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Research Article

Study of Cardio Vascular Diseases in HIV Infected Patients in HAART Era

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Abstract: Cardiovascular disease is an increasingly important cause of death in HIV infected patients. Furthermore, cardiovascular manifestations of HIV have been altered by the administration of highly active antiretroviral therapy (HAART) regimens. We aimed to study the cardiovascular diseases (CVDs) in HIV infected patients taking highly active antiretroviral therapy (HAART). Observational study conducted in 100 HIV infected patients receiving highly active antiretroviral. Majority of patients included in the study were newly diagnosed and patients with HIV status stage IV were excluded from the study. Patients were screened for complications and differentiated. Various CVD parameters have been studied .The data collected includes BMI, Echo, Mitral Inflow velocity, ECG. In the study majority of patients were in stage I.37%patients were having CD-4 count in range of 50-100. 94%patients had BMI<25kg/m^2.88% patients had no ECG abnormalities and 12% had diastolic dysfunction. HIV infected patients exhibit multiple cardiac abnormalities. Although this study did not find any correlation between HIV and occurrence of cardiac disease except diastolic dysfunction but it cannot be attributed to HIV related. Furthermore study has several shortcomings, as the study has performed on younger subjects and number of patients is also limited.
Keywords: HAART, HIV, BMI, Dyslipidemia, NRTI+, NNRTI

INTRODUCTION

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is a major global public health crisis assuming epidemic form with an estimated 35.3 (32.2–38.8) million people living with HIV infection worldwide [1]. India has a population of over one billion and there are expected 2.5 million people living with HIV in India, which equates to a prevalence of 0.3% [2]. Around half of these are adults in the sexually active age group [3]. The first AIDS case in India was detected in 1986; since then, HIV infection has been reported from all the states and union territories [3].

Cardiac abnormalities were appreciated early in the epidemic of AIDs, seen before the etiologic agent HIV was isolated and characterized [4]. In the small autopsy series, major cardiac pathology was noted in 24% cases. Symptomatic cardiac disease was described first in children, it is also common in HIV infected adults. Patients with AIDs can have cardiac pathology related to opportunistic infections that include bacterial, fungal, protozoan pathogens and viruses like Cytomegalo, Coxsackie virus and tumors like Kaposi's sarcoma and non lymphoma. The most common cardiovascular disorders in infected patients are pericarditis, pulmonary vascular disease and hypertension, valvular disease, mayocarditis, and an increased incidence of coronary artery disease.

At the beginning of the epidemic, heart muscle disease was reported as the dominant cardiac complication of HIV infection in the developed world. Tubercular pericarditis was the most important cardiac manifestation of the disease in Africa. The arrival of highly active antiretroviral therapy (HAART) has changed the pattern of disease in developed countries. Premature coronary artery disease and other manifestations of atherosclerosis are found to be the most common cardiovascular disorder now. It is partly caused by HAART- induced metabolic problems, particularly insulin resistance and Hyperlipidemia. It also reflects a high prevalence of conventional cardiovascular risk factor such as smoking. Cardiovascular problems associated with advanced immunodeficiency, continue to predominate in resource poor countries where <5% of patients are able to access antiretroviral drugs [5, 6].

MATERIALS AND METHODS

Patient and methods

The study comprised of 100 HIV seropositive patients attending the ART center, associated with the department of Medicine, Nehru Chikitsalaya, BRD medical college, Gorakhpur between may 2009 to October 2010.Patients with positive ELISA for HIV-1 and 2 as per guidelines of NACO on accepting the consent are included in the study and hospitalized patients with HIV status stage 4 are excluded from the study**.** A detailed analysis of all the patients was carried out and data were collected from ART centre.

Demographic Survey

Socio-demographic survey includes name, age, sex, marital status, language and occupation of the patient.

A detailed medical history and functional status survey with complete examination of the participant is carried out, which consists of chief complaints, number of days since HIV diagnosis ,prescription history and ART, any past history of diabetes, hypertension, tuberculosis. Detailed personal history about sexual behavior (homo/hetero/bisexual) and family history (about spouse and children) was taken. Assessment staging based on WHO-HIV stage was done. Blood samples at first visit were collected for CD4 count, general systemic examinations, routine investigation, blood for blood sugar and serum lipid profile with serum electrolyte estimation, hepatitis B and C, ECG, echocardiography of all participants done for evaluation.

Statistical Analysis

All statistical analysis were carried out by calculating the differences in the mean or percentage of the patients value and values at different parameters by using standard error of the mean or the percentage difference.

RESULTS

Demography

Age and sex distribution

The HIV seropositive individuals participated in the current study (n=100) were having the age range from 10-65 years with maximum incidence in 4th decade (40%) followed by 3rd and 5th decade (31% and 23%) respectively. Male to Female ratio was 2.5:1 (Fig.1).

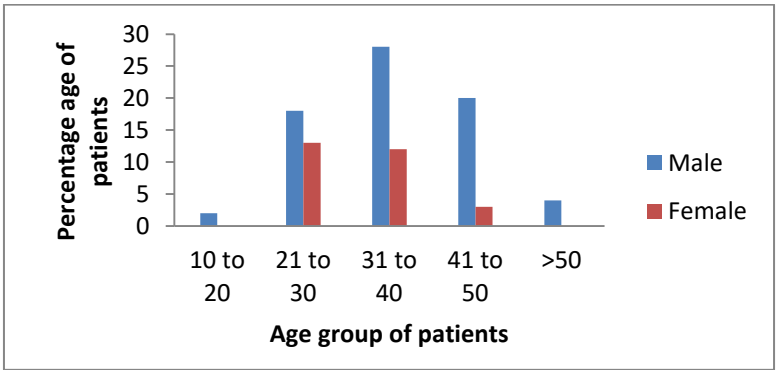


Fig. 1: Shows the incidence of HIV seropositivity

Clinical Features

Duration of HIV diagnosis

Majority of the patients 61(61%) were diagnosed HIV seropositive 6 months before attending the ART centre, while 2 cases came to ART centre two year after the diagnosis by seropositivity (Fig. 2).

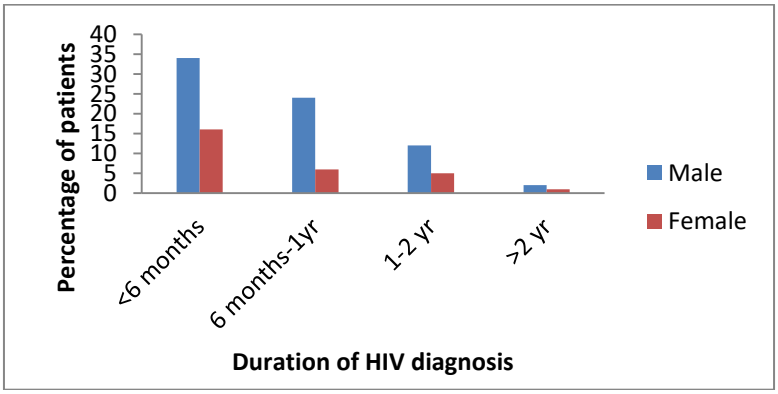


Fig. 2: Shows the duration of HIV diagnosis in participants

Presenting complaints of patients

In the study group, 84 participants (84%) were asymptomatic and 16 participants (16%) were symptomatic. 7 % symptomatic patients were having predominant Respiratory system (7 cases) in the form of pulmonary tuberculosis and bronchitis .6% patients were having cardiovascular (6 cases) presented having pericardial effusion and myocarditis and 3 % patients were having other symptoms (Fig. 3).

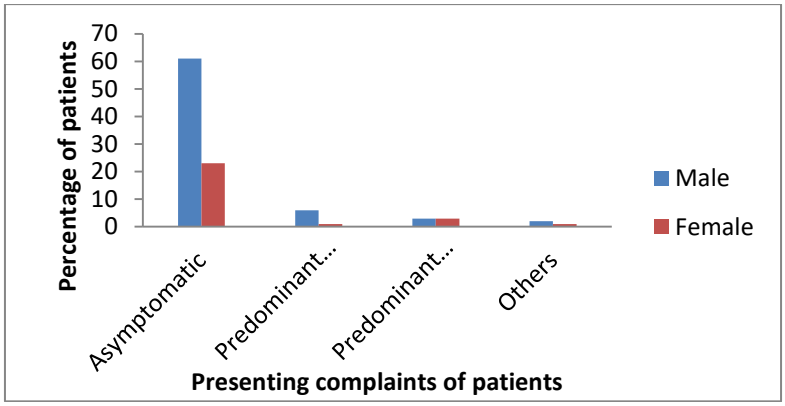


Fig. 3: Shows the presenting complaints of patients participating in the study

WHO-HIV Stage of patients

Clinical Stage I

- Asymptomatic
- Generalised lymphadenopathy
- In some cases symptoms similar to those of cold flue would be manifested.

Performance scale: 1: asymptomatic, normal activity.

Clinical Stage II

- Weight loss, < 10% of body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Herpes zoster within the last five years
- Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

And/or performance scale 2: symptomatic, normal activity.

Clinical Stage III

- Weight loss, > 10% of body weight
- Unexplained chronic diarrhoea > 1 month
- Unexplained prolonged fever (intermittent or constant), > 1 month
- Oral [candidiasis] ([thrush])
- Oral hairy leucoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (i.e. pneumonia, py omyositis)

And/or performance scale 3: bedridden < 50% of the day during last month.

Clinical Stage IV

The declaration of AIDS

- HIV wasting syndrome *
- Pneumocystis carinii pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus disease of an organ other than liver, spleen or lymph node (ex: retinitis)
- Herpes simplex virus infection, mucocutaneous (>1 month) or visceral
- Progressive multifocal leucoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of esophagus, trachea, bronchi
- Atypical mycobacteriosis, disseminated or lungs
- Non-typhoid Salmonella septicemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV encephalopathy **

And/or performance scale 4: bedridden > 50% of the day during last month.

(*) HIV wasting syndrome: weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month) or chronic weakness and unexplained prolonged fever (> 1 month).

(**) HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

In the study group, 85 patients (85%) were in stage-I WHO HIV stage, 4 patients (4%) were in stage II and 11 patients were in stage III. Maximum number of patients was under stage-I WHO-HIV (Fig. 4).

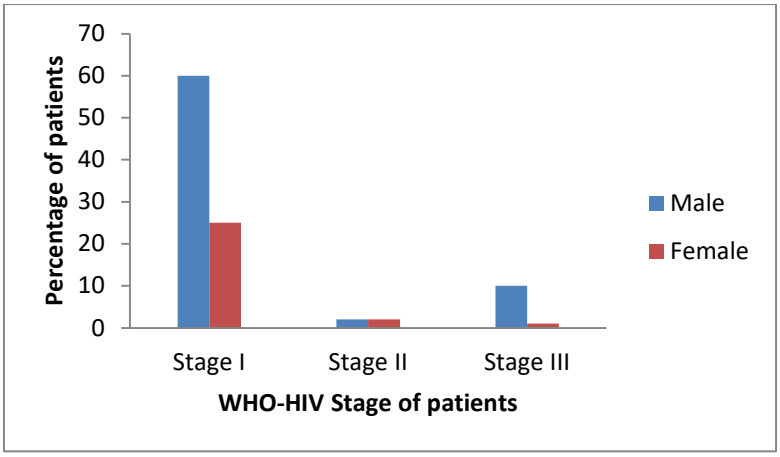


Fig. 4: Shows the WHO-HIV stages of participants

CD4 count of patients

In the study CD4 count of 37 patients (37%) were in between 50-100, 36 patients (36%) having CD4 count between 200-500,14 patients (14%) having CD4 count >500 and of which 3 patients (3%) had CD4 count of less than 50 (Fig. 5)

Duration of ART

46% of patients were on ART at the time of attending the ART centre while most of them (30%) were on ART from last 6 months (Fig. 6).

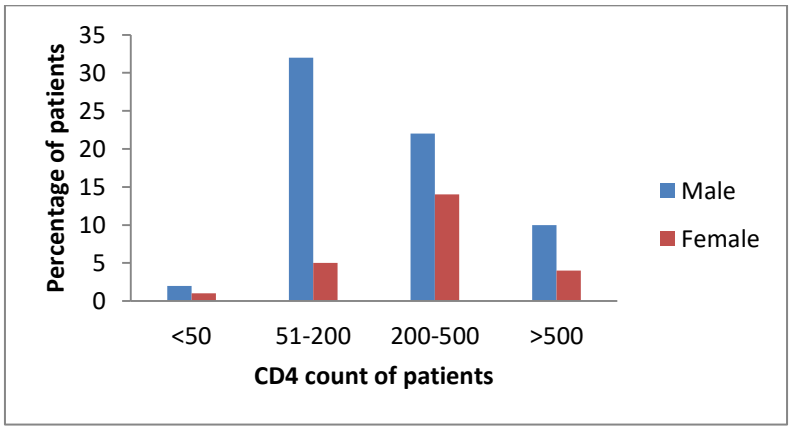


Fig. 5: Shows the CD4 count of patients participating in the study

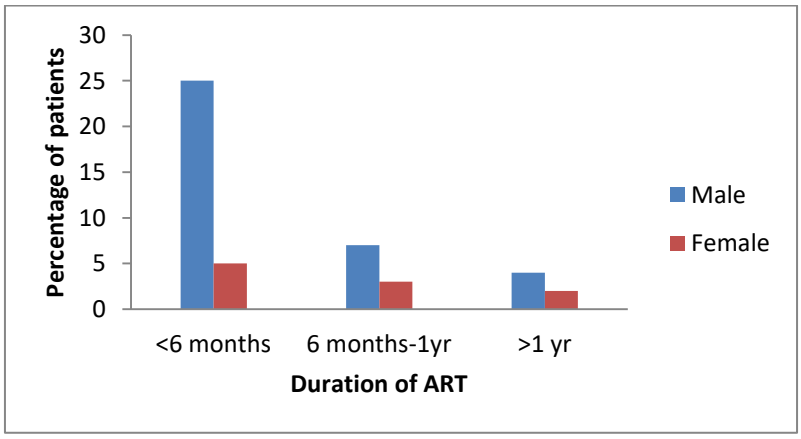


Fig. 6: Shows the duration of ART in the participants

BMI of patients

In the study 94% of patients were having BMI <25, and were lean and thin and few of them (3 cases) were obese having BMI > 30% (Fig. 7).

Laboratory Finding

52 cases were modreately anaemic having haemoglobin 8 – 10 gm % and only 3 cases were having less than 8 gm % other serum values of blood sugar, serum lipid and electrolyte were whithin normal range. None of them were positive for heapetitis B and heapetitis C.

Echo findings of patients

In study group, 4% were having valvular diseases and 1% having pericardial effusion (Fig 8). The pericardial effusion patient 1 case was aspirated and pericardial fluid came to be positive for tuberculosis.

Mitral Inflow velocity

Mitral Inflow velocity of 85% patients was in normal limit, 12 % patients have diastolic dysfunction (Fig. 9).

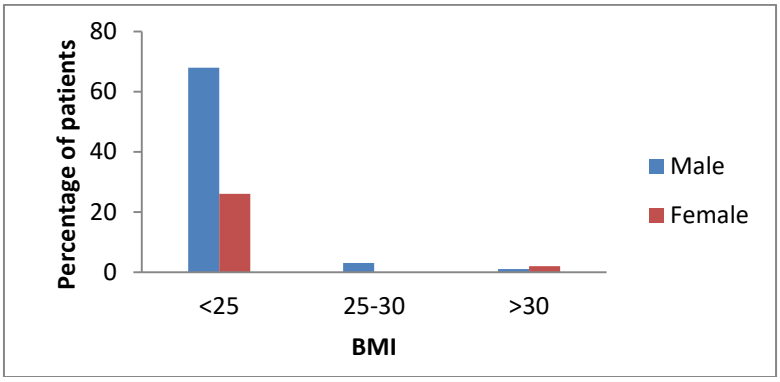


Fig. 7: Shows the BMI of the participants

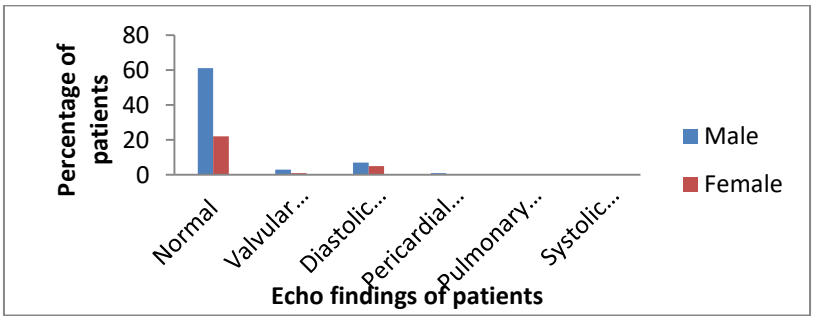
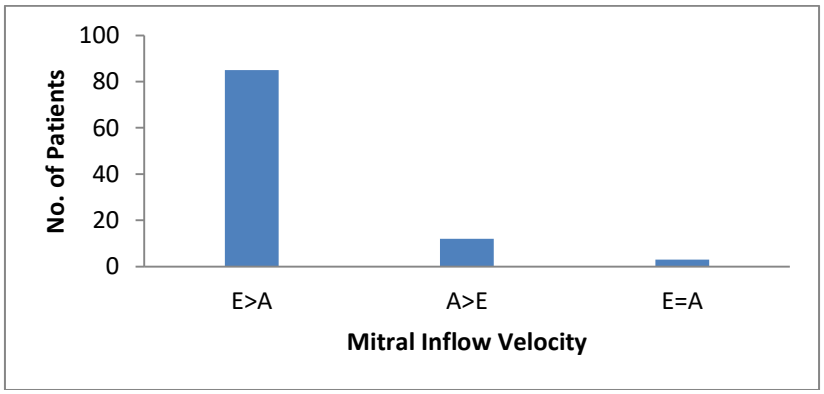


Fig. 8: Shows the Echo findings of the participants



E=Early peak velocity A=Late peak velocity

Fig. 9: Shows the Mitral velocity of participants

ECG findings according to clinical staging of patients

Maximum patients participated in the study belonged to stage 1 and finding are within normal limit. Comparisons of various parameters of ECG in various stages were found to be statistically insignificant (Table 1).

Cardiac parameters on duration of ART and non ART

Comparison of cardiac parameters on duration of ART and non ART were found to be statistically insignificant (p value>0.05) (Table 2).

Cardiac parameters according to CD4 count

Comparison of cardiac parameters according to CD4 count (<200 and >200) were found to be statistically insignificant (p value>0.05) (Table 3).

Cardiac parameters of patients on ART and non ART

Comparison of cardiac parameters of patients on ART and non ART (p value>0.05) (Table 4).

Table 1: ECG findings according to clinical staging of patients

ECG (Mean)	Stage 1 (n=85)	Stage 2 (n=4)	Stage 3 (n=11)
Heart Rate	89.6±17.9 / bpm	88.0±16.8	94.54±23.4
PR Interval	130.35±15.6 sec	135±19.1	129.09±16.4
QRS Duration	77.41±20.18 sec	73.33±11.51	81.81±20.8

Table 2: Comparison of various cardiac parameters on duration of ART and non ART

Patients	PR Interval	QRS duration	QTc Interval	LVID	AO	LA
On ART<6 months (n=36)	131.1±16.8	80±20	294.0±43.8	3.96±.78	2.17±0.49	2.82±0.54
On ART>6 months (n=10)	130±16.9	84±24.5	263.2±53.5	4.32±0.57	2.09±0.51	2.59±0.57

Table 3: Comparison of various cardiac parameters according to CD4 count

Patients	PR Interval	QRS duration	QTc Interval	LVID	AO	LA
<200 mean (n=38)	127.3±13.4	77.8±19.6	281.3±42.2	3.99±.69	2.05±0.45	2.82±0.65
>200 (n=52)	132.6±16.8	73.3±11.5	290.9±41.6	4.02±0.68	2.08±0.48	2.69±0.9

Table 4: Comparison of various cardiac parameters of patients on ART and non ART

Patients	PR Interval	QRS duration	QTc Interval	LVID	AO	LA
On ART (n=46)	130.8±16.7	80.8±20.8	287.3±47.3	4.04±.75	2.15±0.49	2.77±0.55
Non ART (n=54)	130±14.9	75.1±19.0	285.8±39.3	3.91±0.70	2.00±0.40	2.74±0.68

DISCUSSION

Variety of cardiac abnormalities has been described in HIV/AIDS patients. These includes cardiac pathology related to opportunistic infections that include bacterial, fungal, protozoan pathogens and viruses like Cytomegalo virus coxsackie virus and tumors like Kaposi's sarcoma and non- Hodgkin's lymphoma or due to HIV itself.

The most common cardiovascular disorders in HIV infected patients are pericarditis, pulmonary vascular disease and pulmonary hypertension, valvular heart disease, myocarditis, cardiomyopathy and an increased incidence of coronary artery disease [7]. There is also an increased incidence of ECG abnormalities in patients with HIV [8, 9]. The ECG abnormalities described are QTc prolongation, ectopic beats, sinus tachycardia, ventricular tachycardia, mitral valve prolapse, myocarditis etc. [10, 11]. Cardiac abnormalities could also be due to adverse effects of HAART.

The present study was done in 100 HIV infected patients attending ART centre, department of medicine, BRD medical college, Gorakhpur from May 2009 to October 2010. A detailed clinical history and examination, ECG and 2D echocardiography was done in all patients. The age range of HIV seropositive individuals who participated in this study (100 cases) was 10-65 years with maximum incidence in 4th decade (40%). With predominance of males (72%).

Majority of the patients (61%) were diagnosed as having seropositive status for the last 6 months, only 22% were known seropositive for more than 6 months but less than a year, 15% were known positive for upto 2 year and only 2% were diagnosed for more than 2 years.

In our study group 85% were in stage-1, 4% were in stage –II and 11% were in stage-III. Patients with stage-IV disease are not included. Thirty seven percent patients were having CD4 count in range of 50-100, 36%, 200-500, 14%, ≥ 500 had only 3% patients were having CD4 count 50 or less. Forty five percent

patients were on antiretroviral therapy at the time of inclusion, most of them (36%) were on ART since last 6 months, 5% were on ART for more than 6 months but less than a year and 5% were on ART since more than a year. In the study group 94% of the patients had BMI < 25, 3 % in between 25-30 and 3% had > 30.

Majority of the patients did not have any symptoms related to cardiac disorder. Only six patients had complaints of either dyspnea on exertion or chest pain. None of the patients had any abnormality on clinical examination. The chest pain in these patients was not angina in nature nor was the dyspnea attributable to any cardiac cause. No ECG or Echocardiographic abnormality was found in these patients.

All the patients had sinus rhythm, 12% of patients had sinus tachycardia due to high body temperature. In the study, all patients had normal P-R interval i.e. 120-200 msec. The mean PR interval of the patients was 130.4 ± 15.6 msec. The QRS duration of all patients was within normal limit i.e. < 120 msec. The mean QRS duration of the patients was 77.8± 20.7 msec. Corrected QT interval of all patients was within normal range i.e. < 440 msec. The mean QTC interval of the patients was 286.5± 54.3 msec. A study done by S. Lubega et al. the prevalence of sinus tachycardia among children with AIDS related complex (ARC-21.2%) and AIDS (33.3%) was significantly higher than that of children with symptomatic HIV disease (3.1%) even after adjusting for hemoglobin concentration and fever in a multivariate analysis. The autonomic imbalance and neuropathy, which are present in early HIV infection and progress with worsening HIV disease[9],are possible explanations of the sinus tachycardia. Other ECG abnormalities were rare and symptomatic .We tried to correlate the various parameter of ECG with duration of illness, CD4 count and the ART status of patient but no positive correlation was found.

A study done by Gianotti *et al*. [12] to compare various findings of ECG in HIV patients under treatment with Atazanavir, has reported that the QRS interval of 56 out of 75 (74.7%) HIV-infected, drug experienced patients (66.7% men) increased during treatment with boosted or unboosted Atazanavir by a median 5 ms (interquartile range 0-9; P< 0.0001). The PR and the QTc intervals did not change significantly.

Other studies have shown that QTc interval is increased in HIV/AIDS patients on ART [13].

In the study, we did not find any ECG abnormality. All of the patients in the study were on therapy with NRTI+ NNRTI combination without addition of PI according to national guidelines on ART. Majority of the patients who were under therapy had duration of therapy less than six months.

No patient in the study had HCV co-infection.HCV has been found to be commonly associated with HIV infection, in a study of the 2800 patients who have undergone HCV testing at the ART centre, only three patients have been found to be HCV positive (.107%). Our cohort of 100 patients did not include these three patients but the analysis of ECG of these three patients did not show any increase in QTc interval.

Pericardial effusion was detected in one patient only while literature material mentioned it as common cardiac abnormality and pericarditis common cardiac abnormalities found in HIV/AIDS autopsy studies. Pericardial effusion was found in upto 38 percent of patients was supposed to be in association with generalized fluid retention and advanced disease [14].

Echocardiographic studies have detected a pericardial effusion in approximately 20% (range 10-40%) of these patients, and the effusion was large in 4% [15].

Pericarditis has also been reported as the first manifestation of AIDs [16]. In the study 11 patients had active pulmonary tuberculosis or past history of TB and only one out of these patients had mild pericardial effusion. This is in contrast to the previously reported literature. We cannot explain the discrepancy but probably it may be due to a lesser number of patients with very low CD4 counts and exclusion of stage 4 patients.

In the study group, 12% patients had diastolic dysfunction; the remaining 88% patients had no echocardiographic abnormalities.

Reinsch N *et al*. [17] reported that the prevalence of diastolic dysfunction in HIV infected patients was 48%. Patients with diastolic dysfunction were characterized by older age, higher body mass index, arterial hypertension, dyslipidaemia, and diabetes mellitus. Diabetes mellitus and arterial hypertension were found to be associated with approximately four times the risk for diastolic dysfunction in patients with HIV.

In current study group patients did not have diabetes or hypertension hence a relatively low prevalence of diastolic dysfunction. We tried to correlate the prevalence of diastolic dysfunction with various parameters of ECG, mean CD4 count, mean BMI, mean systolic BP but no positive correlation was found. Although cardiac abnormalities have been described in HIV/AIDS in the literature but in our study we did not find any correlation between HIV and occurrence of cardiac disease and ECG abnormalities. The only abnormality was found were diastolic dysfunction in echocardiography but we cannot

attribute it to HIV related cardiac disease. Moreover these patients were asymptomatic and hence it is probably of no clinical importance. Thus our observations show that practically the incidence of overt heart disease in this study is nil.

Early studies have reported a higher prevalence of heart disease in HIV but most of the studies have been done in patients who were either not prescribed ART or were taking single or dual drug combination which have now been proven to be ineffective in the alteration of natural history of HIV. The threshold for starting ART has also been lowered in recent years. The low prevalence of heart disease may be due to early diagnosis of HIV and timely distribution of ART consisting of three drugs. Nonetheless the study has several shortcomings like most of the patients were younger and had no associated hypertension, diabetes or known coronary artery disease. Disease duration was lesser than 2 year in patients. It is likely that the cardiac problems might appear with increased duration of HIV/AIDS disease. National guidelines recommend the use of NRTI+ NNRTI combination as first line therapy and reserve PIs only for resistant cases. PI use is associated more often with Dyslipidemia and subsequent CAD.

CONCLUSION

HIV/AIDs has maximum incidence in 4th decade and seropositivity is more in males. Most common rhythm abnormalities had sinus tachycardia due to presence of fever. No correlation of ECG has been found with duration of illness, CD4 count and ART status of patients. In Echocardiographic examination only 12% patients had diastolic dysfunction, the remaining have no Echocardiographic abnormalities. Found no correlation of diastolic dysfunction with various parameters of ECG, mean CD4 count, mean BMI, mean age and mean systolic BP. The current study did not find any incidence of overt heart disease probably due to early stages of disease and no use of protease inhibitor (PI) in the patients.

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