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Left ventricular dysfunction in patients with HIV/AIDS on HAART in correlation with CD4 count

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ABSTRACT

Background: According to World Health Organization (WHO) global HIV report 2019, people living with HIV is about 38 million. Especially after the advent of antiretroviral therapy (ART), in PLHIV, cardiovascular complications signify an increasingly important health concern. This vastly active HAART regimen has provided more efficient prophylactic treatment. With the increased duration of survival, this has progressed to an increased episodes of cardiovascular complications associated with PLHA.
Aim of the study: The following review overviews the left ventricular dysfunction in patients with HIV infection on HAART focusing on early diagnosis, therapy and prognosis.
Materials and Methods: It is a Cross sectional study conducted on HIV infected patients attending ART clinic and admitted in medicine wards of MKCG medical college & Hospital from MARCH 2017 to OCTOBER 2018 were included in the study.
Results: Maximum patients were in the age group 25 – 49 years (68.44%) in our study. Mean age of the study group 41.32 + 11.24 years. Gender distribution shows that 82.46% of the patients were males and 14.04% were females. 4 (7%) patients have cardiac disorder. All the patients having cardiac disorders are male. Only 2 patients (3.5%) had left ventricular dysfunction with reduced ejection fraction.
Conclusions: Males are involved more than females. Most patients are in the middle age group between 25 – 49 years. Heterosexual mode was the most common mode of transmission. Most of the study population belonged to rural area 61.4%. Three patients (5.3%) were on anti tubercular drugs. The systolic LV dysfunction was found in 50% of PLHA patients with cardiac disorders. CD4 count was positively correlated with fractional shortening. Presence of cardiac dysfunction was significantly associated with the adherence to ART treatment.

1. Introduction

Universally, HIV infection is an important health issue. According to World Health Organization (WHO) global HIV report 2019,people living with HIV (PLHIV) is about 38 million. New HIV infection is around 1.7 million and AIDS-related deaths are about 690,000 in 2019.[1] As per National AIDS Control Organization (NACO) India HIV Estimation 2019 report, the total number of patients infected with HIV in India is estimated at 23.49 lakh. 0.69 lakh new HIV infections were estimated in the same year; 190 new infections every day and eight new infections every hour. In the year 2019, 0.59 lakh people death due to AIDS-related complications nationally was estimated.[2] Nationally, the prevalence of HIV among adults (15–49 years) in India is estimated at 0.22% (with range 0.17–0.29%) in 2019.[2] HIV prevalence among adult males and females were estimated at 0.24% (0.18–0.32%) and 0.20% (0.15– 0.26%)

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respectively, in the same year.[2]

Especially after the advent of antiretroviral therapy (ART), in PLHIV, cardiovascular complications signify an increasingly important health concern. According to Boccara et al,[3] the number of PLHIV is ascending resultant to the initiation of highly active antiretroviral agents (HAART). This has reduced morbidity and mortality to a great extent associated with HIV infection. This vastly active HAART regimen has provided more efficient prophylactic treatment which allowed these HIV infected individuals on HAART to live longer. With the increased duration of survival, this has progressed to an increased episodes of cardiovascular complications associated with PLHA, which were frequently undiagnosed in the initial period of the epidemic.[4]

Milei et. al. study revealed that some cardiac problems were found in about half of the HIV population.[5] Among HIV infected population, the incidence of cardiac abnormalities varies in the range from 25%-75%.[6] Dilated cardiomyopathy (DCM) with left ventricular (LV) dysfunction (reduced ejection fraction), pericarditis, pericardial effusion /tamponade, myocarditis, endocarditis, pulmonary hypertension (PAH), coronary artery disease (CAD), cardiac autonomic dysfunction, and a few uncommon neoplasms are included in the cardiovascular lesions reported in patients with HIV infection.[7]

HIV itself can cause direct toxicity to the heart. Other than this, immune-mediated predominantly cytokines, nutritional deficiencies, and HAART are few probable mechanisms of cardiac abnormalities in AIDS.[8]

Globally, pericarditis is one of the most frequent cardiac complications in HIV.[9] HIV-HEART study which included 802 outpatients infected with HIV, 85% PLHIV were receiving conventional ART; pericardial effusion was only present in 0.25% of the patients.[10]

HIV-1 is identified to be one of the foremost causes of DCM associated with biventricular dilatation.[11] In the pre-ART era, the incidence of HIV-associated dilated cardiomyopathy (HIV-DCM) is estimated to be nearly 16/1000 per annum.[12] As per the data available from the clinical and autopsy studies, the prevalence of HIV-DCM is found within a wide range from about 4% to as high as 75% in different reports.[12,13] In chronic HIV infection, the incidence of cardiomyopathy declines along with HIV-related mortality in patients infected with HIV; which shows the benefit from initiation of ART.[14] HIV-DCM is considered WHO Clinical Stage IV (AIDS). When compared with HIV-negative controls with idiopathic DCM, it is associated with a poor prognosis with an adjusted mortality hazard ratio of 4.0.[15,16] Subsequent to the larger use of HAART for prophylactic treatment among PLHIV; the prevalence of cardiomyopathy has been decreased by 30% in developed countries.[8,17]

Infective endocarditis (IE) is accounted for about 5-20% of hospitalized patients and about 5-10% of total deaths in HIV-infected intravenous drug abusers.[18] Subsequent to the introduction of HAART; the incidence of non-bacterial infective endocarditis has also reduced to a large extent.[8]

About 6–15% of all deaths are accounted for CAD in HIV-infected patients.[19] A study by Boccara et al. revealed that HIV-infected patients, above all those on HAART (predominantly protease inhibitors) have an augmented tendency for acute myocardial infarction (AMI) as compared to the general residents.This is attributable to increased predisposition toward metabolic syndrome ensuing from hyperlipidemia and atherosclerotic heart disease.[3]

The incidence of heart failure in PLHIV receiving ART is often about 4:1 ratio with the general populace.[20] Preceding articles have produced that CD4 T-cells also have effects on myocardial healing and remodeling,[21] and there is an association between low baseline CD4 T-cell counts and deterioration of heart failure.[22]

As per NACO India HIV Estimation 2019 report, a total of 49.15 thousand persons was detected with HIV positive in Odisha, out of which 21.5 thousand (43.74%) were women.[2] 2.17 thousand new HIV-positive patients (38.33% decline as compared to 2010) were detected with 1.74 thousand AIDS-related deaths (32.73% decline as compared to 2010). Adult (15–49 years) HIV prevalence in Odisha is estimated at 0.14% in 2019.[2] According to the report by Odisha State AIDS Control Society (2016-17), Ganjam is the most prevalent district.[23]

2. Aim of the study

The following review overviews the left ventricular dysfunction in patients with HIV infection on HAART focusing on early diagnosis, therapy, and prognosis.

3. Materials and Methods

It is a Cross-sectional study conducted after getting the ethical committee clearance from the institute. Fifty-seven HIV-infected patients attending ART clinic and admitted in medicine wards of MKCG medical college & Hospital from MARCH 2017 to OCTOBER 2018 were included in the study.

3.1. Inclusion criteria

All patients with HIV infection/ AIDS are diagnosed after three rapid kit tests supplied by the NACO to the microbiology department. The three rapid kit test supplied included:

1. COMBAIDS test
2. PAREEKSHAK HIV $\frac{1}{2}$ Trilene card test
3. HIV $\frac{1}{2}$ Trispot test

3.2. Exclusion criteria

Patients having

1. Pre-existing valvular heart disease
2. Congenital heart disease
3. Systemic Hypertension
4. Chronic kidney failure
5. Diabetes mellitus

3.3. Data collection

After obtaining informed consent from the patients, they were assessed clinically by relevant history, general and systemic examination with special emphasis on the cardiovascular and respiratory system and specific investigations were undertaken to ascertain diagnosis and screening of opportunistic infections. CD4 count was measured by BD FACS CALIBUR automated machine using flow cytometry.

All the patients underwent Two-dimensional transthoracic echocardiographic images, including M mode. With the person in the left lateral decubitus position, cross-sectional and pulsed wave Doppler images were obtained. The echocardiographic examinations were performed by an experienced cardiologist in the department of cardiology using Philips machine HD7XE with 3.0 and 3.5 MHz transducers.

The following variables were calculated: left ventricular dimensions in end-diastole (LVEDd) and end-systole (LVESd), inter ventricular septum and left ventricular posterior wall thickness in diastole, left ventricular ejection fraction, early peak velocity (E wave), and late peak velocity (A wave).

The recommended calculations are as follows:

1. Fractional shortening (FS) (%) = (LVEDd – LVESd) × 100/ LVEDd
2. The normal range of FS is 28–41%, with a mean of 33 ± 5%.
3. Fractional area change (FAC)
4. Ejection fraction, EF (%) = stroke volume × 100/ LVEDd
5. Stroke volume (SV) = LVEDV – LVESV.

Left ventricular end-diastolic volume (LVEDV) = LVEDd

Left ventricular end-systolic volume (LVESV) = LVESd

EF was usually calculated by using the existing software in the equipment using the Teichholz formula.

Depressed LV systolic function is a fractional shortening of ≤ 28% or ejection fraction of less than 50% with normal left ventricular dimensions.

Dilated cardiomyopathy was diagnosed using three criteria: LVEDd > 60mm, with EF < 45%, and global hypokinesia.

The four recommended variables with their abnormal cut-off values; annular e velocity (lateral e < 10 cm/sec, septal e < 7 cm/sec), average E/ e ratio > 14, peak TR velocity > 2.8 m/sec, and LA volume index > 34 mL/m2; are used for identifying diastolic dysfunction. LV diastolic dysfunction is established if more than half of the obtainable parameters meet these cut-off values.

3.4. Data analysis

Data collected tested statistically. All the results coded in MS Excel and analyzed with SPSS version 21.0 Software. Description of demographic characteristics of the study population was made using Univariate analysis. Discrete variables were accessed as frequency and percentages. Continuous variables were presented as means and standard deviation (SD) for unpaired data; a Student t-test was used to compare mean values (for two groups). Pearson's correlation was used to find out the association between eGFR and other variables. Chisquare test with Yate's correction was used to determine the significant associations between categorical variables. A $p < 0.05$ was considered as statistically significant and $p < 0.001$ was considered as statistically extremely significant for all tests conducted.

4. Results

Maximum patients were in the age group of 25 – 49 years (68.44%) in our study with 7.0% of the patients in the age group of 15-24 years and 24.56% of the patients above 50 years age group as shown in figure-1. The mean age of the study group was 41.32 + 11.24 years with an age range of 20 and 65 years.

Gender distribution shows that 82.46% (47) of the patients were males and 14.04% (8) were females. 3.5% (2) included the transgender population as shown in Figure 1.

61.4% (35) of patients studied belonged to the rural areas, whereas 38.6% (22) belonged to the urban area. The majority of our patients have a monthly income in the range of 1001-5000 (39 = 68.4%) with minimum being 250 and maximum being 21,000 with a mean of 4250 + 3539.

The clinical symptoms of fever (15.8%), cough (14%), breathlessness (8.8%), and chest pain (8.8%) were non-specific which can be attributed to pulmonary diseases as well. Out of 3 (5.3%) patients having pulmonary tuberculosis, 1 had TB pleural effusion and the other two pulmonary infiltrations.

Most of the patients (71.9%) have CD4 less than 500/microl as shown in Figure 2. The mean CD4 count of the study population is 434.79 + 204.84.

Out of 57 patients, 4 patients have cardiac disorders (7.0%) as shown in Figure 3. All the patients having cardiac disorders are male.

Figure 4 shows the distribution of the study population based on the start of ART.

70.2% of our study population was on TLE regimen, whereas 22.8% of patients were on ZLN, 3.5% on ZLE, and

1.75% each on TLN and on pre ART phase as shown in Figure 5.

Out of the 54 patients who attended ART clinic only 1 patient had mild LV dysfunction. Whereas admitted patients having symptoms, LV dysfunction was found in one out of three patients (33.33%) as shown in Table 1. Concentric LVH was also found in two (3.5%) patients. Two (3.5%) patients have valvular heart disease in our study.

3.5% of the total patients studied showed a reduction in fractional shortening as shown in Table 2.

Only 2 patients (3.5%) had reduced ejection fraction as shown in Table 2.

Both the cases with reduced FS had a CD4 count less than 500. For those with reduced ejection fraction, 1 patient had a CD4 count less than 500 and another patient with a CD4 count above 500. Lower CD4count is not significantly associated with reduced FS as shown in Table 2.

Echocardiographic parameters are not significantly associated with CD4 Count as shown in Table 3.

Table 4 demonstrates 89.5%of patients are having good adherence to ART treatment whereas 7% shows average adherence and 1 patient only with poor adherence to ART.

Out of the 4 patients having cardiac disease, 2 are having average adherence and the association is statistically significant (P-value < 0.05) as shown in Table 4.

The cardiac disorder is seen in patients with < 1 year of start of ART, but it is not statistically significant. P-value 0.086 (>0.05) as shown in Table 5.

As shown in table 6, out of the various echocardiographic parameters that are negatively correlated with CD4 count, fractional shortening is positively correlated with CD4 count but not statistically significant. All the correlations are statistically insignificant. (P-value > 0.05).

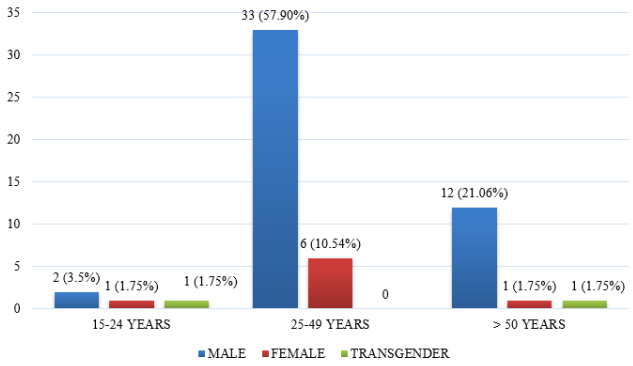

Fig. 1: Age and gender distribution of patients studied

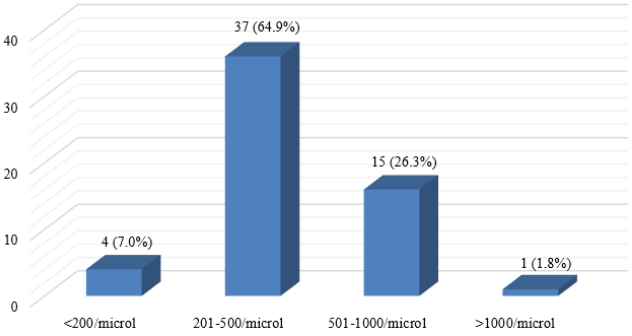

Fig. 2: CD4 count of the study population

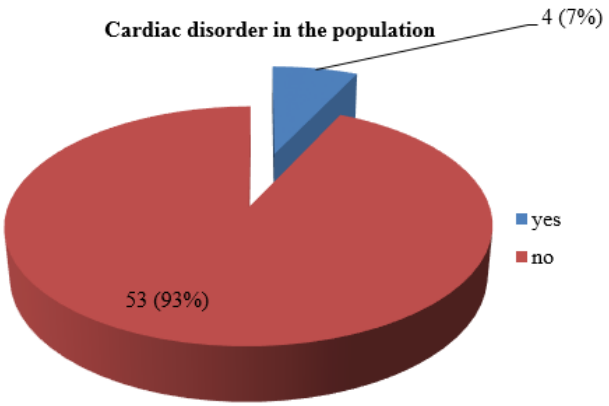

Fig. 3: Prevalence of cardiac disorder

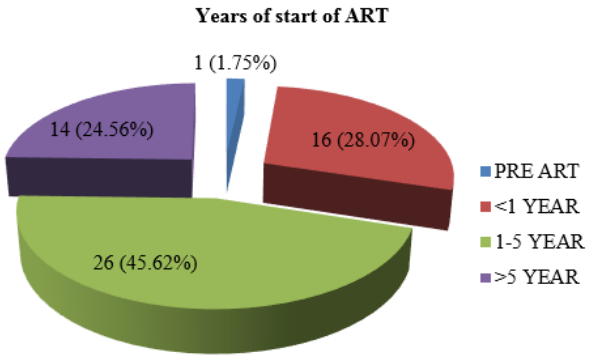

Fig. 4: Division of study population based on the start of ART

5. Discussion

In our study, 82.46% (47) of the patients were males, 14.04% (8) were females and 3.5% included in the study were transgender (2) population. We found men were affected more than females with M: F 5.87:1. Sharma et. al. also found male preponderance with male to female ratio of 3:1.[24] Around 44% of the total estimated (15+ years) HIV-infected patients were women as per the estimation by NACO in the year 2019.[2]

The mean age of the study group 41.32 + 11.24 years with an age range of 20 and 65 years; with a mean age of 42.68 ±10.69 years in males and 34.63 ±10.78 years in females respectively. Sharma et al. also found a similar

Table 1: Distribution of cases with echocardiographic abnormalities

Cardiac disorder	Frequency	Percentage
LV dysfunction	2	3.5%
Concentric LV hypertrophy	2	3.5%
Valvular disease	2	3.5%

Table 2: Associations of 2D Echocardiographic findings with CD4 count

Cardiac manifestation	CD4 count in microl			
	<200	201-500	501-1000	>1000
Reduced FS	0	2 (100%)	0	0
Reduced EF	0	1 (50%)	1 (50%)	0

Table 3: Comparisons between 2D Echocardiographic parameters and CD4 count

2D Echo cardiographic parameters	CD4 count <200 (n=4)	CD4 count >200 (n=53)	P value col 2 vs. col 3	CD4 count >500 (n=16)	P value col 2 vs. col 5
LVIDd	44.50+_4.51	43.60+_2.81	0.57	43.56 +2.66	0.5879
LVIDs	27.75+_3.5	28.02+_3.3	0.878	27.19 + 2.83	0.7383
FS	37.6+_4.6	35.7+_6.18	0.551	37.46 + 6.21	0.9670
EF	60.75+_1.5	61.8+_5.09	0.682	61 + 3.85	0.9016

Table 4: Associations between cardiac disorders and adherence to ART among the study population

Adherence	2D Echocardiography		Total	P value
	Normal	Disorder		
Good (>95%)	49 (96.1%)	2(3.9%)	51 (89.5%)	
Average (80 -95%)	2 (50%)	2(50%)	4 (7.0%)	
Poor (<80%)	1 (100%)	0	1 (1.75%)	$\chi 2$ =5.844 df = 1 p =
PRE ART	1(100%)	0	1 (1.75%)	0.0156
Total	53	4	57	
% within adherence	93%	7%	100%	

Table 5: Association of cardiac disorder with the start of ART

year of ART start	2D Echocardiography		Total
	Normal	Disease	
PRE ART	1 (100%)	0	1 (1.75%)
<1 Year	13 (81.25%)	3 (18.75%)	16 (28.07%)
1-5 Years	26 (100%)	0	26 (45.61%)
>5 Years	13 (92.9%)	1 (7.1%)	14 (24.56%)
Total	53 (93%)	4(7%)	57(100%)

Table 6: Correlations of various echocardiographic parameters with CD4 count

2D Echo parameter	CD4 COUNT	
	Correlation Co-efficient(r)	P value
LVID d	-0.124	0.358
LVIDs	-0.144	0.285
IVS	-0.075	0.579
LVPW	-0.034	0.802
LA	-0.074	0.584
AO	-0.192	0.152
EF	-0.159	0.237
FS	0.095	0.482

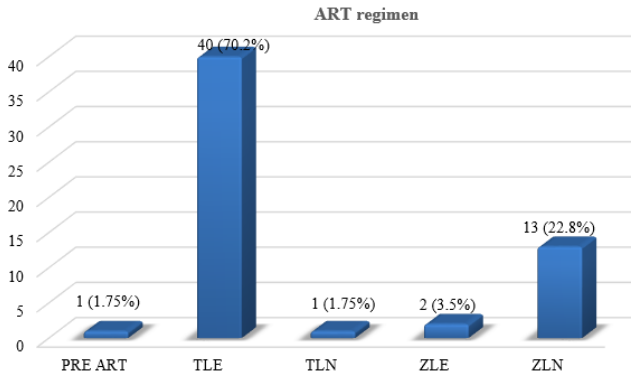

Fig. 5: Distribution of ART regimen among study population

mean age of 41.37 ±11.86 years in males and 41.37 ±9.47 years in females respectively with ages ranged between 15 and 80 years.[24] In this study, 75.44% of the patients were in the age group of 15-49 years and 24.56% were of 50 years and above. The majority of patients were young and belonged to the age group of 25-49 years. The NACO report has shown that the majority of PLHA in India were young adults.[2] According to the report by Odisha State AIDS Control Society (2016-17), the maximum number of persons infected with HIV positive was between the age group 25-49 with 78%, 9% of patients were under the age group of 15-24 years, 7% of patients were below 14 years of age and 6% of patients were above 50 years of age in Odisha.[23]

98% of the patients in our study were heterosexual, whereas 2% due to exposure to contaminated blood products. According to NACO, heterosexual mode of transmission, being the commonest form of transmission, accounts for 88.2% of HIV positive cases detected and blood products account for 1% of HIV infections. Other modes of transmission include mother-to-child transmission 5%, homosexual 1.5%, and detected during 2011-12.[25] Sharma et al. also established sexual mode of transmission as the most common mode of transmission, out of which hetero-sexual accounted for 94.4%, homosexual 2.8% of cases, and blood transfusion 2.2% cases which is quite similar to our study findings.[24] In contrast, in the west, homosexuality is the commonest mode of transmission among 75% of the newly affected males followed by 25% due to other modes of transmission.[26] It is evident that there is a noticeable difference in the type of sexual contact responsible for causing HIV infection in different populations.

Clinical features such as cough, breathlessness, fever, and chest pain are non-specific and can be attributable to pulmonary disease. 7% of our patients with HIV infection in our study develop multiple pulmonary opportunistic infections.

The mean CD4 count in our study is 429.53 ± 202.48/ microl whereas in Sharma et al. study found mean CD4 count 220.18 ± 158.31/ microl. Most of the patients (64.9%) have CD4 count between 201-500/microl. CD4 count was < 200/micro L in 7.0% in our study whereas, in the Sharma et al. study, CD4 count was < 200/micro L in 61.9%. Most of the cases studied had a CD4 count of > 200/microl, the reason behind this is that the patients studied were mostly asymptomatic and were those attending ART clinic, and the majority were on ART with good adherence.

The number of patients with cardiac disease in our study is less which is contrary to the various previous studies. Most of the cardiac manifestations as per Khunnawat et al[8] Sharma et. al.,[24] Lipshultz Se et. al[27] were seen in the late stage of the disease. Since the patients included in our study is almost clinically stable, they were lacking so much LV dysfunction.

Our study refuted the various studies showing the presence of cardiac disorders in the pre ART era as high as > 50%, especially in the sub-Saharan African population. Now the declining trend in systolic dysfunction was observed in studies and an increase in diastolic dysfunction on comparing with systolic dysfunction. But our study did not find any patients having diastolic dysfunction may be because in our 2D Echocardiography isovolumetric relaxation time was not calculated. Even then any significant clinical correlated dysfunction may not be found. Out of the 54 patients who attended the ART clinic only 1 (1.85%) patient had mild LV dysfunction. Whereas admitted patients having symptoms, LV dysfunction was found in one out of three patients (33.33%). Concentric LVH was also found in two (3.5%) patients. Two (3.5%) patients have valvular heart disease in our study as compared to 3 (3%) patients in the Sharma et. al. study.

2 (3.5%) patients had reduced FS. There is a positive correlation of reduced FS with low CD4 count though it is not significant. This was comparable with the studies conducted in Europe by Cerrato et al[20] as well as in India by Aggarwal et al[28] and Ayaskant Singh et al.[29] No positive correlation was obtained between other parameters with low CD4 count like reduced EF.

According to Hakim et al,[30] 9% of patients showed dilated cardiomyopathy in HIV patients in a study conducted in Zimbabwe and in the United States by Himelman[31] whereas none of our patients had DCM. Cardiac manifestations other than left ventricular dysfunction which is described in various studies are pericardial involvement, infective endocarditis was not found in our study.

It can be attributed to the treatment taken by the patients leads to improvement in cardiac function despite the metabolic side effect of some HAART drugs. After NACO 2016 revised regimen which offers ART treatment for all the HIV patients irrespective of their CD4 count is really a boon

for the patients. It has led to a gross reduction in multi-organ dysfunction and opportunistic infections.

6. Conclusion

Males are involved more than females with the transgender population included 3.5% in our study. Most patients are in the middle age group between 25 – 49 years. The heterosexual mode was the most common mode of transmission. Most of the study population belonged to rural areas 61.4%. The mean monthly income of the patients was 4250. Three patients (5.3%) were on anti-tubercular drugs. Out of which one was for tubercular pleural effusion. The systolic LV dysfunction was found in 50% of PLHA patients with cardiac disorders. The valvular disease found in two patients. No patients had diastolic dysfunction, dilated cardiomyopathy, or pericardial disease. Dysfunction was more common in admitted patients than those attending ART clinic. Concentric LVH was also found in two (3.5%) patients. CD4 count was positively correlated with fractional shortening. The presence of cardiac dysfunction was significantly associated with adherence to ART treatment. 50% of patients with cardiac abnormality had fewer adherences i.e. average (80-95%).

Cardiac disorders are not that frequent in patients attending ART CLINIC or in the early stages of HIV in our country. It is common in advanced HIV infection in other studies. Clinical manifestations are a nonspecific and more direct assessment of cardiac function using echocardiography helps in early detection and treatment of cardiac dysfunction in advanced HIV infection.

7. Limitations

Furthermore, studies are needed to establish any cardiac dysfunction is solely associated with HIV/AIDS. As the sample size is low, this study if continued could establish or rule out the association.

8. Author's Contributions

Dr. Jagannath Sadangi made the design of the study, redaction of the manuscript, and guiding all the way through. Dr. Teena Thomas is the primary investigator, worked in data collection, redaction of the manuscript, statistic study, analysis of data, and data interpretation. Dr. Bibhu Prasad Behera and Dr. Ranjan Kumar Sen helped in a statistical study, analysis of data, data interpretation, and manuscript writing. Dr. Bibhu Prasad Behera is also the corresponding author.

9. Source of Funding

None.

10. Interest of Conflicts

None.

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