

# Study of Cardiac Manifestations in Patients with HIV Infection and Their Correlation with CD4 Count in Indian Population.

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## ABSTRACT

**Background:** HIV continues to be a major global public health issue. In 2014 an estimated 36.9 million people were living with HIV, a global prevalence of 0.8 %. The clinical spectrum of HIV infection encompasses a spectrum ranging from an acute syndrome associated with primary infection to a prolonged symptomatic state to an advanced cardiac disease in HIV affected patients is becoming more prevalent as therapy and longevity improve. Infection HIV is one of the causes of acquired heart disease in these patients. With advances in the management of patients living with HIV and AIDS (PLHA), not only survival has increased but manifestations of late stage HIV infection are encountered more often including cardiovascular complications. **Aims and Objectives:** To determine the prevalence and characteristics of cardiac manifestations in patients with HIV infection and to evaluate their correlation with CD4 count. **Methods:** During the period of 1 year from July 2015 to September 2016, total 100 cases of HIV/AIDS were included. The occurrence of cardiac involvement in HIV/AIDS cases was determined based on cardiac enzymes, ECG findings & 2D Echocardiography findings. An attempt was made to correlate various cardiac findings with CD4 T cell count. **Results:** Male to female ratio was 3:1. Common clinical symptoms were fever (68%), cough (44%) & exertional breathlessness (33%). Echocardiographic abnormalities were seen in 54.3% of patients. Reduced ejection fraction (below 50%) and fractional shortening below 30% were the most common cardiac abnormality (46.3%) followed by pericardial effusion (16.66%), pulmonary artery hypertension (11.11%), dilated cardiomyopathy (9.25%), diastolic dysfunction (9.25%), regional wall motion abnormality (1.85%) and valvular regurgitation (5.55%) respectively. Significant statistical positive correlation was observed between low CD4 count and echocardiographic abnormalities ( $p < 0.001$ ). Pericardial effusion was seen more in patients with CD4 count below 200 ( $p < 0.05$ ). Maximum number of echocardiographic abnormalities was seen in WHO clinical stage IV. **Conclusion:** Echocardiographic abnormalities are more prevalent in HIV/AIDS patients and their prevalence increases as the CD4 count falls and occur more in advanced stage of the disease. So we should aim at starting ART early in HIV infected patients so as to improve the quality of life of people living with HIV/AIDS.

**Keywords:** HIV, AIDS, PLHA, CD4 Count, Echocardiographic Findings.

## INTRODUCTION

HIV infection has become a global pandemic with more than 33.3 million people infected throughout the world by the end of 2014 India is estimated to have 2.1 million infected individuals.<sup>[1,2]</sup>

Acquired immunodeficiency syndrome (AIDS) is characterized by an acquired, profound, irreversible, immune suppression that predisposes the patient to multiple opportunistic infections, malignant neoplasms and a progressive dysfunction of multiple organ systems.<sup>[5]</sup> With the availability of a large armamentarium of anti-retroviral drugs and recent advances in the diagnosis, treatment and monitoring of persons living with HIV and AIDS (PLHA), there has been visible improved survival of such patients.<sup>[6]</sup> Due to the longer survival of PLHA, the manifestations of late stage HIV infection are now being met with more commonly

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than before, which includes HIV related cardiac diseases.<sup>[6]</sup>

Although not fully recognized in the early days of HIV epidemic, cardiac involvement has been reported with increasing frequency in recent years.<sup>[7]</sup> Despite this, cardiac involvement can be over looked in HIV-positive patients, because symptoms of breathlessness, fatigue and poor exercise tolerance are frequently ascribed to other conditions associated with HIV patients is extremely useful to identify cardiac conditions common in HIV-positive patients. The prevalence of cardiac involvement in AIDS patients have been reported to range between 28% and 73%.<sup>7</sup> The cardiac diseases in HIV infections include pericardial effusion, left ventricular dysfunction myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, malignant neoplasm, coronary artery disease and drug related cardiotoxicity.<sup>[8]</sup>

The most important clinical application of HIV-related immunology is measurement and interpretation of the absolute CD4 cell count. It is currently recommended that patients have this test performed at the time of HIV diagnosis and then again approximately every 3 to 4 months, usually in conjunction with an HIV RNA (viral load) test. Recovery of the CD4+T cell count in response to anti-retroviral treatment has been shown to be the most important predictor of clinical outcome, even more so than the virologic response. The relation of CD4 + T cell count is also important as it correlate with severity of cardiac involvement.<sup>[8]</sup>

Echocardiography is very helpful in detecting cardiac dysfunction at an early stage, much before overt clinical manifestations develop.<sup>[9]</sup> The most common sign of cardiac involvement is impairment of LV fractional shortening This could be explained by reduction of cardiac contractility.<sup>[8]</sup> Early detection of cardiac involvement in HIV cases in pre-AIDS or AIDS phase of disease is therefore important to prevent significant morbidity from cardiac involvement.<sup>[10]</sup> The present study is therefore undertaken to detect occurrence of symptomatic or asymptomatic cardiac involvement in HIV/AIDS cases and their correlation with CD4+Tcell count.

#### **Aims and Objectives**

The present study is undertaken with the objectives to evaluate the cardiac manifestations in HIV/AIDS cases; to determine type of cardiac involvement in HIV/AIDS cases; and to correlate CD4+T cell count with pattern of cardiac involvement.

## **MATERIALS AND METHODS**

The present study was prospective cross sectional study, carried out in the Department of Medicine, Government Medical College Amritsar during the period of 1 year from July 2015 to September 2016.

One hundred consecutive patients with HIV infection were studied. A total of 400 patients were randomly chosen at the start of the study. Three hundred patients were excluded from study because of exclusion criteria. Among the 100 patients 75 males and 25 females in the study group were divided into four groups depending on the CD4 count. Group I included patients with CD4 count  $\leq$  50 cells / mm<sup>3</sup>. Group II included patients with CD4 count  $>$ 50-199 cells / mm<sup>3</sup>. Group III included 200-499 cells / mm<sup>3</sup> while Group IV included patients with CD4 count  $>$ 500 cells / mm<sup>3</sup>.

#### **Inclusion Criteria**

Patients who have been diagnosed as HIV positive by ELISA method

#### **Exclusion Criteria**

1. Age less than 18 years
2. Ischemic heart disease
3. Congenital heart disease
4. Hypertension
5. Rheumatic heart disease.

#### **Clinical Examination Focused in the Study**

As the subjects under study were patients hospitalized to this tertiary care centre, consent was taken at the point of hospitalisation for conducting the required investigations as detailed below. All patients were assessed clinically by detailed history taking and general physical examination for the presence of anaemia, cyanosis, clubbing, pedal edema, dyspnoea, jaundice, generalized lymphadenopathy and skin and mucous membrane lesions. Respiratory rate, pulse rate, jugular venous pressure, blood pressure (both in supine and erect posture) were also recorded. A thorough clinical examination of the cardiovascular system, respiratory system, abdomen and central nervous system was done.

Hemoglobin estimation was done by Drabkin's method, Total and differential leucocyte count was performed in all cases. The CD4 T cell count was carried out in all cases using flow cytometry by BD FACS count. The CD4 count was done using kits supplied by the National AIDS Control Organisation of India (NACO) to Anti-Retroviral Therapy (ART) Centre, Amritsar. Staging of the disease was done according to revised WHO clinical staging of the disease.<sup>[11]</sup>

All patients were evaluated using M Mode and Two dimensional transthoracic echocardiography and colour flow Doppler examination using Philips Sonos (MCM- D02AA) in the Department of this institution. Each two dimensional study consist of parasternal long and short axis, and apical two and four chamber views. The conventions of American

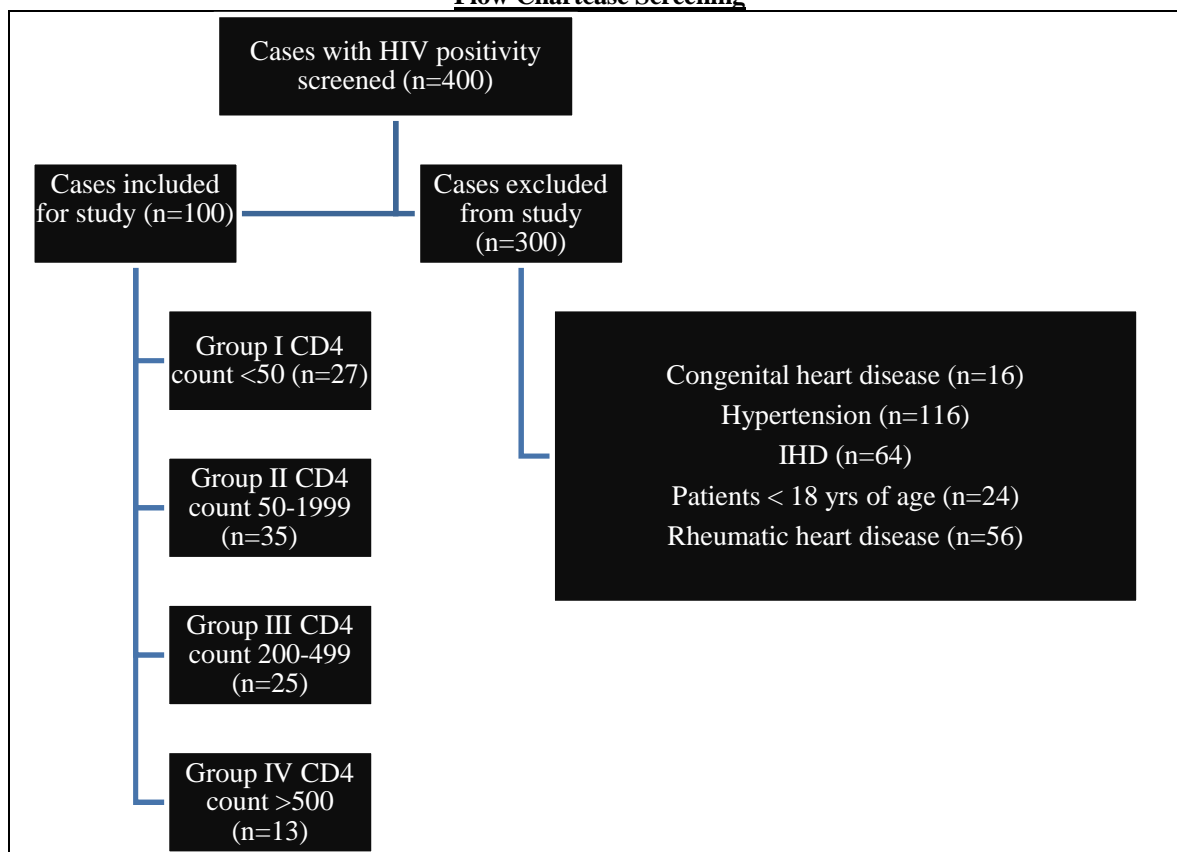
Society of Echocardiography were followed in obtaining left atrial dimensions, left ventricular end systolic and end diastolic dimensions, right ventricular end diastolic dimensions and left ventricular fractional shortening (FS). Left ventricular volumes were measured and ejection fraction (EF) was calculated. The occurrence of cardiac involvement in HIV/AIDS cases was then determined based on cardiac enzymes, ECG findings

& 2D echocardiography findings. An attempt was made to correlate various cardiac finding with CD4 T cell count.

**Statistical Analysis**

Statistical analysis of data was done using SPSS 16 software, chi-square test and results were summarized. “P” value less than 0.05 was considered as significant.<sup>[33-35]</sup>

**Flow Chartcase Screening**



**RESULTS**

One hundred consecutive patients with HIV infection who were hospitalized to inpatient ward of the department of medicine were studied. There was a gender predominance with male to female ratio being 3:1. Table no 1 showed the age of the patients studied ranged between 15 and 80 years, with a mean age of 41.37 (±11.86) years in males and 41.37 (±9.47) years in females respectively. Majority of the patients, 75% males and 25% females were young and were in the age group of 19 to 40 years. Sexual mode of transmission was the most common, out of which hetero-sexual accounted for 94.4% and homosexual 2.8% of cases. The other modes were blood transfusion (2.2%), IV drug abuse (1.9%) and vertical transmission (1.6%) respectively. The clinical features of the patients under study with relevance to cardiovascular system were fever (77.8%), cough (20%), breathlessness (24.3%),

pedal edema (10.2%), chest pain (8.1%) and palpitation (5%).

Table 2 showed mean CD4 count of all four groups taken into study Out of 100 cases, CD4 count was less than 50/micro L in 27.3%, 34.6% of cases had CD4 count between 50 to 199/micro L, 25.4% had CD4 Count 200-499/micro L while 12.7% had CD4 count >500/micro L. The maximum number of patients studied were in clinical stage 4 (41.2%) followed by Clinical stage 3 (35.5%), Clinical stage 2 (14.4%) and only 10% of cases were in Stage 1 respectively.

In the present study, out of 100 cases studied 58% of the patients had normal X-ray chest. Cardiomegaly was present in 12% patients. Pleural effusion was seen in 9% cases and fibrocaceous lesion was seen in 8% patients. In 12% cases X ray chest was showed bilateral reticulonodular shadows & cavitary lesions were noticed in 3% cases. In the present study, out of 100 cases studied 66% patients had normal ECG.

Commonest abnormalities were sinus tachycardia observed in 15% cases and low voltage complexes in 26% cases. The results were found to be non-significant.

In the present study 92 % (92 cases) showed normal CPK-MB levels. 8 % (8 cases) showed CPK-MB abnormality in this study. 50% of them i.e. 4 cases fell in <50 micro/l CD4 range group and 50% i.e. 2 cases in 50-199 micro/l CD4 range group. The results were found to be non-significant according to statistical analysis.

As shown in Table 3, echocardiographic abnormalities were seen in 54.3% of cases. Reduced EF (<50%) was seen in 14.3%. This study showed reduction in FS (<30%) in 46.3% of cases. Pericardial effusions were seen in 16.6% while pulmonary artery hypertension was noted in 11.1%

of cases. Dilated cardiomyopathy and diastolic dysfunction was found in 9.25% of cases. One case had regional wall motion abnormality (RWMA) involving the anterior wall. (1.86%) As presented in Table 4, maximum number of echocardiographic findings were seen in patients with CD4 count less than 50. Out of the total 14 patients with reduced EF, 9 patients had CD4 count less than 50. Similarly reduction in FS, 10 patients out of total 25 had CD4 count less than 50. 4 out of 5 cases of dilated cardiomyopathy had CD4 count less than 50. Maximum number of cases with pericardial effusions, diastolic dysfunction and pulmonary artery hypertension had CD4 count less than 50. The lone case with RWMA also had CD4 count less than 50.

**Table 1:** Age and Sex Distribution.

Age group (years)	Male (%)	Female (%)	Total (%)
19-30	15	5	20
31-40	23	7	30
41-50	24	9	33
51-60	10	3	13
61-70	2	1	3
71-80	1	0	1
Total	75	25	100

**Table 2:** The Groups of HIV Patients Based on CD4 Cell Count.

CD4 GROUP	NUMBER OF PATIENTS	CD4 COUNT CELLS/mm <sup>3</sup>	MEAN CD4 CELLS/mm <sup>3</sup>
I	27	<50	48.44 ± 26.33
II	35	50-99	178.97 ± 102.69
III	25	200-499	342.92 ± 162.29
IV	13	>500	630.64 ± 88.96
TOTAL	100		220.18 ± 158.31

**Table 3:** 2D Echocardiographic findings of the cases studied.

Cardiac Manifestations	No of cases	Percentage (%)
Reduced ejection fraction (<50%)	14	14.3
Fractional shortening (<30 %)	25	46.29
Pericardial effusion	9	16.66
PAH	6	11.11
Dilated cardiomyopathy	5	9.25
Valvular regurgitations	3	5.55
RWMA	1	1.86
Diastolic dysfunction a>e	5	9.25
Patients having cardiac manifestations	54	54.33

Table 5 shows association of 2D echocardiographic findings with revised WHO clinical staging. Maximum number of echocardiographic findings were seen in patients in clinical stage 4. Out of the total 14 patients with reduced EF, 9 patients were in stage 4, similarly in those with reduced FS, 10 out of total 25 were in stage 4. Out of 5 cases of dilated cardiomyopathy, 4 cases were in stage 4. Maximum number of cases with pericardial effusions, diastolic dysfunction and pulmonary arterial hypertension were also in stage 4. The lone case of coronary artery disease was also in Stage 4. Mean CD4 counts was found to be 128 ± 108 in patients with echocardiographic abnormalities, whereas it was

312.6 ± 180.4 in patients without echocardiographic abnormalities (p < 0.0001). Pericardial effusions was seen in 9 patients. Most of the patients had mild effusions (16.66%). Mean CD4 count with pericardial effusion was 74 + 93.38 (n = 9) and mean CD4 count without pericardial effusion was 227.8 + 219.59. P < 0.0001.

In our study of 100 cases 3 patients showed valvular regurgitations (5.55%). 2 cases found in <50 micro/l CD4 range group (7.40%). In our study of 100 patients diastolic dysfunction was present in 9.25% of the total i.e. 5 cases. 3 patients of diastolic dysfunction found in <50 micro/l CD4 range group (11.11%).

**Table 4:** Association Of Echocardiographic Findings With CD4Count.

Cardiac manifestations	CD4 in Micro L				Total
	<50	50-199	200-499	>500	
Reduced ejection fraction (<50%)	9	4	1	0	14
Fractional shortening (<30%)	10	9	4	2	25
Pericardial effusions	6	2	1	0	9
PAH	2	3	1	0	6
Dilated cardiomyopathy	4	1	0	0	5
Alular regurgitations	2	1	0	0	3
RWMA	1	0	0	0	1
Diastolic dysfunction	3	1	1	0	5

**Table 5:** Association of 2D Echocardiographic Findings With Who Clinical Staging

Cardiac manifestations in 2D Echocardiography	Clinical staging of HIV infection			
	I	II	III	IV
Reduced ejection fraction (<50%)	0	0	4	10
Fractional shortening (<30%)	1	3	7	14
Pericardial effusions	0	0	2	7
PAH	0	1	1	4
Dilated cardiomyopathy	0	0	0	5
Valvular regurgitations	0	0	0	3
RWMA	0	0	0	1
Diastolic dysfunction	1	0	1	3

## DISCUSSION

One hundred consecutive patients with HIV infection hospitalized to the inpatients ward of the department of medicine were included in the current study. Average age in our study was 41.3 years and a similar study by Guha et al also had the average age of 33.24 years [12] Majority of the patients, 75% males and 25% females and similar study by Chengat et al on 284 patients had 63.1% males and 36.9% females [13] while maximum cases were in the age group of 31-40 years of age and male to female ratio was 3:1. In a study carried by Shrinivas et al (2006) most of the patients belonged to young age between 26 to 40 years and male to female ratio was 4:1. [14] It was in concordance with NACO annual report 2009 – 2010. [10] The NACO report has shown that most PLHA in India were young adults. Men were more affected than females by a ratio of 2:1. 45 patients (64.3%) were males and 25 patients (35.7%) were females. The gender difference was also at par with NACO report, where 39% of the total HIV patients in India were females, 57.5% were males. [15] Sexual contact was the most common mode of transmission (94%) with heterosexuality being the cause for 92%. The homosexual route of transmission was 2.8% while infected blood transfusion was responsible for 2.8% of cases in our study. Globally, sexual contact is the commonest mode of transmission. [8] In the west, 75% of newly affected males are due to homosexuality, 14% consequent to heterosexual contact, 8% due to injection drug use and a meager 3% due to other

modes of transmission. [8] The socio-cultural picture in India is different from the West and therefore homosexual mode of transmission was less in this study as compared to the West. [8] However, our data is comparable with NACO annual report 2009-2010. [10] where heterosexual route of transmission was 87%. This confirms that there is a visible difference in the type of sexual contact responsible for causing HIV infection in different population. Clinical features such as fever 74.3%, cough 30%, breathlessness 28.6% respectively was similar to as reported in other studies from India. [16] However, most of the symptoms were non-specific and could be attributable to secondary pulmonary infections. 16 CD4 count was less than 50/micro L in 27.3% of cases while 34.6% of cases had CD4 count in between 50 - 199/microL. Thus most of the cases studied had CD4 count less than 50/microL and categorized under WHO revised clinical stage 4 (41.2%) and clinical stage 3 (35.6%) respectively. The reason behind low CD4 count is that, the patients studied were hospitalized case as they had presented in advanced stage of the disease. Echocardiographic abnormalities are summarized in Table 2. The study showed that echocardiographic abnormalities were common in HIV infected patients. Echocardiographic abnormalities were seen in 54.3% of cases in the present study while it was 42.3% in studies done by other workers from India. [10] In Mirri et al study, prevalence of echocardiographic abnormalities was 17%. [17] Commonest manifestation found in our study was



reduction in FS. (46.29%) This was consistent with studies done in Europe by Corallo et al<sup>[7]</sup> as well as from India by Aggarwal et al<sup>[10]</sup> Reduction in EF was seen in 14.2% of cases in the present study. In a study done by Twagirumukiza et al, 17% had low LVEF.<sup>[18]</sup> Reduction in ejection fraction without global hypokinesia or chamber enlargement but without any symptom probably represented a mild form of cardiac disease that will progress to a clinically evident form of dilated cardiomyopathy.<sup>[7]</sup> Dilated cardiomyopathy was seen in 9.25% of the cases whereas studies published by Moreno et al<sup>[19]</sup> and Hakim et al<sup>[20]</sup> had detected 6% and 5% respectively. Pulmonary artery hypertension was noted in 6 cases (11.1%) which was higher than normal population and comparable to studies done by Pellicelli et al<sup>[21]</sup> and Mehta et al<sup>[22]</sup> who also found higher incidence of pulmonary artery hypertension in HIV patients than normal population. According to Quezada et al, PAH was diagnosed in 9.9% patients.<sup>[23]</sup> Diastolic dysfunction was seen in 9.25% of total positive echocardiographic findings of this study which was consistent with the study done by Hakim et al<sup>[20]</sup>. In study by Padhiyar et al, 26.4% of their patients had Diastolic Dysfunction(DD).<sup>[24]</sup> According to a study by Reinsch et al the prevalence of Diastolic Dysfunction in HIV infected patients was 48%.<sup>[25]</sup> In a study by Chang et al LV systolic and Diastolic dysfunctions were positively correlated with decreased CD4 count.<sup>[26]</sup> One patient in this study with CD4 counts of 13 and on anti-retro-viral therapy for two years had RWMA in apical and anterior wall. The marked absence of endocardial involvement in this study may be related to the low prevalence of intravenous drug abusers.<sup>[27]</sup> Padhiyar et al showed 23.2% of their patients had Regional Wall Motion Abnormality (RWMA).<sup>[24]</sup> In our study 3 cases of valvular regurgitations were found

(5.55%) The incidence of valvular regurgitations observed in the present study was similar to that noted as in general population suggests that it was a chance finding.<sup>[27]</sup> Pericardial effusion was seen in 16.6% of cases which is at par with Indian studies done by Aggarwal et al (11.5%) and studies done at United States by Himelman et al<sup>[10, 28]</sup>. The pericardial effusion detected was often small in amount and without any hemodynamic significance. Pericardial effusion in HIV patients may be marker of end stage HIV infection because it is associated with low CD4 count. Table 4 depicts the association of echocardiographic abnormalities with WHO revised clinical staging. Most of the echocardiographic abnormalities were seen in WHO clinical stage 4 which at par with studies done by Khunnawat et al<sup>[29]</sup> and Lipshultz et al<sup>[30]</sup> who have shown that cardiac manifestations occur late in the course of the disease. Previous studies have shown that HIV related cardiac manifestations are often seen in a state of severe immunosuppression with low CD4 Count (CD4 < 200/microL).<sup>[27, 31, 32]</sup> This study (Table 4) showed that patients with CD4 count less than 200/microL had a high prevalence of echocardiographic abnormalities than those with CD4 count more than 200/microL. As illustrated in Figures 1(a) and (b), CD4 count had a significant positive correlation with reduction in EF and FS ( $p < 0.001$  and  $p < 0.002$ , respectively). Various studies agree that the most important factor in development of cardiac abnormalities is the level of immunosuppression and there is tight correlation between CD4 count and echocardiographic abnormalities, which is also demonstrated in the present study.<sup>[10, 25, 31]</sup> As shown in Table 6, statistically significant correlation was seen between echocardiographic abnormalities and CD4 count ( $p < 0.0001$ ).

**Table 6:** Mean pattern of study parameters with cardiac dysfunction and their correlation.

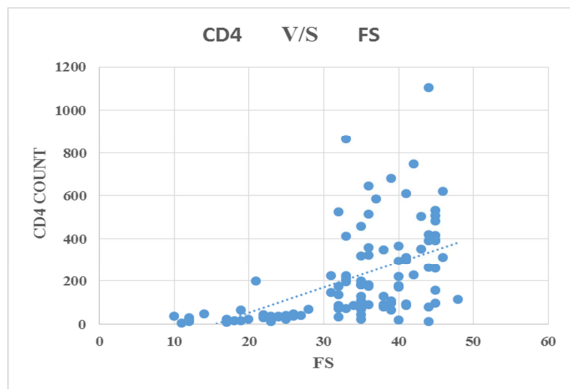
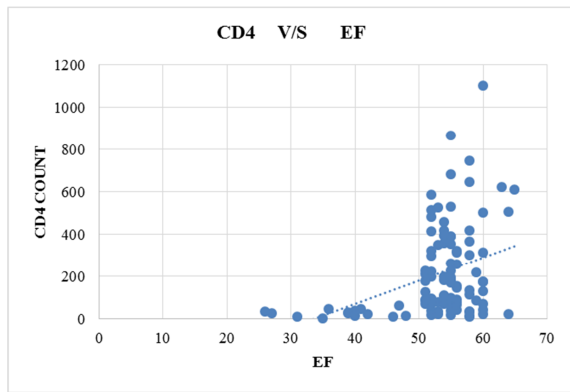
Parameter	Group with echo findings Mean $\pm$ SD (n=54)	Group without echo findings Mean $\pm$ SD (n=31)	Statistical significance “p” value
Haemoglobin	9.76 $\pm$ 2.005	8.32 $\pm$ 3.102	0.785 (NS)
Total leukocyte count	8452 $\pm$ 2471.1	8129 $\pm$ 2289.7	0.8117 (NS)
CD4 count/micro L	106 $\pm$ 102	352 $\pm$ 142.8	0.03 (S)
CPK-MB IU/ml	46 $\pm$ 12.32	38 $\pm$ 11.68	0.379 (NS)

## CONCLUSION

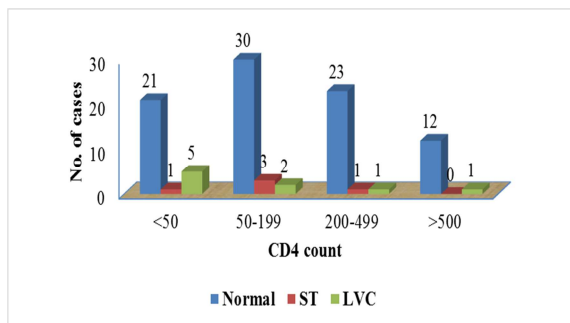
HIV infection in India is more consequent to heterosexual contact than other modes of transmission identified in western population. The results of the study indicate that cardiovascular abnormalities in HIV infected patients are common and can occur without any clinical manifestation. Cardiac involvement is common amongst HIV/AIDS patients with 54.3% of our patients having cardiac involvement. Even asymptomatic patients had positive echocardiographic findings.

Echocardiographic abnormalities are more prevalent in HIV/AIDS patients and their prevalence increases as the CD4 count falls. The most common cardiac manifestations being reduction in EF, FS, pericardial effusions, dilated cardiomyopathy and diastolic dysfunction. The tendency to develop these manifestations increases when CD4 is <200 which further increases as the counts further fall <50. Echocardiography is a useful technique for the early recognition and treatment of cardiac dysfunction in such patients. Thus our aim should be to start ART in these patients as soon as possible so as to improve

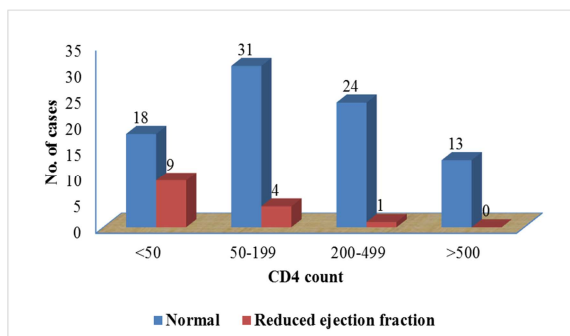
the morbidity and quality of life of people living with HIV/AIDS.



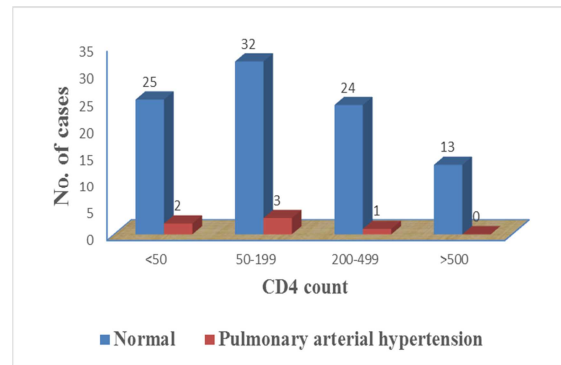
**Figure 1:** (A) and (B) Depicts that CD4 Count/Micro L has significant correlation with ejection fraction (P < 0.005) and fractional shortening (P Value < 0.004).



**Figures 3:** Correlation between abnormal ECG findings and CD4 counts.



**Figures 4:** Correlation between reduced ejection fraction and CD4 counts.



**Figures 5:** Correlation between pulmonary artery hypertension and CD4 counts.

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