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Original Research Article

Study of cardiovascular manifestations in treatment naive HIV patients and patients on HAART and its correlation with CD4+ cell counts in a tertiary care centre

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ABSTRACT

Background: Highly active anti-retroviral therapy (HAART) increases the longevity of the patients infected with Human immunodeficiency virus (HIV) so mortality due to opportunistic infections is reducing and late complications like cardiovascular manifestations are on its rise. Cardiac involvement can be over-looked in HIV positive patients because symptoms of breathlessness, fatigue and poor exercise tolerance are ascribed to other conditions associated with HIV patients.
Objective: Primary objective was to evaluate cardiac manifestations and determine type of cardiac involvement in both HAART naïve patients and patients on HAART and correlate with CD4+ counts.
Methods: 200 HIV infected patients presenting in outpatient department (OPD) and inpatients are included. Information is collected and detailed history is taken using pre-formed proforma. At the time of admission or follow up, steps are taken to send for all the investigations and detailed clinical examination of the patient done, focusing more on cardiovascular system.
Results: 41% of the patients with normal cardiac function were not on HAART and 62.7% of the patients with cardiac dysfunction were HIV naïve and it was found to be statistically significant (p value 0.003). Tricuspid regurgitation (42.1% verus 57.9%, p value 0.035) and Ischemic heart disease (IHD) (0% versus 100% p value 0.049) found to have significant association in patients who were on HAART. Systolic dysfunction (p value 0.048) and IHD (p value 0.019) were both significantly associated with the low CD4+ counts in patients not on HAART.
Conclusion: There was significant association of HAART on the occurrence of cardiac dysfunction. Cardiac dysfunction is noted with low CD4+ counts, it is therefore important to undergo 2-dimensional echocardiography (2-D Echo) at diagnosis and at regular intervals in all HIV infected patients and to initiate early treatment for the same.the rural population.

Keywords: HIV, HAART, Cardiac dysfunction

INTRODUCTION

Human immunodeficiency syndrome (HIV) infection is a major health problem in the entire world including India and globally 36.7 million [34.0-39.8 million] people were living with HIV at the end of 2015.[1]

As per the National AIDS control organization (NACO), India HIV estimation 2015 report, National adult (15-49) years HIV prevalence in India is estimated at 0.26% in 2015 with 0.30% among males and 0.22% among females.

The total number of people living with HIV in India is estimated at 21.17 lakhs (17.11-26.49 lakhs) in 2015.[2]

The prevalence of cardiac involvement in Acquired immune deficiency syndrome (AIDS) patients have been reported to range between 28% and 73%.[3]

Cardiac involvement in AIDS/HIV infected persons may be attributed to virus itself, the effects of anti-retroviral medications; or altered immune mechanisms associated with the infection.[4]

From the beginning of AIDS epidemic, cardiac involvement was recognized at autopsy and later by non-invasive techniques such as electrocardiogram (ECG).

Patients with HIV infection can have variety of cardiovascular manifestations.

The most common are pericarditis, pericardial effusion, pulmonary vascular diseases, myocarditis, cardiomyopathy and increased incidence of coronary artery disease, malignant neoplasm, coronary artery disease and drug related cardio toxicity.[5] The prevalence of heart muscle disease is around 15% and has 3 forms global left ventricular dysfunction, isolated right ventricular dilatation and borderline left ventricular dysfunction.

Dilated cardiomyopathy is an independent adverse prognostic factor. It is strongly associated with very low CD4 cell count.

Present study is undertaken to determine type of cardiac involvement in both HAART naïve patients and patients on HAART and correlate pattern of cardiac involvement with CD4+ counts.

Objectives

Primary objective of the study was to evaluate cardiac manifestations and determine type of cardiac involvement in both HAART naïve patients and patients on HAART and correlate pattern of cardiac involvement with CD4+ counts.

Secondary objective of the study was to evaluate cardiac manifestations in patients having opportunistic infections.

METHODS

Source of data

The study would be conducted in patients with HIV treatment naïve and on HAART admitted in Victoria, Bowring and lady Curzon hospitals which are attached to Bangalore Medical Collage and Research Institution during the study period of January 2018 to April 2019.

Methods of collection of data (including sampling procedure, if any)

Study design

The present study design was cross sectional.

Study period

The study was conducted from January 2018 to April 2019.

Study site

The study was conducted at Victoria Hospital and Bowring and Lady Curzon Hospital, Bangalore Medical Collage and Research Institution, Bangalore.

Sample size

The sample size of the study was 200 HIV infected patients both on HAART and naive patients.

Inclusion criteria

The inclusion criteria was as follows: patients diagnosed to have HIV infection/AIDS after Enzyme linked immune sorbent essay (ELISA) test being positive.

Exclusion criteria

The exclusion criteria was as follows: congenital heart diseases, pre-existing valvular heart disease, hypertension and diabetes mellitus.

Investigation

Investigations required were as follows: routine investigations, blood HIV 1 and 2 (ELISA), CD4, CD8 count, ECG, chest X-ray, echocardiography.

Sample procedure

200 HIV infected patients presenting in outpatient department and as inpatients are included in this study. Information is collected and detailed history is taken using preformed proforma. At the time of admission or follow up, treatment for specific opportunistic infection is initiated and steps are taken to send for all the investigations and detailed clinical examination of the patient is done, focusing more on cardiovascular system.

As cardiovascular manifestations can be symptomatic or asymptomatic cardiovascular work up is done in all patients. Cardiac manifestations are determined based on clinical, radiological, ECG and echocardiographic criteria later to correlate the observed study with CD4+ cell counts and whether the patients are on HAART or not.

Statistical methods

Student t test was used to match the HIV positive patients on HAART and not on HAART on the basis of age and sex. Chi-square and fisher exact test have been used to test the association of cardiac dysfunction in relation to HAART and categories of CD4+ count. Mann Whitney U, Student t test were used to compare the median CD4+ counts and duration of disease among those with cardiac dysfunction and normal heart.

RESULTS

A cross sectional study including 200 ELISA positive HIV infected individuals was taken for a period of two years. Following results and observations were made during the study.

Table 1: Age distribution of patients studied.

Age in years	Group I	Group II	Total
	N (%)	N (%)	N (%)
<20	0 (0)	2 (2)	2 (1)
20-30	6 (6)	9 (9)	15 (7.5)
31-40	35 (35)	38 (38)	73 (36.5)
41-50	43 (43)	38 (38)	81 (40.5)
>50	16 (16)	13 (13)	29 (29)
Total	100 (100)	100 (100)	200 (100)
Mean ±SD	43.08±7.61	42.01±10.05	42.55±8.91

Group I was HIV naïve patients i.e., patients not on HAART and Group II patients were not on HAART.

43% of the patients in Group I is in the age group of 41-50 years, and 38% in the age group of 31-50 years in group II. On comparing the proportions across the two groups using student t test, it was found the 2 groups were matched by age as the differences were not statistically significant.

Table 2: Gender distribution of patients studied.

Gender	Group I	Group II	Total
	N (%)	N (%)	N (%)
Female	24 (24)	22 (22)	46 (23)
Male	76 (76)	78 (78)	154 (77)
Total	100 (100)	100 (100)	200 (100)

Most of our patients are males in both Group I and Group II, 76% and 78% respectively. No significant difference was noted in the gender distribution.

56% of the patients in Group II had HIV duration between 1-5 years and most of the patients in Group I are newly diagnosed (62%) and few patients (23%) had disease duration between 1-5 years but who were lost to follow up or not on medications.

Among 69 patients with normal cardiac function 62 (89.8%) were on first line Anti-retroviral therapy (ART) and among 31 patients with cardiac dysfunction 26 (83%) were on first line and 5 (16.1%) were on second line ART.

Table 3: Duration of HIV distribution in two groups of patients studied.

Disease duration	Group I	Group II	Total
	N (%)	N (%)	N (%)
<6 months	9 (9)	5 (5)	14 (7)
6-12 months	4 (4)	4 (4)	8 (4)
1-5 years	23 (23)	56 (56)	79 (39.5)
6-10 years	2 (2)	26 (26)	28 (14)
>10 years	0 (0)	7 (7)	7 (3.5)
Newly diagnosed RVD	62 (62)	2(2)	64 (32)
Total	100 (100)	100 (100)	200 (100)

Table 4: Type of ART distribution.

Type of ART	Normal cardiac function	Cardiac dysfunction	Total	P value
First line	62 (89.8)	26 (83)	88	0.507
Second line	7 (10.1)	5 (16.1)	12	
Total	69	31	100	

Table 5: WHO Stage distribution in two groups of patients studied.

WHO stage	Group I	Group II	Total
	N (%)	N (%)	N (%)
I	7 (7)	11 (11)	16 (8)
II	38 (38)	45 (45)	83 (41.5)
III	39 (39)	30 (30)	69 (34.5)
IV	16 (16)	14 (14)	30 (15)
Total	100 (100)	100 (100)	200 (100)

41.5% of patients were in WHO stage II of which 45% were in Group II. 39% of the patients belonged to stage III.

The maximum proportion of patients were in the CD4+ category 51-200 which had 64% and 54% in Group I (not on HAART) and II (on HAART) respectively.

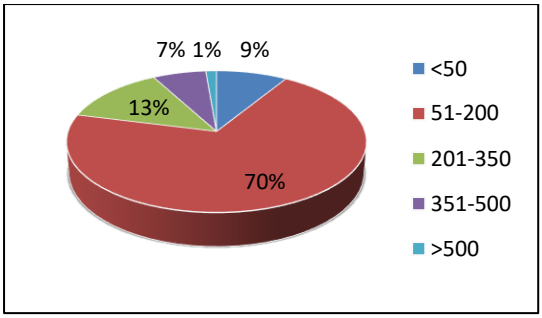

Figure 1A: CD4+ count distribution in 'not on HAART' group.

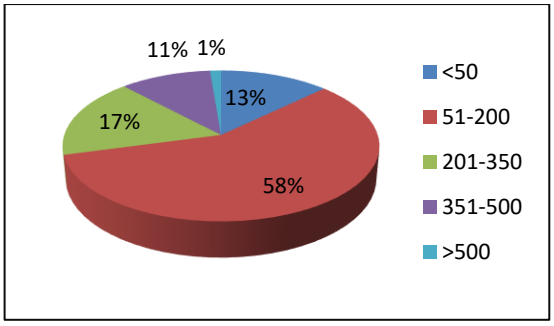

Figure 1B: CD4+ count distribution in 'on HAART' group.

Table 6: CD4+ counts distribution in normal and cardiac dysfunction.

Attribute	Cardiac function				P value
	Normal		Cardiac dysfunction		
	Median	Interquartile range	Median	Interquartile range	
CD4+ counts	123.	77-236	102	78-278	0.776
Duration of disease	1.00	0-4	0.67	0-3	0.140

Table 7: Lipid profile comparison in two groups of patients studied.

Lipid profile	Group I	Group II	Total	P value
Total cholesterol	102.84±18.07	126.55±45.21	114.70±36.34	<0.001**
LDL	79.93±21.02	79.63±36.36	79.78±29.62	0.943
VLDL	46.99±24.62	36.92±21.51	41.96±23.61	0.002**
TG	87.07±21.86	121.85±77.02	104.46±59.1	<0.001**
HDL	22.10±5.31	27.66±10.40	24.88±8.70	<0.001**

Table 8: ECG distribution in two groups of patients studied.

ECG	Group I (n=100)	Group (n=100)	Total
	N (%)	N (%)	N (%)
Normal	80 (80)	78 (78)	158 (79)
Abnormal	20 (20)	22 (22)	42 (21)
Sinus tachycardia	8 (8)	10 (10)	18 (9)
Low voltage complexes	5 (5)	0 (0)	5 (2.5)
IHD	1 (1)	3 (3)	4 (2)
LVH	3 (3)	0 (0)	3 (1.5)
RBBB	1 (1)	2 (2)	3 (1.5)

CD4+ counts in patients with normal cardiac function had median value of 123 (77-236) and those who had cardiac dysfunction had median value of 102 (78-278) but this difference was not found to be statistically significant.

We found a statistically significant association between the two groups with total cholesterol, very low-density lipoprotein (VLDL), Triglycerides (TGL) and high-density lipoprotein (HDL).

Majority of our patients had normal ECG (79%), abnormal ECG was found slightly high in Group II patients where the common being sinus tachycardia (10%).

44 patients (37.6%) had normal cardiac function who belonged to WHO stage II and 39 patients (47%) had cardiac dysfunction under the same stage but no significant difference was found in the distribution. 62.7% of the patients with cardiac dysfunction were HIV naive and

37.3% were on HAART. And statistically significant difference observed between 2 groups (p<0.003).

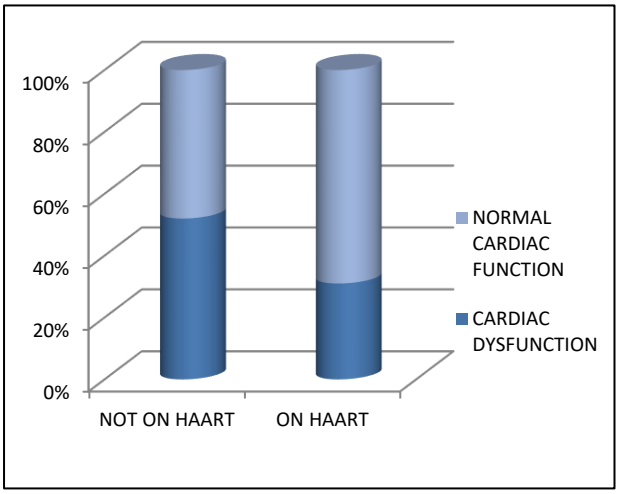

Figure 2 A: HIV naïve and on HAART and not on HAART patients association between normal and cardiac dysfunction.

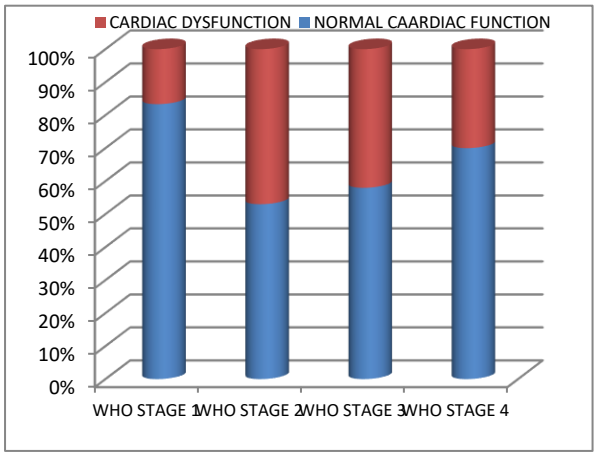

Figure 2B: WHO Staging and on HAART patients association between normal and cardiac dysfunction.

21 out of 52 patients who were not on HAART and 8 out of 31 who were on HAART had pericardial effusion, but no significance was elicited (p value 0.17). But 8 patients who were not on HAART and 11 patients on HAART had TR and also it implies that HAART was significantly associated with the occurrence of TR (p value 0.03). Similarly, out of 3 patients who were on HAART had Ischemic heart disease (IHD) and it appeared to have significantly associated with HAART (p value 0.04).

Considering the whole data of 200 patients, cardiac dysfunction was more commonly found in the CD4+ count category of 51-200 except IHD. Systolic dysfunction (p value 0.048) and IHD (p value 0.019) were both significantly associated with the low CD4+ counts.

IHD is absent in all these categories.

Among the patients who were not on HAART, 85.71% of patients who had pericardial effusion had CD4+ counts till 200. This difference in distribution could have been possibly significant if a larger sample size was chosen. However, 66.67% of patients who had systolic dysfunction had CD4+ count of 200 or less and this association of CD4+ category with SD type of cardiac dysfunction was found to be significant (p=0.003).

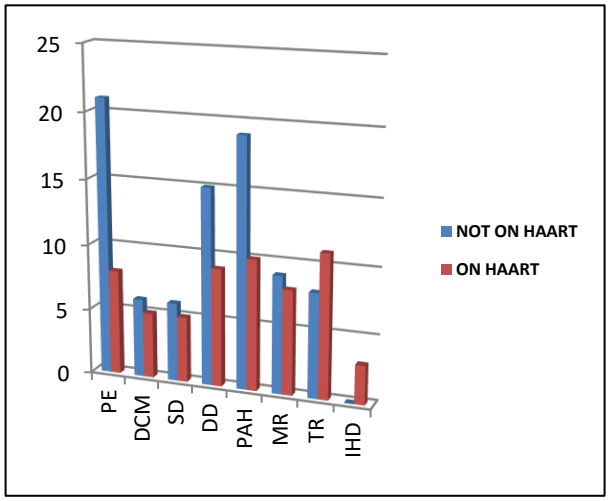

Figure 3: Correlation of patients not on HAART and on HAART with cardiac dysfunction.

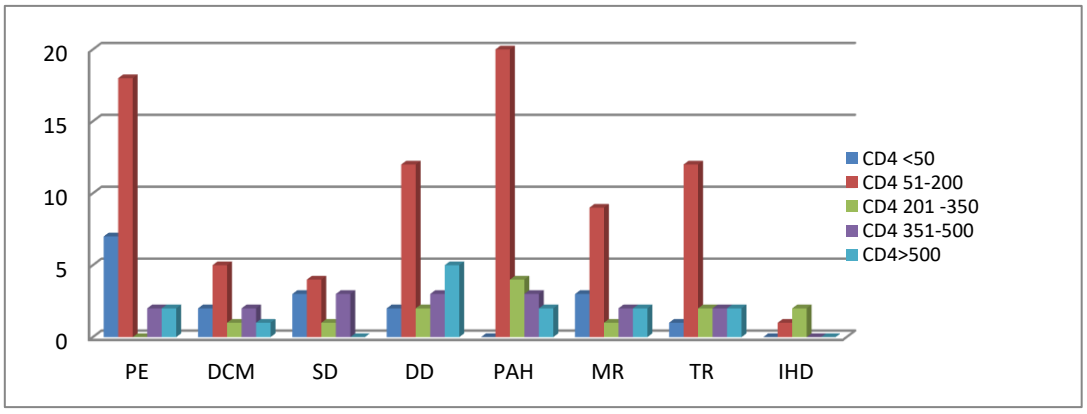

Figure 4: Correlation of CD4+ counts with cardiac dysfunction.

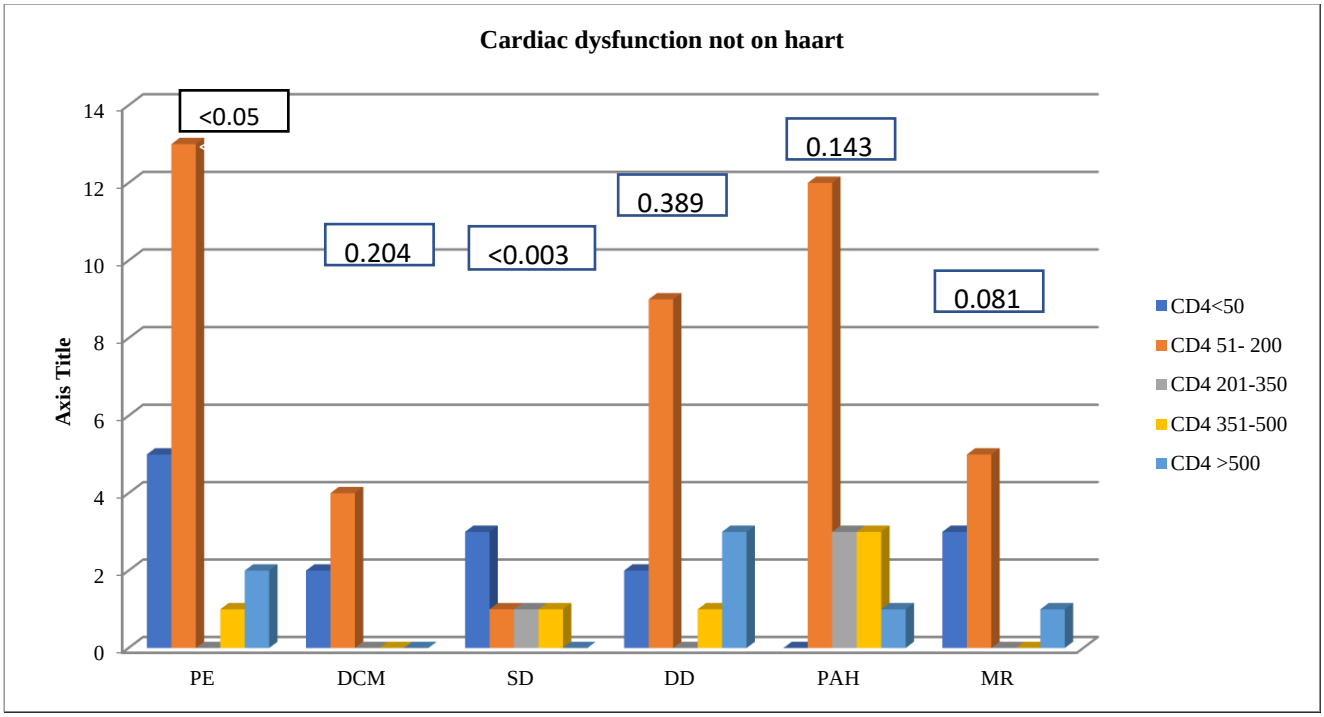

Figure 5: Correlation of CD4+ counts with cardiac dysfunction in patients not on HAART.

Though other types of cardiac dysfunction also showed that proportion of patients with lesser CD4+ counts had more cardiac dysfunction, it was not statistically significant.

DISCUSSION

HIV infection has become a chronic and manageable disease. Patients with HIV infection share many cardiovascular risk factors with the general population, but in addition the HIV virus itself, chronic inflammation, opportunistic infections and exposure to ART may increase the cardiovascular risk. Cardiac dysfunction is clinically quiescent in the early stages and later it may become direct cause of death.

The present study was carried out at Victoria Hospital and Bowring and Lady Curzon Hospitals attached to Bangalore Medical College to study the cardiovascular manifestations in treatment naïve HIV patients and on treatment (HAART) and its correlation with CD4+ counts.

200 patients were considered for the study where 100 patients were not on HAART (treatment naïve; Group I) and 100 were on HAART (Group II). Mean age group in Group I was 43.08±7.61 years and 42.01±10.05 years in Group II. Most of our patients were males in both the group I and II (76% and 78% respectively) male to female ratio was around 3:1 in both the Groups. Maximum cases were in the age group of 31-50 in both the Groups. In a study by Mehul Merwadi et al., maximum cases were in the age group of 31-40 years of age and male to female ratio was 3:1.[6]

Commonest symptoms noted in our study were easy fatiguability (53%), weight loss (41.5%) followed by breathlessness (29.5%), cough (28%) and fever (27.5%), but in the study done by Basavaraj et al, noticed commonest symptoms in their study as fever (82.5%), cough (67.5%) and breathlessness (45%).[7]

64% of patients in Group I and 54% of patients in Group II had CD4+ counts in the category 51-200 /cumm which is similar to study done by P. Shravan Kumar et al., where maximum no. of patients had CD4+ count below 200 /cumm though no categorization was done below 50 /cumm.[8]

Maximum number of patients were in WHO stage III in Group I and Stage II in Group II.

Table 9: Percentage of patients having cardiac dysfunction in different studies.

Studies	Cardiac dysfunction (%)
Present study	41.5
Marwadi et al[6]	49
Kumar et al[4]	58.3
Singh et al[9]	55.7

Cardiovascular dysfunction in HIV

Cardiac dysfunction was present in 62.7% in patients who are treatment naïve (Group I) and 37.3% were on HAART (Group II). Total 83 (41.5%) patients of 200 having

patients both not on HAART and on HAART had cardiac dysfunction.

ECG manifestation in HIV infected individuals

In the present study sinus tachycardia was the most common ECG manifestation which also was more commonly found in the other studies mentioned.

Table 10: Different ECG findings in different studies.

Studies	Sinus tachycardia (%)	Low voltage complexes (%)	IHD (%)	LVH (%)
Present study	9	2.5	2	1.5
Marwadi et al[6]	24	6	0	8
Kumar et al[8]	16	0.5	3	0.5
Kumar et al[4]	1.7	0	1.5	0.3

Table 11: Different X ray findings in different studies.

X-ray findings	Present study	Mehul Marwadi et al[6]
Cardiomegaly	6%	8%
Right pleural effusion	7%	6%
B/L reticulonodular pattern	4.5%	12%

X ray abnormalities in HIV infected individuals

Right pleural effusion was found in 7% of cases followed by cardiomegaly found in 6% of cases but these results, were not similar to other study.

2D-Echo abnormalities in HIV infected patients

Most common 2D-Echo abnormality found in the present study was pericardial effusion (34.9%) and pulmonary artery hypertension (34.9%) followed by diastolic dysfunction (28.9%).

All the above studies showed cardiac manifestations in patients with HIV but did not specify whether patients were on HAART or not on HAART.

In our study, out of 29 (14.5%) patients having pericardial effusion 21 (72.4%) were not on HAART and 8 (27.6%) were on HAART but no significant association was found. In a study by Lind A et al only 0.25% had pericardial effusion who were on HAART.[10]

We did not find any significant association of HAART with dilated Cardiomyopathy in our study. However, one study by Domanski MJ et al stated that cardiomyopathy would develop was 8.4 times greater in children who had previously used Azidothymidine (AZT) than in those who had never taken AZT.[11]

We found that IHD and TR was more common in patients who were on HAART than not on HAART (p value 0.049), further studies are warranted to know the causal association of ART and Myocardial infarction (MI).

All the 3 patients who had IHD were on (tenofovir + lamivudine + efavirenz) TLE regimen. This result is consistent with a study done by Jens et al., where they've found that the incidence of MI increased with increasing exposure to combination antiretroviral therapy ($p<0.001$).

When we tested for association of CD4+ counts with the type of cardiac dysfunction, all showed increased prevalence with decrease in CD4+ counts but only Systolic dysfunction ($p=0.048$) and IHD ($p=0.019$) showed statistical significance. Ayaskantha Singh et al found 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.[9] CD4 count had a significant positive correlation with reduction in Ejection fraction (EF) and Fractional shortening ($p<0.001$ and $p<0.002$, respectively).

Left ventricular concentric hypertrophy had an inverse relation with CD4+ count and it was statistically significant in a study by Kumar SKK et al.[4]

Lower CD4+ counts had a higher prevalence of cardiac dysfunction and this association was found to be statistically significant for systolic dysfunction. Pericardial effusion correlation could be significant in a larger sample size.

There was no significance in the group of patients on HAART with the CD4+ counts. In a study by, Bijl M et al 96 patients out of 105 were on ART and 3 of them had Systolic dysfunction with low CD4+ counts. No previous studies have showed groups which have seen the pattern of CD4+ counts and cardiac dysfunction stratifying equally based on HAART and not on HAART.

In the present study, larger proportion of patients with cardiac dysfunction belonged to WHO stage II and III but no significant association was derived, even in subgroup analysis of Group I and Group II, patients did not show any significant association with cardiac dysfunction and WHO stages. In study by Ayaskantha Singh et al patients belonged to WHO stage IV more commonly compared to other stages.

Table 12: Echo abnormalities observed in HIV infected patients.

Echo abnormalities	Present study (%)	Singh et al[9] (%)	Kumar et al[4] (%)	Kumar et al[8] (%)
Pericardial effusion	14.5	17.4	13.3	12
Dilated cardiomyopathy	5.5	8.5	15	5.5
Systolic dysfunction	5.5	22.8	-	9
Diastolic dysfunction	12	8.4	25	33
Pulmonary hypertension	14.5	11.42	10	8
Mitral regurgitation	8.5	10	-	3.5
Tricuspid regurgitation	9.5	-	-	-
Ischemic heart disease	1.5	1.4	-	-

Strength of our study

There are very few studies which have divided the sample size equally into those who are treatment naïve and on HAART. We have correlated the cardiac dysfunction with WHO clinical staging.

Limitations

As the sample size was small, cardiac dysfunction like pericardial effusion did not show statistical significance. Due to resource limitations further evaluation of IHD patients could not be done.

CONCLUSION

There was significant association of HAART on the occurrence of cardiac dysfunction i.e, being on HAART or not on HAART has significant association with cardiac dysfunction. 2D-Echo is an important diagnostic tool for the evaluation of cardiac dysfunction in these patients. Cardiac dysfunction is noted with low CD4+ counts and was found to be statistically significant. Pericardial effusion, diastolic dysfunction, pulmonary arterial hypertension and dilated cardiomyopathy was frequently found in groups not on HAART but was not statistically significant. It is therefore important to undergo 2D-Echo at diagnosis and at regular intervals in all HIV infected patients including both on HAART and not HAART.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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