for diagnosis of disease.[5]

Chronic HIV infection causes immunodeficiency

Corresponding Author: Dr. Muhammad Iqbal Javaid
Assistant Professor Pathology, Allama Iqbal Medical College, Lahore-Pakistan.
Email: driqbaljavaid@hotmail.com

and enhances the danger of co-infection by pathogens which are restricted by innate and adaptive immune system, some are limited by antibody-mediated phagocytic response. There are five important infectious diseases which are causing morbidity and mortality in HIV infected people worldwide: tuberculosis, hepatitis B virus, malaria, hepatitis C and cryptococus.[7]Many studies have revealed that clinical manifestations such as diarrhoea, fever, joint pains oral candidiasis, and herpes zoster can anticipate disease progression from HIV-infection to AIDS.[8-11]

As more and more HIV-infected persons becoming immunocompromised and adding to the number of AIDS patients, the burden on the health care delivery system is expected to increase in the near future. The epidemiology and clinical presentation of the disease varies greatly from country to country and from region to region in same country and even from patient to patient. Thus for planning targeted interventions, it is essential to know the clinical pattern of the disease in a particular area.[12] From developing countries point of view, identifying clinical conditions which can predict low $CD4^+$ counts and hence progression to AIDS might prove to be useful.

This study was aimed to detect clinical characteristics of HIV infected subjects before diagnosis that may be used to predict early detection of HIV infection in basic health care. We conducted a cross sectional study in HIV infected peoples referred to Reference Centre Punjab AIDS Control Program (PACP) to identify the profile of clinical conditions among HIV-infected persons and assess their association with $CD4^+$ counts. Few clinical/demographic studies have been carried out across Pakistan, no such study has been undertaken in Lahore till date. Keeping this in mind, it was proposed to study clinical profile of HIV/AIDS peoples at a tertiary care centre in Lahore, Pakistan.

METHODS

A descriptive cross-sectional study was conducted in Pathology department at Allama Iqbal Medical College, Lahore after approval from ethical review board of institute (vide letter No.1705/ERB/17) and informed consents from patients. A total of 106 diagnosed subjects of HIV in-fection with all genders with age range between 18-65 (years) were enrolled in the current study through non-probability purposive sampling referred from Punjab AIDS Control Programme. Exclusion criteria were, taking antiretroviral therapy, self reporting patients and patients having documented evidence co-morbidity with other medical conditions (e.g. tuberculosis, endocarditis, congenital immune disorder and acute viral infections) that could significantly modify hematologic parameters.

The study subjects were classified into three groups according to the classification system of the Centers for Disease Control and Prevention Criteria (CDC), which highlights the importance of $CD4^+$ T lymphocyte testing in the clinical management of HIV-infected people. The groups were: $CD4^+$ counts (1) ≥ 500 cells/µl; (2) 200–499 cells/µl; and (3) < 200 cells/µl.

Responses about socio-demographic factors like age, gender, marital status and clinical signs and symptoms were entered on pre designed structured proforma by history and clinical examination.

Five ml of venous blood samples were taken from every patient in EDTA vacutainer tubes between 09:00 am and 12:00 pm and analyzed within 6 hours. $CD4^+$ lymphocyte count were evaluated on BD FACS Calibur, "an automated four colour" flowcytometer which performs both cell sorting and analysis. The counts were determined by a monoclonal antibody cocktail comprised of CD^{3+}PerCp, CD^{4+} FITC and CD^{8+}PE in a Tru-Count tube.

STATISTICAL ANALYSIS

Data was analyzed by using Statistical Package for Social Sciences software SPSS 23. Frequencies, percentages, mean and SD (standard deviation) were calculated. Cross tabulations were carried out. Comparison of $CD4^+$ counts was made with other variables like clinical features and associated ailments. Chi-square and ANOVA were utilised for comparison of proportions and means. *P-value < 0.05* was taken as statistically significant. The objective of the study was to evaluate the clinical profile and its relationship with CD4 counts in HIV-infected persons.

RESULTS

One hundred and six subjects with HIV/AIDS, ART naive were taken in the study by fulfilling exclusion and inclusion criteria in department of Hematology, AIMC Lahore. Mean age of HIV cases incorporated in the study was 31.4 ± 8.5 with age range of 18-65 years. Majority, 58 (57.4%) of the total cases were in age group of 18-29 year and thirty two (30.2%) in the age group of 30-39 years. Sixty five (61.3%) of the study cases were mar-ried and 41 (38.7%) were singles. There were 83 (78.3%) males, 17 (16%) females and 6 (5.7%) trans-genders out of the 106 cases.

Common clinical features were weight loss, fever and cough in 79.2%, 94.3% and 34.9% respectively of the total cases. Prevalent signs were generalized lymphadenopathy and pallor in 22.6% and 54.7% of the subjects. Frequency of signs and symptoms seen in the study population are shown in the (Table- 1). The results were analysed to assess the relationship between the clinical conditions and the $CD4^+$ cell count. Comparison of mean $CD4^+$ counts of patients with or without multiple clinical conditions are given in the (Table-1). *P value < 0.05* is statistically significant in some of clinical conditions.

In this study, in addition, some of the subjects

were also having other ailments. HCV infection in (17%) was most prevailing followed by tuberculosis in (12.3%). Frequencies of co-morbidities or ailments are given in (Table- 2).

Mean $CD4^+$ count in present study was 480.7 ± 298.7. HIV patients were categorized as to $CD4^+$ count: < 200 cells/cmm, 200–499 cells/cmm and ≥500 cells/cmm according to CDC classification. $CD4^+$count < 200 cells/cmm was present in 18 (17%) of the cases, 200–499 cells/cmm was present in 38 (35.8%) of the cases. Majority of the study subjects 50 (47.2%) had $CD4^+$ count ≥ 500 cells/cmm.

The illnesses suggestive of HIV associated infections with reference to their $CD4^+$ counts are analyzed in (Fig.1). Comparing the individu-als with higher $CD4^+$ counts, those with $CD4^+$ count <200 cells/µl had more cases with symptoms, like gen-ital ulcer, bruising and oral thrush etc.

As observed in (fig.2), of all the associated illnesses tuberculosis and diabetes were seen in higher proportion in category of the patients with $CD4^+$ count < 200 $CD4^+$ cells/µl.

Table- 1: *Clinical conditions and comparison of mean $CD4^+$ count.*

Clinical Conditions	*Response*	*Mean CD4 Count*	*Number*	*Percent*	*P-Value*
Fever	No	612	06		0.27
	Yes	473	100	94.3	
Breathlessness	No	580	51		0.001
	Yes	504	55	51.9	
Pallor	No	639	48		0.000
	Yes	350	58	54.7	
Cough	No	535	69		0.010
	Yes	379	37	34.9	
Diarrhea	No	566	58		0.001
	Yes	377	48	45.3	
Bruising	No	495	102		0.013
	Yes	120	4	3.8	
Weight loss	No	657	22		0.002
	Yes	435	84	79.2	
Oral thrush	No	518	76		0.042
	Yes	387	30	28.3	
Genital Ulcer/Boil	No	484	105		0.231
	Yes	123	1	0.9	
Tuberculosis	No	498	93		0.103
	Yes	354	13	12.3	
Diabetes	No	487	102		0.304
	Yes	329	4	3.8	
Rash	No		62		
	Yes		44	41.5	
Lymph nodes	No		82		
	Yes		24	22.6	
Jaundice	No		84		
	Yes		22	20.8	
Urethral discharge	No		98		
	Yes		8	7.5	
Numbness	No		98		
	Yes		8	7.5	
Pains	No		101		
	Yes		5	4.7	
Weakness	No		102		
	Yes		4	4.7	
Anal discharge	No		105		
	Yes		1	0.9	
Ankle edema	No		105		
	Yes		1	0.9	

DISCUSSION

The HIV is an epidemic which is no longer limited to people with high-risk behavior in urban territory, but is also reaching rural areas. Patients with HIV infection have now started reporting to healthcare facilities in various stages of immunodeficiency with variety of clinical features and associated ailments due to increasing awareness. There is rising prevalence of HIV among patients with tuberculosis, thereby indicating that many patients presenting with tuberculosis were subsequently investigated and diagnosed as being co-infected with HIV and vice versa.[6]

Although the absolute $CD4^+$ cell count is known to be an adequate marker for progression of HIV disease, the investigation is expensive and the capability and expertise is available only at a few centers in Pakistan.

HIV has a potential to disturb every organ in the body by direct viral damage or render the host vulnerable to opportunistic infection.[13] This study

Table-2: *Co-morbidities or ailments with HIV infection.*

Co-morbidities or Ailments	Number	Percentage
HCV	18	17.0
HBV	1	0.9
Tuberculosis	13	12.3
Diabetes Mellitus	4	3.8
Anal fistula	1	0.9
Flu	1	0.9
Piles	1	0.9
Pregnancy	1	0.9
Tonsillitis	1	0.9

showed that the commonest signs symptoms experienced by HIV patients were fever, weight loss, pallor, breathlessness, diarrhea, rash, cough, oral thrush, lymphadenopathy, jaundice, urethral discharge and numbness etc. We observed that the HIV-infected persons presenting with most of the clinical conditions, the CD4+ counts were lower. Moreover, majority of cases with skin lesions, oral thrush and genital ulcers had advance immunosuppression as shown by lower CD4+ counts (< 200/µl). These findings were comparable with earlier studies conducted by Deshpande et al., Nayak et al., and Tsega.[14-16]

A study from Nigeria showed that majority of patients had advanced disease and immunosuppression at the beginning, with weight loss, fever, diarrhea and skin ailments are the most frequent presenting complains.[17] Other study from Chinese children showed weight loss in 43 cases (65.2%), anemia in 42 cases (63.7%), fever in 40 (60.6%), fatigue in 38 (57.6%), skin rash in 31 cases (47.0%), persistent cough in 28 (12.1%), chronic diarrhea in 24 (36.4%), CNS involvement in 16 (24.2%), oral thrush in 13 (19.7%), and hepatosplenomegaly in 12 (18.2%) HIV infected patients.[18]

Comparably another study from Karachi like ours, the most frequent symptoms were weight loss in 31 (59.6%), fever in 22 (42.3%), loose motions in 16 (30.8) and persistent cough in 15 (28.8%) patients where as the commonest signs were pallor in 33 (63.5%) and muscle wasting in 21 (40.4%) subjects. Hepatomegaly was seen in 7 (13.5%) and lymphadenopathy in 5 (9.6%) HIV patients.[13]

In present study HCV infection (17%) was most prevalent among HIV/AIDS followed by tuberculosis (12.3%). Comparable findings were seen in a study at Dhaka, among all the patients with HIV infection, the most common associated illness was TB in 25 cases (23%).[19] In a study at Jaipur in India tubercular disease was seen in 66% and 30% had atypical presentations.[20] In another study pulmonary tuberculosis was seen in only (4%) of the cases.[21]

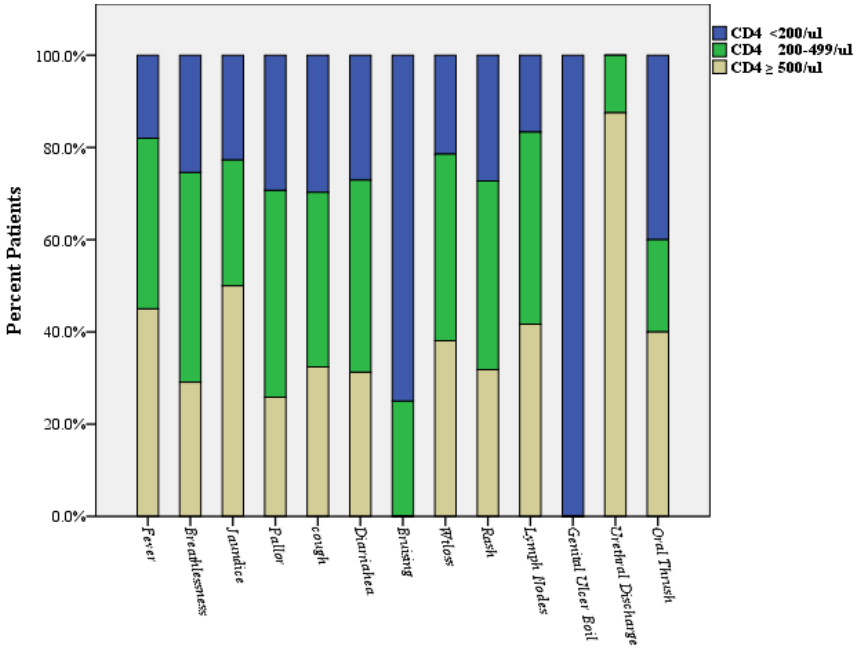

Fig. 1: *Presenting complaints and CD4+ category-wise distribution of cases (n = 106).*

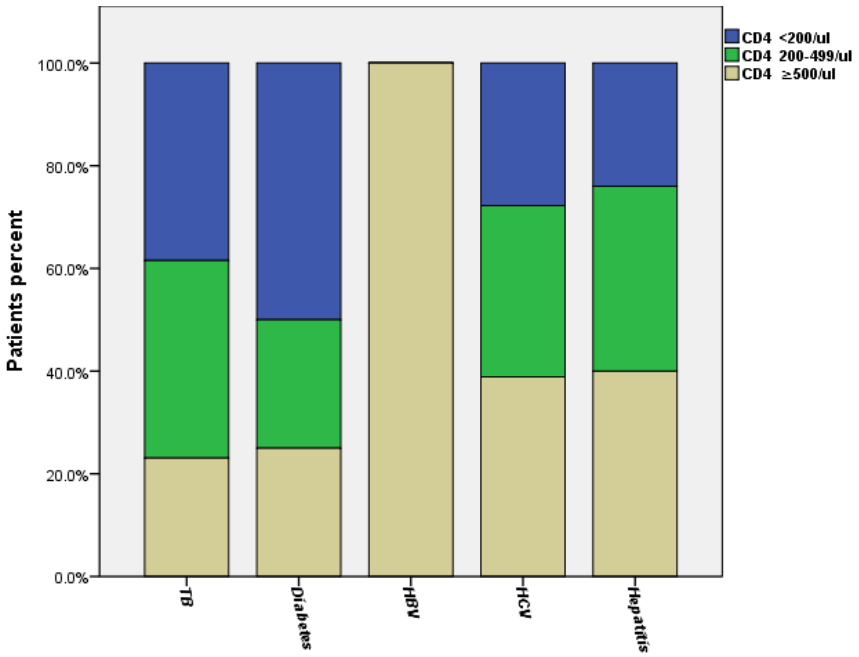

Fig. 2: *Associated illness and CD4+ count category-wise distribution of cases (n = 106).*

Mean CD4+ counts in patients with multiple clinical conditions (breathlessness, fever, weight loss,

diarrhea and rash etc) was lower than the patients who do not have those. Statistically significant difference was observed between mean $CD4^+$ counts of patients having or not having clinical conditions with P value < 0.05. Similar results were seen in a study from India conducted by Ghate et al.[6]

According to CDC classification, $CD4^+$ count < 200 cells/cmm was present in 18 (17%) of the cases, 200–499 cells/cmm was present in 38 (35.8%) of the cases. Majority of the study subjects 50 (47.2%) had $CD4^+$ count ≥ 500 cells/cmm. In a study conducted by Wondimeneh, $CD4^+$cell counts of < 200 cells/cmm were seen in 96 patients (24%) slightly more than our study.[22]

Similar findings showed by Gautam et al, twenty one percent belong to group < 200 cells/µl.[23] In a study at Dhaka 56% of the HIV subjects belonged to group $CD4^+$ count < 200 cells/µl, much higher than our study.[19]

Majority (54.7%) of patients in present study were within the sexually active age group of 18-29 years. These findings are similar with the studies conducted by Vaseem et al, and S Joge et al. which reported that highest count of patients were within 21-40 years age group.[24,25] Contrary to this, majority (73.8%) of patients in a study by Singh A et al were within the age group of 41-60 years.[26]

Our study has focused on assessing the likelihood of using clinical features to predict HIV infection progression in a resource constraint outdoor setting in developing countries. This small cross-sectional study highlights the association between the presence of a variety of clinical conditions and low $CD4^+$ counts. Therefore it is necessary to plan and execute natural history studies on larger samples in different parts of the country. Such studies will help in the identification of clinical conditions in HIV-infected people, better understanding and utilization of $CD4^+$ counts, and may also provide guidelines at various points of intervention.

CONCLUSION

Oral thrush and weight loss predicted low $CD4^+$ counts and these may be considered as indicator of disease progression in HIV infection. This study focuses the association between the presence of a variety of clinical conditions and low $CD4^+$ counts and will also aid in better understanding and use of $CD4^+$ counts in patient management.

LIMITATIONS OF STUDY

This study was self-funded with limited resources. So it is necessary to plan natural history studies on larger scales in different parts of the country. Such studies will be helpful to identify clinical profile in HIV-infected subjects.

ACKNOWLEDGMENT

The authors are thankful to the administration and technical staff of Pathology Department of AIMC for their support and cooperation. We are grateful to the Punjab AIDS Control Programme for referring the patients to us.

AUTHOR'S CONTRIBUTION

MIJ: Principal investigator, topic selection, Data analysis and interpretation.
HMNI: Co-investigator, drafting the manuscript. MG: Co-investigator, revision of manuscript for important intellectual content.
SH: Co-investigator, statistical analysis of data.
SM: Co-investigator, drafting the manuscript.

CONFLICT OF INTEREST

None to declare.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

None to disclose.

REFERENCES

1. Al-Jabri AA. Mechanisms of host resistance against HIV infection and progression to AIDS. Sultan Qaboos Univ Med J. 2007; 7 (2): 82-7.
2. Arafa A, Rida S, Khalil M. Fractional modeling dynamics of HIV and CD4+ T-cells during primary infection. Nonlinear Biomed Phys. 2012; 6 (1): 1-9.
3. Ingole N, Nataraj G, Mehta P, Paranjpe S, et al. CD4 counts in laboratory monitoring of HIV disease—experience from Western India. J. Int. Assoc. Provid. AIDS Care. 2014; 13 (4): 324-7.
4. Nabatanzi R, Bayigga L, Ssinabulya I, Kiragga A, et al. Low antigen-specific CD4 T-cell immune responses despite normal absolute CD4 counts after long-term antiretroviral therapy an African cohort. Immunol Lett. 2014; 162(3): 264-72.
5. Rumbwere Dube BN, Marshall TP, Ryan RP, Omonijo M. Predictors of human immunodeficiency virus (HIV) infection in primary care among adults living in developed countries: a systematic review. Syst Rev. 2018; 7 (1): 82-6.
6. Ghate MV, Mehendale SM, Mahajan BA, Yadav R, et al. Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. Natl Med J India. 2000; 13 (4): 183-7.
7. Chang CC, Crane M, Zhou J, Mina M, et al. HIV and co-infections. Immunol Rev. 2013; 254 (1): 114-42.
8. Klein RS, Harris CA, Small CB, Moll B, et al. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. N Engl J Med. 1984; 311 (6): 354-8.
9. Greenspan D, Greenspan JS, Hearst NG, Pan LZ, et al. Relation of oral hairy leukoplakia to infection with the human immuno-deficiency virus and the risk of developing AIDS. J Infect Dis. 1987; 155 (3): 475-81.

10. Melbye M, Grossman RJ, Goedert JJ, Eyster ME, et al. Risk of AIDS after herpes zoster. Lancet. 1987; 1 (8535): 728-31.
11. Moss AR, Bacchetti P, Osmond D, Krampf W, et al. Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. Br Med J. 1988; 296 (6624): 745-50.
12. Kumawat S, Kochar A, Sirohi P, Garhwal J. Socio-demographic and clinical profile of HIV/AIDS patients in HAART era at a tertiary care hospital in North-West Rajasthan, India. Int J Community Med Public Health, 2017; 3 (8): 2088-93.
13. Siddiqui MH, Siddiqui JA, Ahmed I. Demographic profile and clinical features of admitted HIV patients in a tertiary care teaching hospital of Karachi, Pakistan. PaK J Med Sci. 2009; 25 (5): 861-64.
14. Deshpande JD, Giri PA, Phalke DB. Clinico-epidemiological profile of HIV patients attending ART centre in rural Western Maharashtra, India. South East Asia J Public Health. 2012; 2 (2): 16-21.
15. Nayak U, Lenka S, Achappa B. Clinical and socio demographic profile of attendees at ART centre in a tertiary care hospital in Mangalore,India. Asian J Med Sci. 2015; 6 (5): 61-5.
16. Tsega E. The demographic, social and clinical presentations of one hundred Ethiopian patients with human immunodeficiency virus (HIV) infection. Ethiop Med J. 1990; 28 (2): 81-8.
17. Ojini FI, Coker A. Socio-demographic and clinical features of HIV-positive outpatients at a clinic in south-west Nigeria. Afr J AIDS Res. 2007; 6 (2): 139-45.
18. Li ZC, Zhao Y, Dou ZH, Yu L, et al. Clinical features of 66 children with acquired immunodeficiency syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2009; 11 (2): 93-5.
19. Matin N, Shahrin L, Pervez MM, Banu S, 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 (1): 14-9.
20. Kothari K, Goyal S. Clinical profile of AIDS. J Assoc Physicians India. 2001; 49: 435-8.
21. Altuntas OA, Karaosmanoglu HK, Korkusuz R, Nazlican O. Clinical profile of HIV/AIDS patients admitted to a tertiary outpatient clinic in Istanbul, Turkey. J Int AIDS Soc. 2010; 13 (S4): P220-27.
22. Wondimeneh Y, Ferede G, Yismaw G, Muluye D. Total lymphocyte count as surrogate marker for CD4 cell count in HIV-infected individuals in Gondar university hospital, Northwest Ethiopia. AIDS Res Ther. 2012; 9 (1): 21-8.
23. Gautam H, Bhalla P, Saini S, Dewan R. Correlation between baseline CD4 + T-Lymphocyte count and plasma viral load in AIDS patients and their early clinical and immunological response to HAART: a preliminary study. Indian J Med Microbiol. 2008; 26 (3): 256-8.
24. Vaseem B, Madhusudan S, Bhardwaj AK, Rathore M, et al. A study on socio-demographic profile and risk factors present in HIV infected patients attending ART centre in tertiary care hospital in Rajasthan, India. Nat J Community Med. 2012; 3 (2): 5-10.
25. Joge US, Deo DS, Lakde RN, Choudhari SG, et al. Sociodemographic and clinical profile of HIV/AIDS patients visiting to ART Centre at a rural tertiary care hospital in Maharashtra state of India. Int J Biol Med Res. 2012; 3 (2): 1568-72.
26. Singh A, Mahajan S, Singh T, Deepti SS. Socio-demographic and clinical profile of HIV/AIDS patients attending the ART centre of Amritsar, Punjab. Int J Community Med Public Health. 2018; 5 (5): 2059-65.

- Received for Publication: 27-04-2019
- Revision received: 22-06-2019
- Accepted for publication: 17-09-2019