Original Article

Cardiovascular manifestations of people living with HIV/AIDS: Report from a hot spot in eastern India

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ABSTRACT

Objective: To study the profile and characteristics of cardiovascular abnormalities among patients living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) at a tertiary care hospital in India. The association of cardiovascular abnormalities with the CD4 count and disease stages, according to the World Health Organization (WHO) classification, was also analyzed.
Methods: A total of 200 patients with HIV/AIDS were compared with 50 healthy controls. All patients underwent blood investigations, chest X-ray, electrocardiography, and echocardiography.
Results: The mean age of the patients was 38.66 ± 9.22 years, with a male-to-female ratio of 3.25:1. Echocardiographic abnormalities were found in 52% of the patients and 12% of the controls, with the most common abnormality being left ventricular diastolic dysfunction. Echocardiographic abnormalities were markedly more common in patients with a CD4 count of $<200/\mu L$. The advanced stage of the disease, according to the WHO classification, was also associated with an increased incidence of echo-cardiographic abnormalities.
Conclusions: Cardiovascular abnormalities in the form of electrocardiogram and ECHO findings were present in 54.5% and 52% of patients, respectively. Echocardiographic findings showed significant correlation with CD4 count and WHO disease stage.
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1. Introduction

Acquired immunodeficiency syndrome (AIDS) is one of the deadliest diseases of the current era. Human immunodeficiency virus (HIV) infection continues to be a major public health issue; in 2017, 9,40,000 HIV-related deaths were reported globally.bib1 With the increased use of highly active antiretroviral therpy (HAART) to prolong lifespan of patients, cardiovascular disorders (CVDs) have increasingly become a leading cause of morbidity and mortality in people living with HIV-AIDS (PLHA).[2] Moreover, clinical CVD tends to appear approximately 10 years earlier in HIV-infected individuals than in the general population.[3]

The National AIDS Control Organization (NACO) has identified Odisha as one of the five highly vulnerable states, largely because of a substantial number of migrant workers.[4] The underdeveloped district of Ganjam with a population of 3.5 million accounts for 33% of patients in Odisha and has been ranked the eighth most HIV-prone district in India because of the high HIV prevalence (>3%) among females attending the antenatal clinics.[5]

There is a paucity of data regarding the cardiovascular manifestations of HIV in eastern India, despite having a substantial number of PLHA. Therefore, we conducted this study at a tertiary care hospital in Ganjam district of Odisha to assess the cardiovascular manifestations in PLHA.

2. Materials and methods

This was an observational, cross-sectional, prospective study conducted at the Department of Cardiology of the MKCG Medical College and Hospital, Berhampur, Odisha, between October 2017 and September 2018. The Independent Ethics Committee of the institute approved the study.

2.1. Inclusion criteria

All patients (age >18 years) who were diagnosed with HIV infection, as per the NACO guidelines (by COMBAIDS dot immunoassay test, HIV 1/2 triline rapid test, PAREEEKSHAK HIV 1/2 spot

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rapid test) and attended the antiretroviral therapy clinic were included in this study. Informed written consent was obtained from all patients.

2.2. Exclusion criteria

Patients who were diagnosed with congenital heart disease, ischemic heart disease (IHD), rheumatic heart disease, cardiomyopathy, systemic or pulmonary hypertension, or chronic respiratory disease before HIV diagnosis were excluded.

From a total of 320 patients, 120 patients were thus excluded, and 200 patients were found eligible for the study. All of these patients were interviewed with a structured questionnaire regarding complaints with duration, personal history (occupation, smoking, sexual activity, drug abuse, etc.), comorbidities, and other relevant information followed by thorough clinical examination. Fifty age-matched and sex-matched healthy HIV negative volunteers without any cardiovascular risk factors or comorbidities were selected as controls.

All patients underwent routine hematological and biochemical investigations. In addition, an enzyme-linked immunosorbent assay—based method was used to detect the serum N-terminal pro-brain natriuretic peptide (NT-pro BNP) level using the Dimension RxL Max Analyzer (Siemens), with a lower detection limit of 5 pg/ml. A single decision value of NT-pro BNP was defined using the previously defined age-stratified cutoff values of 50 pg/ml (<50 years), 75 pg/ml (50—75 years), and 250 pg/ml (>75 years) as optimized rule-out thresholds. The CD4 count was performed by flow cytometry (BD FACS count system) using the kits supplied by NACO to the ART center of this college. Disease staging was performed as per the revised World Health Organization (WHO) clinical staging of HIV/AIDS for adults and adolescent criteria.[6] Next, chest X-ray (posteroanterior view) and electrocardiograms (ECGs) were obtained. On chest X-ray, only cardiomegaly and dilatation of the pulmonary arteries were recognized as cardiovascular abnormalities. The controls underwent all investigations except CD4 count.

Subsequently, transthoracic echocardiography (TTE) was performed by an experienced cardiologist using Philips HD7XE echocardiography machine with 3.5 MHz transducer probe. TTE was performed in the left lateral decubitus position using 2D, M mode, color Doppler, continuous and pulse wave in parasternal long axis,

short axis, apical 4 chamber (A4C), apical 2 chamber (A2C), and subcostal view. All the measurements were obtained as per the American Society of Echocardiography guidelines. The left ventricular end-diastolic and end-systolic diameters, thickness of the interventricular septum and posterior wall in diastole, and the left atrial and aortic root diameters were documented. Left ventricular ejection fraction (LVEF) and fractional shortening (FS) were measured in A4C and A2C views using the modified Simpson biplane disc method.

Dilated cardiomyopathy (DCM) was diagnosed based on the presence of LV dilatation (>112% corrected to body surface area and age) with reduced LV function (FS <25% and/or LVEF<45%). Transmitral flow was assessed in A4C view, and left ventricular diastolic dysfunction (LVDD) was categorized into three grades: mild = E/A<0.75; moderate = 0.75 < E/A<1.5 with DT > 140 ms; and severe = E/A>1.5 with DT < 140 ms. Other echocardiographic abnormalities including pericardial effusion/thickening, regional wall motion abnormalities, and valvular lesions were also assessed.

2.3. Statistical analysis

The data were compared for statistical analysis using the Fisher's test, Chi-square test, student t-test, and analysis of variance, as appropriate. All analyses were performed using the IBM SPSS statistics for Windows, version 23.0. The values were represented as number (%) and mean ± standard deviation. A p value <0.05 was considered statistically significant.

3. Results

A total of 200 PLHA were studied. The mean age of the study population was 38.66 ± 9.22 years (range: 21—55 years). Most of the patients (49%) were in the age group of 31—40 years (Fig. 1). Of 200 patients, 153 were male (male: female ratio: 3.25:1). The mean ages of male and female patients were 40.2 ± 10.26 and 33.5 ± 7.38 years, respectively. Sexual mode (heterosexual contact) was the most common transmission route detected in 93% of all cases. Other modes of transmission included blood transfusion (4%) and intravenous drug abuse (0.5%); however, the mode of transmission could not be ascertained in 2.5% of patients. Approximately 37% of patients were smokers, 23.5% were alcoholic, and 17% were addicted to both smoking and alcohol. Only one patient revealed a
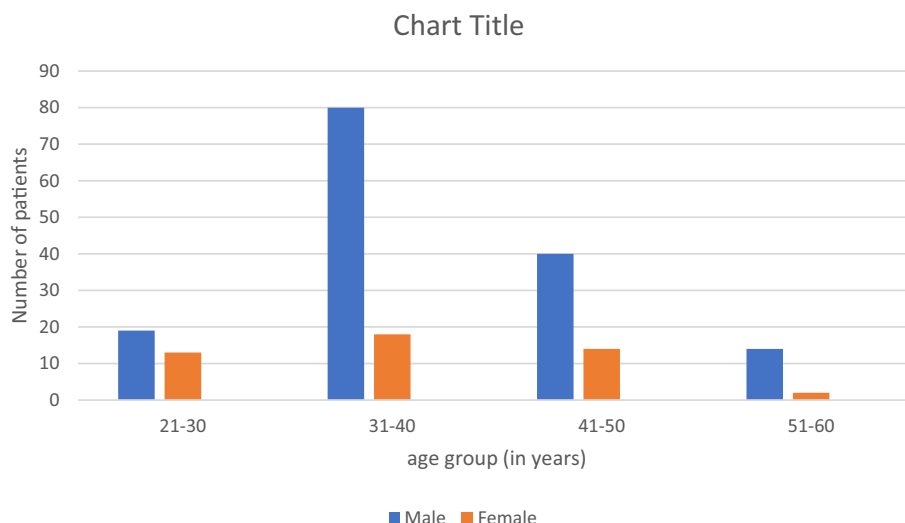

Fig. 1. Age and sex distribution of the HIV/AIDS population. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
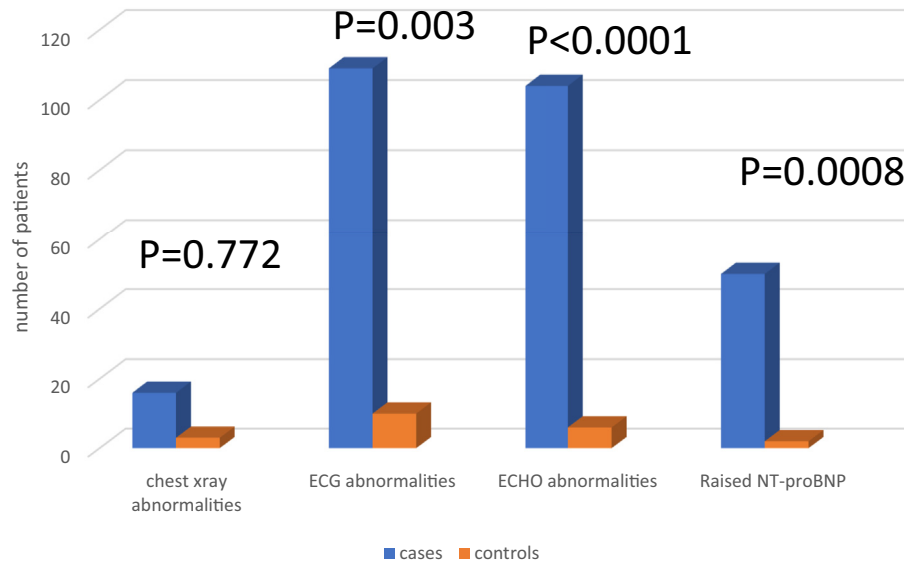
Fig. 2. Distribution of cardiovascular abnormalities in HIV/AIDS patients (*n* = 200) and controls (*n* = 50). ECG, electrocardiogram; NT-pro BNP, N-terminal pro-brain natriuretic peptide; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

history of intravenous drug abuse. A staggering 41.2% of the male patients (63 out of 153) were migrant laborers by profession.

The range of CD4 count was 34−674/μL (mean, 239.45 ± 150.2/μL). The CD4 count was less than 50/μL in 30% of cases, between 50 and 199/μL in 40% of cases, between 200 and 499/μL in 16% of cases, and >500/μL in 14% of cases. About 87.5% of male patients were in clinical stage III and IV, whereas 80% of females were in clinical stage II and III. Of all patients, 54% were on treatment with HAART, and the remaining were either newly diagnosed cases or did not satisfy the NACO criteria for HAART initiation. All patients receiving treatment were prescribed first-line triple drug antiretroviral therapy. Regarding significant medical history, hypertension, diabetes mellitus, dyslipidemia, and tuberculosis were present in 10%, 8%, 13%, and 7% of cases, respectively. The most common symptom possibly related to CVD was cough (42%), followed by fever (33%), breathlessness (27%), and chest pain (12%).

Chest X-ray, ECG, and echocardiographs were available for all 200 patients, and cardiovascular abnormalities were observed on chest X-ray, ECG, and echo in 16 (8%), 109 (54.5%), and 104 (52%), respectively. The corresponding numbers in the control population were 3 (6%), 10 (20%), and 6 (12%), respectively. Serum NT-pro BNP level was obtained for 108 patients, and the value above the cutoff was detected in 50 (46.3%) patients and two (9%) controls (Fig. 2). The most common ECG abnormality was sinus tachycardia (*n* = 50; 45.8%) followed by low voltage QRS complex (23.8%) and ST-T wave changes (20.2%).

The ECG features are tabulated into four groups based on the CD4 count (Table 1). There was no significant correlation between

the ECG findings and CD4 count. When divided depending on the disease stages (WHO classification), ECG findings were similar for different disease stages (Table 2).

Compared with 12% of controls, 52% of patients exhibited echocardiographic abnormalities (p < 0.0001; Fisher's exact *t* test) (Table 3).The most common echocardiographic abnormality was LVDD. Of all patients with LVDD (*n* = 78), 50 (64%) had mild, 24 (31%) had moderate, and 4 (5%) had severe diastolic dysfunction. Of 14 cases of pericardial effusion, eight had mild, four had moderate, and two had massive effusion. The echocardiographic abnormalities were further categorized according to the CD4 count. Reduced FS, LVDD, reduced LVEF (<50%), valvular regurgitation, and pericardial effusion were significantly more common in patients with a CD4 count < 200/μL (Table 4). Similarly, there were significant differences in diastolic dysfunction, reduced FS, reduced EF, and valvular regurgitation between various disease stages (Table 5).

The severity of LVDD was categorized according to the CD4 count. Compared with 82.1% of patients with the highest CD4 count, 41.7% of patients with the lowest CD4 count showed normal diastolic function. The difference in LVDD between the groups was statistically significant (p = 0.003) (Table 6).

4. Discussion

This study was conducted in 200 PLHA diagnosed as per the NACO criteria. The predominantly young cohort of our study represents the HIV/AIDS population of India (Fig. 1). A North Indian study reported that the mean ages of male and female patients are

Table 1
Comparison of ECG abnormalities with CD4 count.

ECG abnormalities	CD4<50/μL (*n* = 60)	CD4 50−199/μL (*n* = 80)	CD4 200−499/μL (*n* = 32)	CD4>500/μL (*n* = 28)	P value
Sinus tachycardia	14	23	8	5	0.69
Conduction abnormalities	1	1	1	2	0.35
Atrial ectopics	2	1	1	1	0.83
Ventricular ectopics	1	1	2	1	0.44
Poor progression of R wave	2	2	1	1	0.98
Low voltage	8	10	5	3	0.95
ST/T wave abnormality	6	8	6	4	0.65

ECG, electrocardiogram.

Table 2
Comparison of ECG abnormalities with WHO class.

ECG Abnormalities	WHO CLASS I (*n* = 23)	WHO CLASS II (*n* = 28)	WHO CLASS III (*n* = 71)	WHO CLASS IV (*n* = 78)	P value
Sinus tachycardia	3	4	18	25	0.13
Conduction abnormalities	1	2	1	1	0.30
Atrial ectopics	1	1	1	2	0.84
Ventricular ectopics	1	1	2	1	0.81
Poor progression of R wave	1	1	1	3	0.80
Low voltage	3	3	6	14	0.37
ST/T wave abnormality	4	3	5	12	0.36

ECG, electrocardiogram; WHO, World Health Organization.

Table 3
Comparison of echocardiographic abnormalities among cases and controls.

Echocardiographic abnormality	Cases (*n* = 200)	Controls (*n* = 50)	P value
LV diastolic dysfunction	78 (39%)	4 (8%)	<0.0001
Valvular regurgitation (MR, AR, PR, TR)	61 (30.5%)	5 (10%)	0.002
Reduced FS(<30%)	64 (32%)	2 (4%)	<0.0001
Reduced LVEF	32 (16%)	2 (4%)	0.035
Dilated cardiomyopathy	24 (12%)	1 (2%)	0.035
Pulmonary hypertension	30 (15%)	3 (6%)	0.106
Regional wall motion abnormality	2 (1%)	0 (0%)	1.0
Pericardial effusion	14 (7%)	0 (0%)	0.079

MR, mitral regurgitation; AR, aortic regurgitation; PR, pulmonary regurgitation; TR, tricuspid regurgitation; FS, fractional shortening; LVEF, left ventricular ejection fraction.

Table 4
Comparison of echocardiographic abnormalities with CD4 count.

Echocardiographic abnormality	CD4<50/μL (*n* = 60)	CD4 50−199/μL (*n* = 80)	CD4 200−499/μL (*n* = 32)	CD4 >500/μL (*n* = 28)	p value
LV diastolic dysfunction	30	36	8	4	0.003
Valvular regurgitation (MR, AR, PR, TR)	20	24	14	3	0.045
Reduced FS(<30%)	10	42	8	4	<0.00001
Reduced LVEF (<50%)	6	20	3	3	0.045
Dilated cardiomyopathy	5	15	2	2	0.119
Pulmonary hypertension	9	15	5	1	0.288
Regional wall motion abnormality	0	2	0	0	0.387
Pericardial effusion	4	10	0	0	0.041

MR, mitral regurgitation; AR, aortic regurgitation; PR, pulmonary regurgitation; TR, tricuspid regurgitation; FS, fractional shortening; LVEF, left ventricular ejection fraction.

Table 5
Comparison of echocardiographic abnormalities with WHO class.

Echocardiographic abnormality	WHO CLASS I (*n* = 23)	WHO CLASS II (*n* = 28)	WHO CLASS III (*n* = 71)	WHO CLASS IV(*n* = 78)	P value
LV diastolic dysfunction	5	6	30	37	0.02
Valvular regurgitation (MR, AR, PR, TR)	4	3	24	30	0.02
Reduced FS(<30%)	4	3	24	31	0.01
Reduced LVEF (<50%)	3	3	6	20	0.02
Dilated cardiomyopathy	3	3	6	12	0.62
Pulmonary hypertension	6	7	7	10	0.10
Regional wall motion abnormality	1	0	0	1	0.78
Pericardial effusion	2	4	3	5	0.35

MR, mitral regurgitation; AR, aortic regurgitation; PR, pulmonary regurgitation; TR, tricuspid regurgitation; FS, fractional shortening; LVEF, left ventricular ejection fraction; WHO, World Health Organization.

Table 6
Comparision of diastolic dysfunction with CD4 count.

Severity of diastolic dysfunction	CD4<50/μL (*n* = 60)	CD4 50−199/μL (*n* = 80)	CD4 200−499/μL (*n* = 32)	CD4 >500/μL (*n* = 28)	P value
Normal	25 (41.7%)	42 (52.5%)	27 (84.4%)	23 (82.1%)	0.003
Mild	22 (36.7%)	20 (25%)	4 (12.5%)	4 (14.3%)	
Moderate	10 (16.7%)	17 (21.2%)	1 (1.5%)	1 (2.3%)	
Severe	1 (4.9%)	1 (1.3%)	1 (1.5%)	1 (2.3%)	

37.13 ± 8.80 years and 32.35 ± 5.14 years, respectively.[7] A cross-sectional study of 60 HIV positive patients found that 53.3% of patients are in the 31–40 years age group, with males constituting 63.3% of the population.[8] Most of the migrant laborers from Ganjam district were male and in the productive age group, which is in line with the above findings. In contrast, a recently published international meta-analysis involving 54 studies has revealed that the average age of patients is 47 years.[9]

Cough and fever were the two most common symptoms in our study patients, which is in line with the findings of previous studies.[10] Chest X-ray revealed cardiomegaly in 8% of cases, which is similar to the findings of Akinbami et al.[11] However, this finding was not significant when compared with controls. ECG and echocardiography-related abnormalities were more common in PLHA than in controls; in addition, serum NT-pro BNP levels were higher in PLHA than in controls. The presence of ECG abnormalities in 54.5% of patients indicated that ECG can be used as an easy and convenient tool for investigating CVD risk. A similar conclusion has been drawn by a study involving 75 PLHA (49.3%).[7] Lipschultz et al. have also revealed that 57% of asymptomatic PLHA show ECG abnormalities.[12] A study from Tamil Nadu[13] reported that low voltage QRS complex is the most common ECG abnormality (27.27%), whereas poor progression of R waves has been reported to be the most common ECG abnormality by Sundarrajan et al.[14]

In the present study, there was no significant correlation between the ECG findings and CD4 count (Table 1). This is consistent with the recent results obtained by Sharma et al[15] and Kumar et al.[8] Chaudhary et al. have also made similar conclusion when comparing the two groups of patients using a CD4 count cutoff of 350/µL.[7] Importantly, Soliman et al. demonstrated that the presence of ECG abnormalities is an independent predictor of CVD incidences.[16] In addition, Sakthidavel et al. have found a strong relation between the CD4 count and ECG abnormalities (p = 0.000).[13] There was no statistically significant association between the ECG abnormality and WHO class (Table 2). This is consistent with the findings of Chaudhary et al[7] but contradictory to the findings of Sundararajan et al,[14] which reports a significant increase in ECG abnormalities with the advancement of WHO class.

LVDD was the most common echocardiographic abnormality in our study population, similar to the findings of several previous studies involving Indian PLHA.[17,18] Interestingly, a study by Nayak et al. have also reported a high prevalence (37%) of LVDD in a cohort of young (median age: 38 years) asymptomatic PLHA without any other risk factor for CVD.[19] A high percentage of young patients in our study group may be responsible for the similar findings. Erquo et al. have reported that the pooled prevalence of grade I to grade III diastolic dysfunction is 29.3% and grade II to III diastolic dysfunction is 11.7%.[9] Sharma et al. have found that the most common echocardiographic manifestations are the reduction in EF and FS, pericardial effusions, dilated cardiomyopathy, and diastolic dysfunction.[15] The incidences of LVDD have been reported to be 26.4% and 48% by Padhiyar et al. and Reinsch et al., respectively.[20,21] In our study, pericardial effusion was noted in 7% of PLHA with a CD4 count of <200/µL. The effusion may be related to the opportunistic infections or malignancy, although a clear etiology could not be established in majority of the cases. The incidence of pericardial effusion in AIDS patients has been reported to be 11% per year, whereas the prevalence of symptomless effusion has been estimated to be 22%. DCM was more prevalent in PLHA than controls (p = 0.035). The prevalence of HIV is increasing in cardiomyopathy patients because of the increased lifespan after the introduction of HAART. Although the incidence of HIV-associated pulmonary hypertension is much higher than the incidence in healthy population, a statistically significant difference could not be established in our study. This is possibly because of the small study population as well as unavailability of cardiac catheterization for pulmonary hypertension diagnosis.

There is widespread agreement that the most important factor for the development of cardiac abnormalities is the level of immunosuppression[21]; the present study also revealed a strong association between the echocardiographic findings and CD4 count. A study from Taiwan revealed that both systolic and diastolic dysfunctions are positively correlated with a decreased CD4 count.[22] Pericardial effusion has often been considered a marker of end-stage disease because it is associated with a low CD4 count. Sakthivadivel et al. have demonstrated that the incidence of echocardiographic abnormalities increases in patients with a CD4 count <350/µL.[15] Sundarrajan et al. have reiterated this principle in a recently published study involving 100 patients.[16]

The advanced disease stage also significantly correlated with the echocardiographic findings. Khunnawat et al. and Zareba and Lipshultz have reiterated that cardiac manifestations occur at the later stages of disease.[23,24] Sundarrajan et al. have also revealed a strong association between the disease stages and echocardiographic manifestations (p = 0.00), indicating that cardiac abnormalities are directly proportional to the disease stage.[14] Hence, an early diagnosis of the disease can potentially prevent cardiovascular complications.

The severity of LVDD increases significantly with a decrease in CD4 count. This is in agreement with the findings of Mankwe et al. who reported that 82.4% of patients with a CD4 count >500/µL have normal diastolic function, whereas only 52.5% of patients with a CD4 count <200/µL have normal diastolic function.[25] In this study, severe diastolic dysfunction was found in 5.9% of patients with a CD4 count >500/µL and 27.5% of patients with a CD4 count <200/µL. Similarly, Hidayat et al. have reported a significant correlation between low CD4 count and diastolic dysfunction grade (p = 0.002). A CD4 count <200/µL has been shown to strongly predict the diastolic dysfunction with an odds ratio of 9.35.[26] A meta-analysis by Erqou et al. revealed a trend of lower prevalence of advanced diastolic dysfunction in studies involving patients with a higher mean CD4 count.[9]

There are several limitations of this study. Only 200 PLHA were evaluated at a single time point. No follow-up was done. The relation between the cardiac abnormalities and HAART was not assessed. Serum NT-pro BNP levels were obtained for only 54% of cases. There was no independent adjudication of echocardiographic findings. Exercise stress testing and coronary angiography were not included in our study protocol, which resulted in an incomplete evaluation of IHD.

5. Conclusion

Symptoms suggestive of cardiovascular disease and abnormal findings on investigation are commonly encountered in the PLHA population. Therefore, routine cardiological evaluations such as obtaining comprehensive history and conducting clinical examinations are essential for PLHA. ECG and 2D echocardiography should be done during baseline evaluation, especially in patients with a CD4 count <200/µL. This might help identify CVD at an early stage. A large number of prospective studies with greater number of participants and follow-up investigations are required for better assessing the epidemiological and clinical scenario and understanding the mechanism involved.

Conflict of interests

All authors have none to declare.

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