Prevalence and patterns of cardiac disorders among adults attending antiretroviral follow up clinic at Jimma University Specialized Hospital, Jimma, Southwest Ethiopia

by

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Abstract

Background: Cardiac diseases are among common complications of HIV infection. The commonly encountered forms of heart diseases among HIV-infected individuals include dilated cardiomyopathy(DCM), coronary artery diseases(CAD), pericardial effusion, pulmonary hypertension, and left ventricular diastolic and systolic dysfunctions. The magnitude of the problem had been reported from other countriesbut there is no study that evaluated the prevalence and patterns of HIV-associated cardiac disorders in Ethiopia. This study was conducted to determine the prevalence, patterns and factors that are associated with cardiac diseases among adults with HIV/AIDS attending antiretroviral therapy (ART) follow up clinic.

Materials and Methods: A cross sectional hospital based study was conducted on 280 HIV-infected sampled adults attending antiretroviral follow up clinic at Jimma University Specialized Hospital from September 16, 2012 -July15, 2013. Structured questionnaire was used to retrieve information on socio-demographic characteristics of participants, symptoms of heart failure, duration since the participants knew their HIV sero-status and CD4+ counts. A detailed transthoracic Echocardiography was performed for all the participants. The data were edited, entered into, cleaned and analyzed using SPSS for windows version 16 of the computer software. Independent variables were assessed for association with the cardiovascular disease using bivariate and multivariate logistic regression analyses to generate odds ratios. A P value of less than 0.05 was used to define statistical significant.

Results: A total 280 participants included in the study; 185(66.1%) were females and 173(64.7%) were on ART. The mean (±sd) age of the participants was 33.62±8.29 years and the mean CD4 count was385.57±237.44. Cardiac abnormalities were found among 119 (42.1%) of individuals; the most common forms being diastolic dysfunction and left ventricular hypertrophy (LVH), each accounting for 8.9%; while DCM was found among 5.4% of the cases. DCM was significantly associated with lower CD4 counts ($p<0.002$), not starting on ART ($p<0.05$) and lower Body mass index (BMI) ($p<0.05$). Pericardial effusion was found among 2.5% of the individuals and was significantly associated with ART status ($p<0.05$).

Conclusion:-The study came up with high prevalence of cardiac abnormalities. The prevalence of DCM was found to be significantly higher among patients with low CD4 counts, poor nutritional status and among those who did not start ART

Acknowledgments

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Abbreviations

AIDS – Acquired immunodeficiency syndrome

ART- Antiretroviral therapy

CAD- Coronary Artery Disease

cART- Combination ART

CD4- Cluster differentiation

CRHD- Chronic rheumatic heart disease

DCM- Dilated Cardiomyopathy

ECHO- Echocardiography

EF – Ejection fraction

HAART- Highly Active Antiretroviral Therapy

HCM- Hyperthrophic cardiomyopathy

HIV- Human Immune deficiency Virus

HRPH-HIV related pulmonary hypertension

IVRT- isovolumic ventricular relaxation time

IVSd- interventricular septum in diastole

IVSs-interventricular septum in systole

JUSH– Jimma University Specialized Hospital

LAD- Left atrial diameter

LVH- left ventricular hypertrophy

NNRTI- Non nucleoside reverse transcriptase

NRTI- nucleoside reverse transcriptase inhibitors

OI- Opportunistic Infections

PH-pulmonary hypertension

PI- protease inhibitors

VSD- Ventricular septal defect

WHO – world Health Organization

CHAPTER ONE

1.1 Introduction

HIV is the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS). It is a retrovirus that results in progressive destruction of the immune system, especially CD4+T-lymphocytes (1). Since the original description in 1981 of unusual cluster of cases of PCP (Pneumocystis Carinii pneumonia) and Kaposi sarcoma in previously healthy homosexual males, substantial advances in our understanding of AIDS have been achieved. The identification of a cytopathic retrovirus in 1983 and development of a diagnostic serologic test for HIV-1 in 1985 have served as the basis for developing improvement in diagnosis. It is transmitted via unprotected sexual intercourse, exposure to contaminated blood, or perinatally (2).

Although HIV predominantly affects the immune system, no system is spared in the human body including the cardiovascular system. The association of HIV infection with cardiac pathology is recognized in the early stages of the HIV epidemic. The pathogenesis of cardiovascular diseases in HIV-infected patients involves effects directly related to HIV, autoimmunity (anti-alpha myosin), opportunistic infections and malignancies, nutritional deficiencies,dyslipidemias and direct toxic effect of ART drugs (3).

WHO classifies HIV-infected patients based clinical signs and symptoms. Around two-third of patients develop “flue-like” symptoms in the first three weeks following the infection (Primary HIV syndrome). After this phase, the virus goes to clinical latency (but not viral latency) in the majority of adult patients. Patients in the first stage present with persistent generalized lymphadenopathy or otherwise are asymptomatic. The occurrence of minor muco-cutaneous manifestations marks the onset of WHO clinical stage II. More deep infections and some recurrent infections will put the patient to clinical stage III. Presence of AIDS definining OIs and/or malignancies along with some diseases presumed to be directly caused by the virus (e.g., HIV-associated cardiomyopathy) are called Stage IV conditions. Patients with CD4+ cell count <200/mm3 are labeled as AIDS regardless of their clinical stage (4).

Standard laboratory diagnosis rests on antibody tests to the virus as well as detection of the viral antigen in the blood PCR, P24 Agantigen. Whereas, the treatment relies on an arsenal of powerful antiretroviral drugs to reduce the viral load which includes :Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)/Non –Nucleoside reverse transcriptase inhibitors (NNRTIs)/Protease inhibitors (PIs)/Integerase inhibitors/Fusion Inhibitors/Entry Inhibitors(1)

1.2. Statement of the problem

HIV infection has affected more than 33million persons and led to more than 2 million annual mortality globally. By far the worst-affected region, Sub-Saharan Africa is now home to 29.4million people living with HIV/AIDS. Sub-Saharan Africa is also where access to HAART is limited to less than 20% of those who need it (5).

The first case of HIV in Ethiopia was reported in 1984. Since then, HIV/AIDS has become a major public health concern, leading the Government of Ethiopia to declare a public health emergency in 2002. In 2011, adult HIV/AIDS prevalence in Ethiopia is estimated at 1.5% (6) . Approximately 1.2million of the country's population were living with HIV/AIDS in 2010.

Ethiopia represents a stable, low-level, generalized epidemic with marked regional variations driven by most-at-risk populations (MARPs).

HIV/AIDS prevalence is higher among women (1.9 percent) than men (1.0 percent). In urban areas, women are more likely to be infected than men (5.2 percent and 2.9 percent, respectively). People living in periurban and small market towns, as well as young women, are the most at risk segments of the population(6) . The burden on socio-economic and health service of HIV infection can never be undermined.

As the CD4 declines below 200cells/mm3, these populations are at high risk of developing OIs, malignancies. One of the systems involved with these conditions is the cardiovascular system. In fact, cardiovascular diseases are becoming the common causes of mortality in HIV-infected patients (7).

Studies done in western countries indicate more than half of HIV-infected patients had cardiac abnormalities at autopsy and around one third had echocardiographic abnormalities. Most of

these studies were done before ART era and have shown high prevalence of dilated cardiomyopathy, pericardial diseases and asymptomatic Left Ventricular diastolic dysfunction (8).

WHO defines HIV-associated cardiomyopathy as Stage IV disease which is an indication to start ART regardless of CD4+ count. HIV by itself along with OIs is said to be the most common cause of Dilated Cardiomyopathy(9,10).

Most of the cases of pericardial effusion in HIV-infected patients in Africa are due to tuberculosis, while it is idiopathic in the high income countries. The occurrence of pericardial effusion in HIV-infected patients is an independent predictor of mortality and poor prognosis (11-12).

Literatures show that most cardiac diseases in HIV-infected patients are asymptomatic and tend to present clinically when they are advanced. The response to treatment of cardiac diseases varies when they are detected late implying that earlier echocardiographic screening will be the most effective approach to such patients (5,11,13).

Though the prevalence of HIV infection is still high in Ethiopia and that there is ample wealth of information on cardiac manifestation in HIV-infected patients in the Western countries, data on the cardiovascular consequences of HIV/AIDS is scarce in Ethiopia.

This research addresses the knowledge gap seen on cardiac diseases among HIV infected patients in the Southwestern Ethiopia.The study came up with evidence on the prevalence of heart diseases in HIV-infected patients and the importance of the timely diagnosis of cardiovascular diseases to prevent complications.

CHAPTER TWO

2.1 Literature Review

Most of the studies that reported the association of HIV with cardiac abnormalities have been carried out mainly in Europe and North America (5). These studies indicated that HIV infection is commonly associated with cardiac abnormalities, which are mainly characterized by cardiomyopathy and pericardial disease, and increase in frequency as the HIV disease progresses. Other cardiac conditions that have been reported in association with HIV infection are pulmonary hypertension, coronary artery disease and endocarditis(5).

According to a study in India, up to 38% of ART-naïve HIV-infected patients have cardiac abnormalities (8). In Africa, as elsewhere in the world, echocardiographic abnormalities are consistently more frequent among HIV infected groups than in HIV-negative controls and cardiac abnormalities are found in about half of acutely ill HIV-positive patients who require hospitalization. High incidence of cardiac abnormality has been reported from follow up studies (11). A prospective study of 157 HIV-positive patients showed that about half of the patients developed a cardiac abnormality over a 7-years period. The commonest cardiac abnormalities that were reported in Africa are cardiomyopathy and pericardial disease, which is a similar to the pattern to the developed countries. Other cardiac abnormalities that were reported are left ventricular diastolic dysfunction, left ventricular hypertrophy, pulmonary hypertension and autonomic dysfunction.

In a prospective, cross-sectional cohort study done in University Hospital in German among 803 HIV-infected adults, echocardiographic measurements showed a structural dilatation of Left Ventricle in 10.1%, IVS and posterior LV wall thickness increased in 18.0% and 11.1% of the patients, respectively. Prevalence of systolic and diastolic dysfunction was observed in 34.3% and 48% patients, respectively. The mean LVEF was 57.5±7.3% and 65.7% of all measurements were within normal range. However, a large proportion of almost one third study participants (32%) exhibited a mild reduction of LVEF(45-54%). Moderate to severe impairment was seen in 2.3% of HIV-infected patients.Furthermore,13.5% of HIV-infected subjects exhibited a regional wall motion abnormality in the form of hypokinesis, akinesis and dyskinetic segments(79.6%, 13.9%, and 6.5%, respectively) (13).

Indian study in showed diastolic dysfunction to be the most common finding (18%) followed by pericardial effusion (13%) and systolic dysfunction (7%). This study has also showed no significant association between diastolic dysfunction and CD4 count as well as systolic dysfunction and CD4 counts(8) .

Cardiomyopathy

Cross –sectional and retrospective studies suggest that cardiomyopathy is the leading cause of heart disease in Africa (14). While some patients had left ventricular dysfunction present with features of cardiac failure, the majority had ventricular dysfunction detected only by echocardiography, without any clinical suggestion of heart failure.

Cardiomyopathy is usually seen when the CD4 counts falls below 400cells/mL. There are multiple factors responsible for dilated cardiomyopathy. However, studies based on myocardial biopsy have confirmed its link with co-infecting viral infections. Viruses demonstrated as co-infectors were: coxsackievirus group B , cytomegalovirus, and Epstein Barr virus, while other organisms implicated include Toxoplasma gondii , Histoplamacapsulatum, Cryptococcus neoformans, Aspergillus species , Candida and Mycobacterium aviumintercellulare. Patients may be asymptomatic however they can present with dyspnoea, paroxysmal nocturnal dyspnoea and ankle oedema(14).

In studies of asymptomatic patients with HIV infection, left ventricular systolic dysfunction is found less frequently. In a study of 49 asymptomatic patients, Longo-Mbenza*et al* found no evidence of systolic dysfunction, but a high frequency of diastolic dysfunction (86%) and left ventricular hypertrophy(47%). However, in other studies, the prevalence of dilated cardiomyopathy in non-hospitalized ambulant HIV-positive patients may have been as high as 28%, suggesting that Africans with HIV infection may be more susceptible to cardiomyopathy than their counterparts in the west, where the prevalence rates of 15% have been reported. The association of cardiomyopathy with more advanced immunosuppression and lower CD4 counts, which was found in African series, is consistent with international experience(5).

In one study in Cameron, patients with dilated cardiomyopathy had a mean CD4 count of 142/mm3 compared with 231/mm3 for those without dilated cardiomyopathy. There was no significant difference in the body mass index of patients with and without dilated cardiomyopathy. Dilated cardiomyopathy occurred in six (31.58%) of the patients with a CD4 cell count <100 /mm3 and two (6.06%) in those with absolute CD4 counts >100/mm3 (15).
Studies in Sub Saharan Africa among HIV-infected individuals also showed a lower BMI is associated with dilated cardiomyopathy (18).

Pericardial disease

Pericardial effusion is recognized as one of the early presenting features of HIV in Sub-Saharan Africa (8). It is a fairly common disease in HIV infected patients. Heidenreich et al, found an annual incidence of 11 per cent of pericardial effusion in asymptomatic patients with AIDS (8). Further, even with matched CD4 counts, the mortality was twice as much with pericardial effusion. Various OIs have been documented to cause pericarditis and pericardial effusions comprising *Mycobacterium tubercu-losis*and lately documentation of multidrug resistant strains ,*Mycobacterium avium-intracellulareStreptoccocuspneumoniaeStaphyloccusaureus*. Other pathogens reported include *Nocardia*,*Crypto-coccusneoformansAspergillus species* , cy-tomegalovirus and herpes simplex . In sub-Saharan Africa and other endemic areas of the developing world, *Mycobacterium tuberculosis* is the main cause of pericar-dial diseases reaching 86-100 per cent. There are numerous patterns of presentation which comprise asymptomatic pericardial effusion, pericarditis, cardiac tamponade and constrictive pericarditis. However, presentation of tamponade requiring intervention is rare but may occur. It is suggested that HIV should be considered as a differential if a young patient presents with unexplained pericardial effusion or cardiac tamponade. Echocardiography remains the most important diagnostic tool in pericarditis with effusion (14).

The prevalence of pericardial effusion in asymptomatic HIV-infected persons is estimated at 22%. Clinically overt pericardial effusion in HIV may be related to OIs or to malignancy, but most often a clear etiology is not found in people living in wealthy countries (5).

In retrospective review of data of patients admitted with pericardial disease in one hospital in Nigeria (68 patients), out of 42 HIV-infected patients 47.6% had pericardial effusion, 28.6% had constrictive pericarditis, 14.3% had effusive-constrictive pericarditis, 9.5% had pericarditis. HIV-positive patients were three times more likely to be male and HIV-negative patients twice as likely (21).

Studies in Iran showed prevalence of pericardial effusion in 5.22% and more commonly in patients with mean CD4 count <300 per milliliter (16).

Statistically significant correlation between CD4 count and pericardial effusion was found in 13% of ART-naïve HIV-infected patients in India. (8)

Pulmonary arterial hypertension

PH is defined as a mean pulmonary artery pressure (mPAP)>25mmHg at rest with a mean capillary wedge pressure ≤15mmHg or an mPAP with exercise >30mmHg (9).

Causative factors implicated include lung infections, venous thromboembolism and left ventriculardysfunction . Animal model had shown that immune response to *Pneumocystis jirovicei*may be disturbed and prolonged with potential development of chronic disorder like pulmonary hypertension. This novel finding should be evaluated by designing prospective, cohort study on patients who survive pneumocystis pneumonia in humans (14).

In recent years, much more insight is given to the pathogenetic role of HIV and to the clinical manifestations of HIV-related pulmonary hypertension (HRPH) that currently represents one of the most severe events during HIV disease (17).

HIV-related PH is mostly seen in young and male patients with major symptom being progressive shortness of breath, followed by non-productive cough, fatigue, syncope or near syncope and chest pain. Diagnostic tools employed include chest x-ray, electrocardiography and echocardiography, however, cardiac catheterization is mandatory to definitively diagnose the disease and exclude any underlying cardiac shunt. Modalities of treatment include individualized assessment for anticoagulation, vasodilator agents as tolerated, diuretics, oxygen as required and endothelin antagonists. A review of the HIV-PAH cases reported in the literature over a twenty-

two year period showed a more favorable outcome in patients treated with PAH-specific therapy than in those treated with antiretroviral therapy only. Nevertheless, HAART could delay the development of PAH in HIV-infected patients and is recommended independent of the CD4 counts (14).

In one prospective study ,the frequency of pulmonary hypertension (PH) in the HIV population was estimated to be 0.5%, which was greater than that observed in the general population.
More recently, in the Registry of PH of Latium, an Italian region with an estimated number of 5000 HIV-infected patients, 60 patients were diagnosed as having PH after undergoing a diagnostic algorithm for clinical suspicion of PH. Nineteen out of 60 patients (0.4%) were diagnosed as having HRPH. Interestingly, 4 of them were found to have PH during an echocardiography screening performed in 510 consecutive asymptomatic HIV-infected patients, suggesting that HRPH could be more frequent than expected and probably latent for many years.
HRPH occurs in early and late stages of HIV infection and does not seem to be related to the degree of immune deficiency. No specific risk factor for HIV-infection is associated with this disease (17). The reported prevalence of HRPH in Zimbabwe, Iran and India was 0.6%-5%, 20% and 12.68%, respectively (16).

Coronary artery disease

Premature atherosclerosis was described in HIV-infected patients shortly after introduction of HAART.In contrast to case reports and autopsy trials analyzing the influence of antiretroviral therapy on myocardial infarction rate, the results of clinical observations appear to be inconsistent.

At present, two major clinical trials have been published, and in one of these trials, a retrospective analysis of 36,500 patients, no rise in cardiac or cardiovascular
events were detected. Nevertheless, in the second trial, the most extensive prospective study to date, including more than 23,000 patients, a 26 % increase in the incidence of myocardial infarction was found with each year of antiretroviral therapy (19).

In patients with HIV cardiovascular disease may be associated with classic risk factors , such as smoking, a direct consequence of HIV infection, or a complication of cART. Rate of CV events was lower in patients on cARTthan ART naïve patients. In one study, baseline CD4 <500cells/mm3 was independent risk factor for cardiovascular disease.(1)

In the Kaiser Permanente database, HIVpositive patients had a significantly higher rate of hospitalizations for coronary heart disease than did people who were not infected. The mechanisms for HIV related CAD includes HIV-related dylipedemia and inflammation. ART is associated with a small but significant risk of CAD but interruption of ART was associated with increased CV events. So the benefit of ART far exceeds its cardiovascular risks.(20)

2.2. Significance of the Study

To our knowledge, this will be the first echocardiographic study to be conducted in the country, to quantify the magnitude of cardiac disease, define its pattern, and assess for potentially associated factors among our local cohort of HIV infected adults on follow up.

Such information will be critical for the development of locally sensitive guidelines, research programs and policies both for diagnosis, prevention and care of cardiac diseases among people living with HIV/AIDS.

This study will be a very good entry point for cardiovascular research, diagnosis, care and overall understanding of cardiac problems in our people living with HIV/AIDS. It will indicate the prevalence, patterns and associated factors of cardiovascular diseases among these study participants and pinpoint where we are in terms of our current practice of diagnosis, care and prevention cardiac diseases and how we should prepare our strategy for better intervention.

The findings will be published in peer reviewed journals for a wider dissemination of the impacts to institutions with similar settings.

CHAPTER THREE – Objectives

3.1. General objective

- To determine the prevalence and patterns of cardiac diseases among HIV/AIDS people on follow up at JUSH ART clinic.

3.2. Specific objectives

- Determine the prevalence of cardiac disease among HIV infected people on follow up at JUSH ART clinic from sept16/2012-July15/ 2013
- Describe the pattern of cardiac diseases among HIV infected people on follow up at JUSH ART clinic from sept16/2012-July15/ 2013
- Identify factors associated with cardiac diseases among HIV infected people on follow up at JUSH ART clinic from sept16/2012-July15/ 2013

CHAPTER FOUR - Methods and Participants:

4.1 Study Area and period

The study was conducted in Jimma University Hospital ART clinic, Jimma University, Jimma Zone from Sept 16/2012 to July15/2013. Jimma zone comprises Jimma town and its nearby woredas. It is located in South West of Ethiopia, Oromia regional state, with estimated population of 2,486,155. The town is located 350 Kilometers from the capital, Addis Ababa.

Jimma University Specialized Hospital (JUSH) which is one of teaching hospitals in the country. JU runs both undergraduate and graduate programmes in several disciplines. The hospital gives health service at inpatient and outpatient level as a referral Hospital for 15 million population in the south west of the country. It has one ART clinic. Total people enrolled in ART clinic are 6000 with ~70% of these taking ART. There are around 4000 HIV-infected people with regular follow up in the clinic currently, of these45% are male and 55% of them are females. At outpatient level, chronic HIV care and service is delivered for these patients at ART clinic by trained nurses, medical interns, residents, and specialists on daily bases.

4.2 Study design

A cross sectional hospital based survey was used.

4.3 Study subjects

4.3.1 Source population

All adult (above 18 years old) HIV-infected patients who were attending the ART clinic of JUSH.

4.3.2 Study population

All HIV population (80% of the calculated sample size) who came to the clinic on the day of appointment were included in the study according to the inclusion and exclusion criteria.

4.4. Inclusion and Exclusion criteria

Each client who came to the clinic during study period was evaluated for eligibility included in the study. Those who fulfilled the criteria and those who gave informed consent to participate in the study were enrolled.

The Inclusion criteria were

1. Appropriate written informed consent.
2. All HIV-infected patients who attended ART clinic.

The exclusion criteria will be

1. Patients with known cardiovascular diseases, hypertension, Diabetes mellitus, Renal failure, Tuberculosis and cardio toxic drugs .These were identified clinically.

2.Clinicallyhemodynamically unstable patients will be excluded as there may be confounding effect with Echocardiography study

3. Children, i.e.,<18years

4.5 Sample size and Sampling technique

4.5.1 Sample size

The sample was calculated using a formula for estimation of single population proportion taking prevalence of cardiac diseases in HIV-infected patients in the ART clinic to be p=50% (prevalence not known) , margin of error 5%, and using 95% confidence level.

$n \geq Z\alpha/2\ p\ (1-p) / d^2$

P = 50% used as the expected prevalence of cardiac diseases in HIV people being unknown.

$Z\alpha/2$ = standard normal variable at 95% confidence level (1.96).

d= precision (tolerable margin of error)

n = $Z\alpha/2$ p(1-p)/w2 =(1.96)2x 0.5(1-0.5)/(.**05**)2 =384patients

Since the source population is less than 10,000, applying a formula for finite population correction the final sample size will be 350.

nf = n/{1+(n/N)}, where

nf is the final sample size

n=384

N=total number of HIV-infected patients follow up at the ART clinic which is 4000

nf = 384/1+384/3100= **350.**

Data were collected from 280 individuals (80%) of the sample size because it was not possible to recruit the 350 patients during the study period.

4.5.2 Sampling technique

Convenient sampling of the 280 HIV-infected participants was conducted. All participants with confirmed HIV infection and attending the follow up clinic during the study period, and who fulfilled the inclusion criteria, were included until 80% of the total sample size is reached.
Echocardiography interrogation was conducted using Portable Echocardiography machine for the participants who were included in the study at the clinic.

4.6 Data collection and Measurement

Data for this study were collected through patient interview using a structured questionnaire. A structured questionnaire containing sociodemographic characteristics and CD4+ count and WHO stage was used.

Echocardiography interrogation was performed with M-turbo Sonosite portable ultrasound machine, manufactured by WRIGHTWOODMEDICAL, INC, to generate variables of interest under study.

A trained Echo cardiographer measured the variables of interest after quality assessment. Participants were placed on left lateral supine position and examined in standard parasternal and apical views. Measurements were made in accordance with American Society of Echocardiography with some modifications. Normal chamber measurement values were defined according to current guidelines including the measurement of ejection fraction (EF) by quantitative biplane method on disk. Each patient underwent pulsed wave Doppler examination of mitral inflow before and after Valsalva maneuver and a pulmonary venous inflow and Doppler tissue imaging of the mitral annulus. One room was organized in the ART clinic of JUSH for performing the echocardiography on every follow up day.

4.7 Data collectors

A total of three personnel one medical resident, one trained echocardiographer and one nurse, who are working in JUSH, will be involved in the data collection using a questionnaire. The principal investigator will lead the overall activities during the data collection period.

4.8 Variables

The following variables will be measured:

4.8.1 Dependent variable

Cardiac disease/abnormality

4.8.2 Independent variables

Age

Sex

Occupation

Marital status

Income

Residence

Duration since diagnosis of HIV

CD4+ cell count

WHO clinical stage

Cardiac Symptoms

Body Mass index

4.9 Data analysis, processing, and Interpretation

The data was edited, entered into, cleaned and analyzed using SPSS for windows Version 16.0. Inter-group comparisons were performed with the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. The variables reported on the questionnaire were assessed for association with the prevalence and pattern of cardiac diseases. In a first step, each variable was evaluated independently in a bivariate analysis. In a next step, all variables associated with the pattern of cardiac diseases on the bivariate analyses with p values of less than 0.25 were entered into a multivariable logistic regression analyses. The variables were entered into the model using a forward stepwise procedure to determine variables that are independently associated with the pattern of cardiac disease. The results are presented with adjusted Odds ratio (AOR) and 95% confidence interval (CI). All tests will be two sided and statistical significance will be declared at P value less than 0.05.

4.10 Data quality assurance

To ensure data quality, pre-test was conducted on 10 patients; training was given to data collectors and supervisors on the data collection process. The collected data were checked for

completeness and consistency on the day of collection. Standards of procedures during echocardiography were also re checked by the principal investigator.

A total of three personnel one medical resident, one echocardiographer , and one nurse were trained for one day on the objective of the study, familiarized on each variable on the questionnaire and its implication. There was also demonstration and a practical session on interviewing and record reviewing. The participants were given appropriate manuals and guidelines during the training.

4.11 Ethical consideration

Ethical clearance was obtained from Ethical Review Committee of Jimma University. The willingness of the respondents and informed verbal consent was obtained from study participants before enrollment into the study.

Patient's confidentiality, equity of services and interests of patients were ensured during the study period. There were no risky procedures applied on patients. Assessment of clients was done using standard universal pre-requisitions of performing echocardiography and the abnormal results were attached to the patients card and proper management was rendered based on the study results.

4.12 Dissemination plan

After approval from Jimma University, the findings of the study will be disseminated to all relevant stakeholders through presentation and publication. Copies of the research will be given to Jimma University, Faculty of public health graduate program and the department of Internal Medicine.

4.13 Limitations of the study

This study was initially planned on ART naïve patients. But, because of slow recruitment of patients we redesigned our study to include those patients taking ART. This could have significant impact on the outcome.

4.14 Definition of terms

AIDS: CD4 <200/mm3 or occurrence of AIDS indicator OIs

BMI: body mass index (Kg/M^2), calculated from the weight of the patient in Kilograms and height in meters.

<18.5—low

18.5-24.9—Normal

>25—overweight

>30---obese

Children: people less than 18years old

Clinical latency : a condition in which the disease doesn't manifest for some time after infection.

Co receptors- are accessory receptors which is expressed on the surface of CD4+lymphocytes and macrophages.

Dilated cardiomyopathy (DCM): it is the condition in which the heart chambers(especially Left ventricle) is dilated and hypokinetic globally. It is a diagnosis by exclusion.

Diastolic dysfunction- E/A ratio below and above 1-2.

Hemodynamically unstable patients-are those patients in cardiorespiratory distress

Hypokinesis –left ventricular wall motion.

Illiterate— a person who can't read and write

Immune system- it is the body-guard which fights off foreign agents when introduced to the body.

Left ventricular hypertrophy (LVH)- LV wall thickness >11mm on average.

Literate – a person who can read and write correctly

Pericardial effusion- fluid collection in pericardial cavity greater than 5mm depth.

Globan LV Systolic dysfunction- Left ventricular ejection fraction(EF) <55%

Semi-literate-can read and write words and numbers, but cannot read and write sentences.

Virologic latency- a condition in which viral replication doesn't occur for some time.

CHAPTER FIVE - Results

5.1 Sociodemographic characteristics of the study participants

A total of 280 HIV infected individuals were evaluated for status of cardiac disorders. Nearly two-third 185(66.1%) were females. The age of the patients ranged from 18years to 60years with the mean age(SD) being 33.6±8.9. The majority of the study participants were married 146(52.1%) and house wife by occupation 58(20.1%).The patients were Predominantly ,233(83.2%) from Urban areas (Table 1).

Table 1.Socio-demographic characteristics of HIV-infected patients at JUSH ART clinic, Southwest Ethiopia,2013.

Socio-demographic variable(N=280)	Number (%)
Sex	
Male	95(33.9%)
Female	185(66.1%)
Age group	
18-30	124(44.3%)
31-40	112(40%)
41-50	34(12.1%)
51-60	10(3.6%)
Marital status	
Married	146(52.1%)
Single	44(15.7%)
Divorced	56(20.0%)
Widowed	34(5.0%)
Occupation	
Farmer	4(1.4%)
Merchant	25(8.9%)
Housewives	58(20.7%)
Employee	117(41.8%)
other	75(26.8%)
Annual Income (Birr/yr)	
<3000	n30%
3000-6000	n42%
>6000(%)	N28%
Literacy status	
Illiterate	N20.4%
Semi-literate	N52.9%
Literate	N26.8%

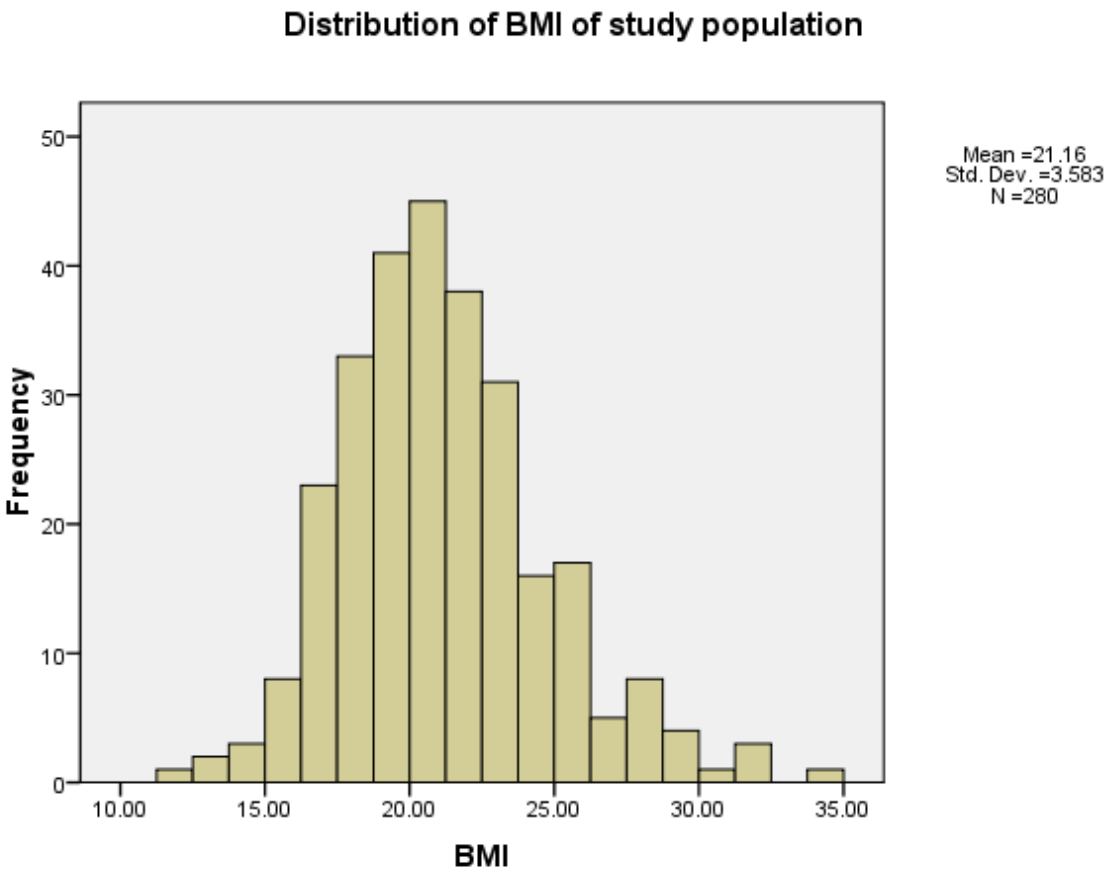

Fig 1. Distribution of BMI of HIV infected patients at ART clinic JUSH, South West Ethiopia,2013.

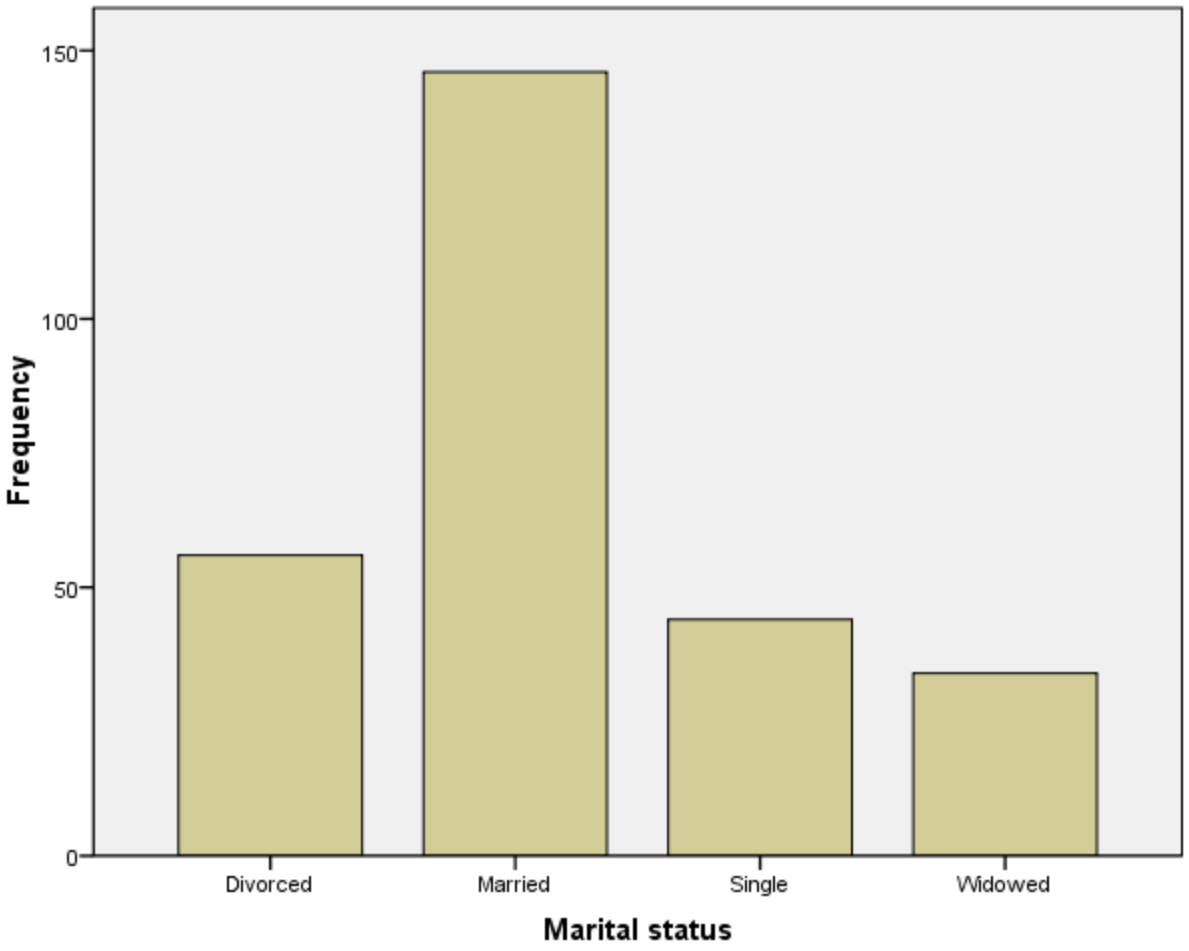

Fig.2. Marital status of HIV infected people at JUSH ART clinic, South West Ethiopia, 2013.

5.2 HIV disease status of the study participants

Most119(42.5%) of the study participants were diagnosed to have HIV infection before 3years and 173(61.9%)were on ART, and 64.74% were females. The mean (SD) CD4 count is 385.5±237.4 with the majority (52.9%) having CD4+T-cell count in the range of 200-499cells/mm3. About 43.2% were in WHO clinical stage of II and 37.9% reported shortness of breath (see table 2).

The mean duration since diagnosis of HIV is 3.31±2.5

Table 2. HIV/AIDS status and major symptoms related to cardiac disease of study population at JUSH ART clinic , South West Ethiopia, 2013.

HIV/AIDS Status(N=280)	Number(%)
Duration since diagnosis	
<6months	36(12.9%)
6month-2years	97(34.6%)
2year-3years	28(10%)
>3year	119(42.5%)
ART Status	
ART naïve	107
Female (%)	73(68.2%)
On ART	173
Female (%)	112(64.74%)
Total female(%)	185(66.1%)
Nadir CD4 category(cells/mm3)	
<200	63(22.5%)
200-499	148(52.9%)
>500	69(24.6%)
WHO stage	
I	121(43.2%)
II	93(33.2%)
III	52(18.6%)
IV	14(5.0%)
Cardiac symptoms*	
Shortness of breath	106(37.9%)
Palpitation	59(21.1%)
Body/leg swelling	37(13.2%)
Chest pain	65(23.2%)
Others	1(0.38%)

Percentages do not add up to 100% as there were cases with more than one symptom*.**

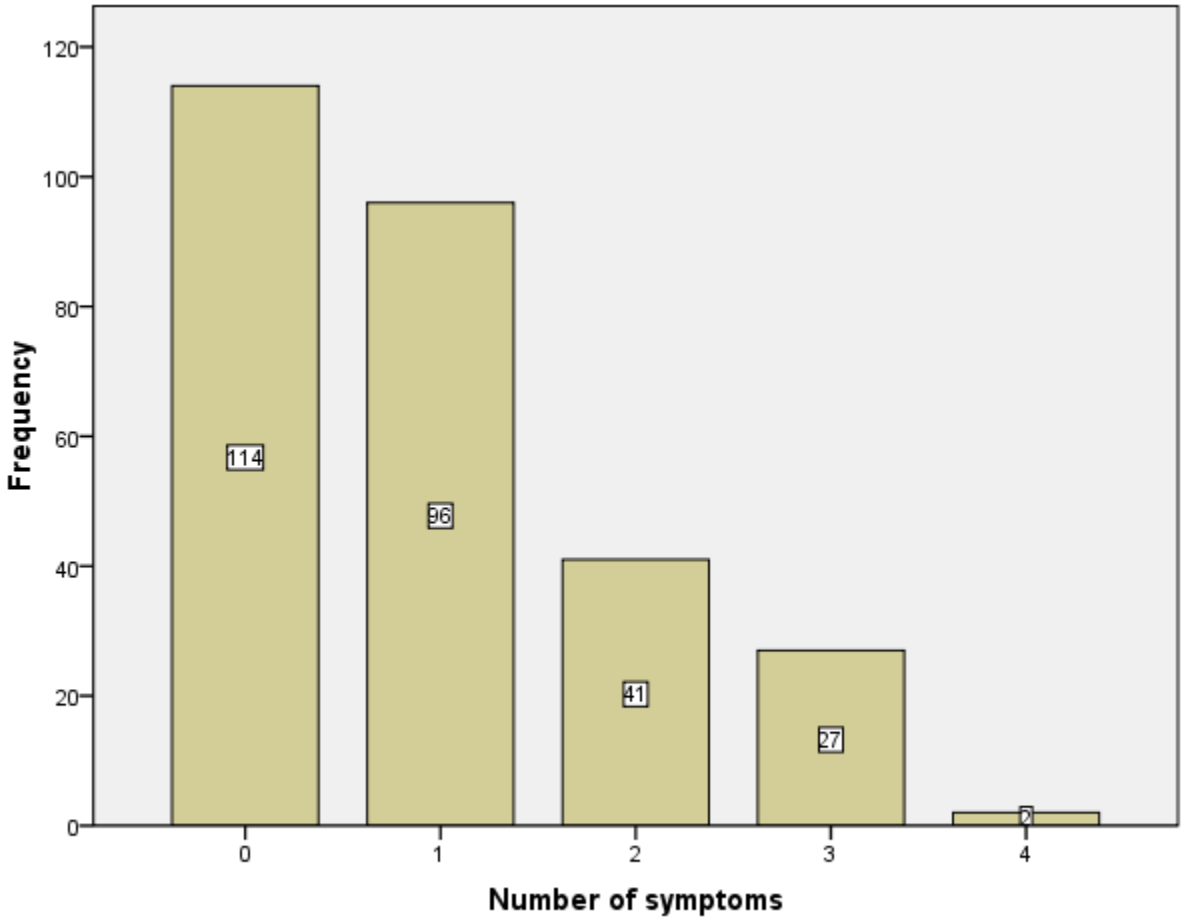

Fig 3. Frequency of cardiac symptoms of HIV infected participants at JUSH ART clinic , South West Ethiopia,2013

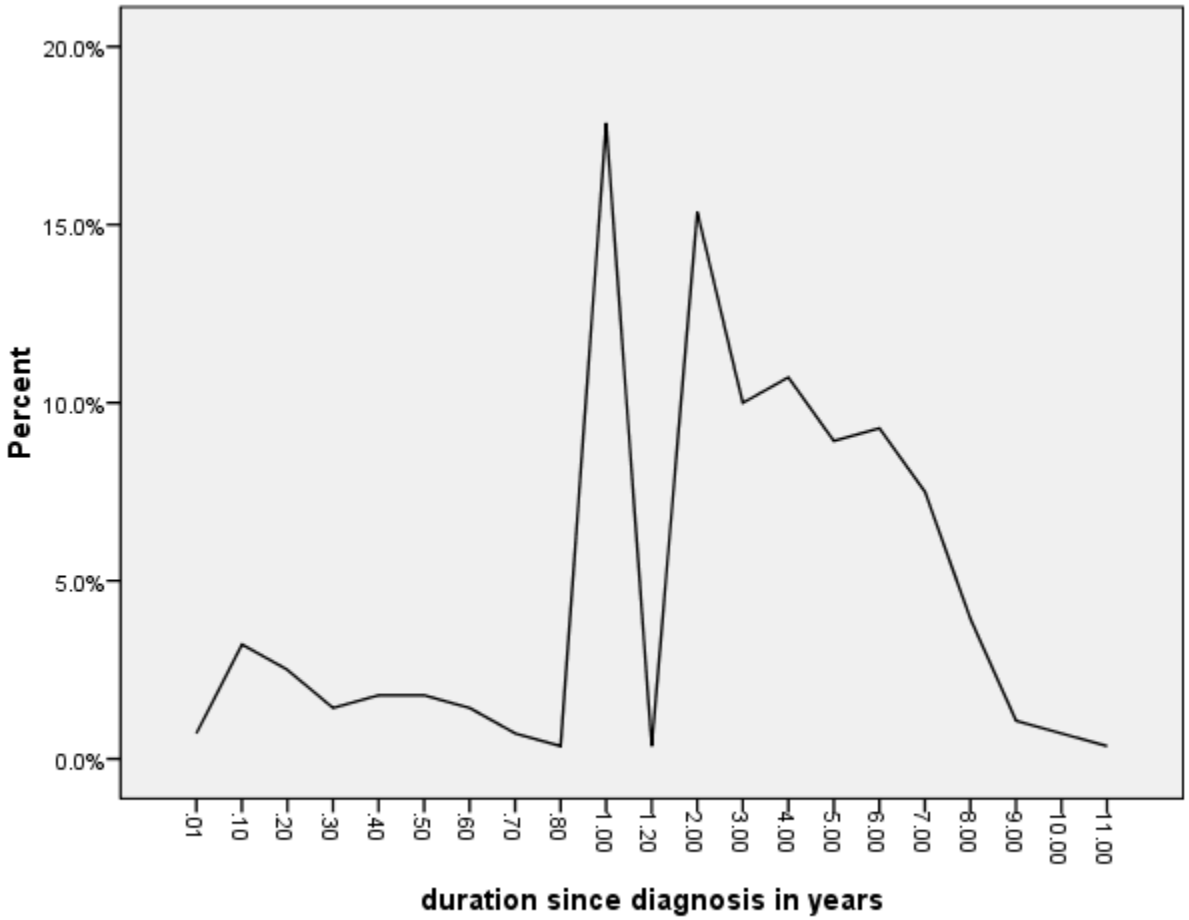

Fig4. Duration since diagnosis (in years) of HIV, in HIV infected individuals at JUSH ART clinic, South West Ethiopia,2013

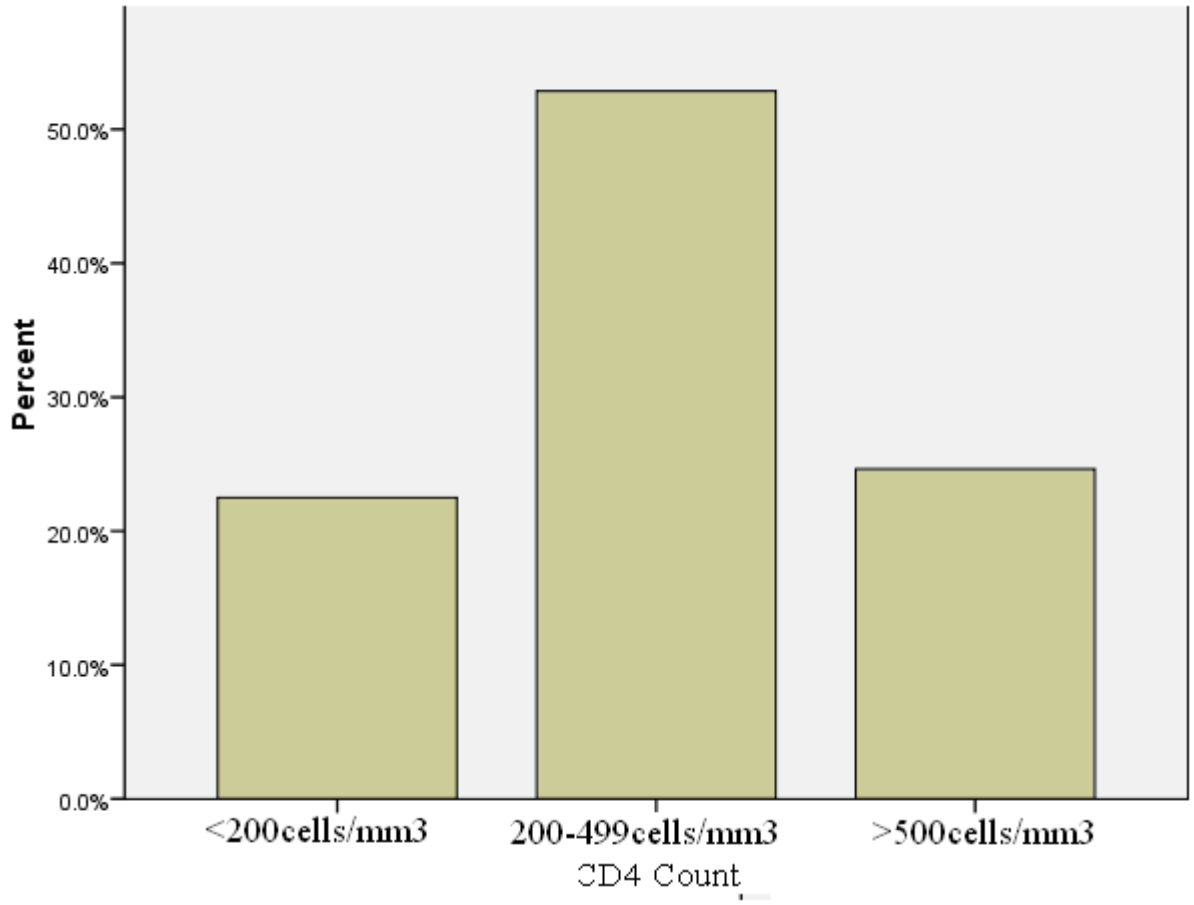

Fig 5. CD4 categories by percentage of HIV infected individuals at JUSH ART clinic, South West Ethiopia,2013

5.3 Clinical and echocardiographic characteristics of study participants

5.3.1 Clinical characteristics

Out of the total population 114(40.7%) had nosymptom, 96(34.3 %) had only one symptom, and 70(24.9%) had two or more symptoms. The most common symptom was shortness of breath 106(37.9%) followed by palpitation 59(21.1%).

5.3.2 Echocardiographic characteristics

Out of the total 280 individuals evaluated 42.1 %(118) had some form of Echocardiographic abnormality. The most common abnormalities were LVH and Ventricular diastolic dysfunction, each accounting 8.9 %(25) followed by systolic dysfunction 6.1% (17). Dilated cardiomyopathy, Coronary artery disease, pericardial effusion, and Pulmonary hypertension account for 5.4%(15), 3.9%(11),2.5%(7), ,and 1.4%(4), respectively

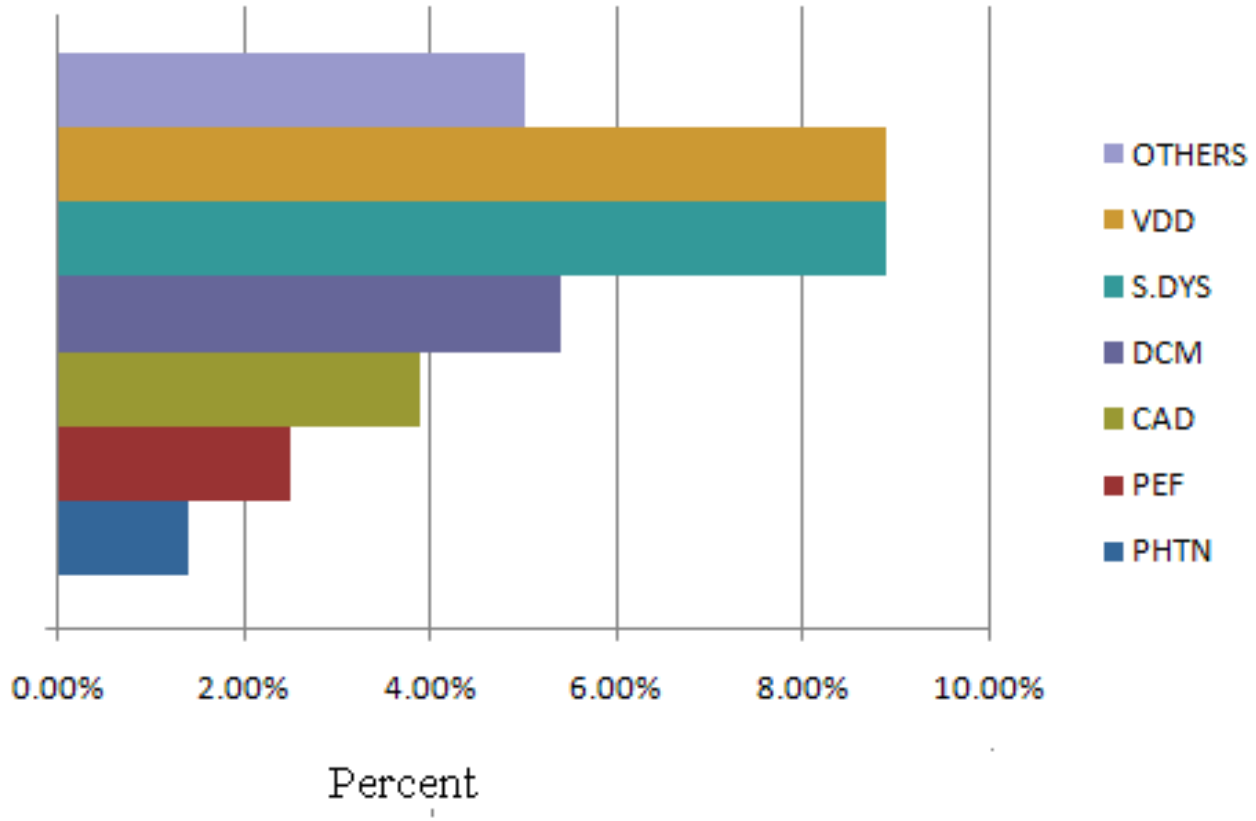

Fig .6 Cardiac abnormalities in HIV infected people at JUSH ART clinic, South West Ethiopia, 21013.

(CAD= Coronary artery disease, DCM=Dilated cardiomyopathy, PEF=pericardial effusion, PHTN= pulmonary hypertension,S.DYS=Systolic dysfunction,VDD= Ventricular diastolic dysfunction, Others=Chronic rheumatic heart disease, Ventricular septal defect, Hypertrophic cardiomyopathy)

Other findings include: Chronic Rheumatic heart disease 2.5%(7), Hyperthrophic cardiomyopathy 2.1%(6), Ventricular septal defect 0.4%(1). The mean Left ventricular ejection fraction(LVEF) is 63.03±9.73%, 83.2% had normal Values. The mean measurements(mm) of interventricular septum(IVS), Left ventricle posterior wall (LVP) are 10.49±2.12, and 9.86±1.75, respectively.

Table 3.Multivariable logistic regression predicting the likelihood of having DCM among HIV positive patients at JUSH ART clinic, South West Ethiopia, 2013

Variables	AOR	95.0% C.I.	P
BMI			
Lower(<18.5kg/m2)	3.226	0.995-10.458	<0.05
Others	1		
Annual Income			
3000-6000Birr	0.384	0.108-1.359	<0.138
Others	1		
Nadir CD4 count			
<200cells/mm3	6.649	2.024-21.847	<0.002
≥200cells/mm3	1		
ART status			
ART naïve	3.344	(1.015-11.013)	<0.047
On ART	1		

On bivariate logistic regression analysis the odds of DCM to occur in females was 0.76(P<0.588).The odds of DCM was 5.4 in those with lower BMI compared to participants with normal or higher BMI group. This was also true in multivariate analysis (AOR=3.2, P<0.05).

The odds of DCM was also higher (COR=7.6, p<0.0001) in those with CD4 count less than 200cells/mm3 compared to CD4 ≥200cells/mm3. This was also true on multivariate analysis (AOR=6.6, P<0.002).

DCM was also higher in those not started on ART compared to those on ART (AOR=3.34, p<0.047).

Other studied factors were not significantly associated with dilated cardiomyopathy both on bivariate and multivariate analyses. Please see tables 3&4 for the details.

CHAPTER SIX- Discussion

This study was conducted in a tertiary teaching hospital on patients with follow up at ART clinic. Prevalence of overall cardiac abnormalities was 42.1%which is similar to studies elsewhere, ~38% to ~50 %(8, 11). We found the prevalence of Ventricular diastolic dysfunction and LVH, each accounting for 8.9%.This is in contrast to the study in German which showed Ventricular diastolic dysfunction ~48%(13), and African study with LVH ~47%(5). This difference could arise from racial differences in the former and difference in inclusion criteria of study subjects in the later ,which included in patients. Other studies showed no significant association between CD4 count and diastolic dysfunction (8) which is true in our case too.The next common cardiac abnormality was systolic dysfunction ~6.4% which is similar to the Indian study,~7%(8) and higher than the African study which showed no abnormality(5) but lower than the German study,~38%(13). Apart from associations done in table 3&4(see above), other echocardiographic findings were not significantly associated with the variables studied.

The prevalence of DCM was 5.4% in this study which is lower than similar studies in the West~15% and African study~28%(5). These studies were done in ART naïve patients only, but our survey included both groups;i.e, ART naïve and people on ART. So there could be dilutional effect of ART both in prevention(by maximally suppressing viral load, raising CD4 count and thence, reducing the incidence of OIs) as well as in causality(Some ARVs like AZT is associated with cadriotoxicity, leading to DCM). But still the odds of developing DCM was 3.3 in those who didn't start ART compared to those on ART ($p<0.047$).The pathogenesis of cardiomyopathy in HIV infected individuals involves direct effect of the virus on the myosites, autoimmunity (anti-alpha-myosin antibodies), OIs and malignancies (Kaposi sarcoma, Toxoplasma gondii,Cryptococcosis) , dyslipidemias and toxic effect of antiretrovirals (3).

In other studies DCM was more common as the CD4 gets lower than 400cells/mm3 (14) with mean CD4 count of 142cells/mm3(15).This issue was properly addressed in our study by the fact that odds of developing DCM was 6.6 in inindividuals with lower CD4 count,i.e; <200cells/mm3($p<0.002$).This can be explained by the fact that as the disease advances ,in the absence of treatment, there will be high rate of viral replication reflected by declining CD4 count

and high viral load.Apart from this , these individuals will be at higher risk of OIs and opportunistic malignancies which involve the myocardium resulting in cardiac abnormality,commonly DCM.

There were conflicting reports concerning the association of BMI with DCM (15, 18), but we showed that a lower BMIis significantly associated with DCM (p=0.05); i.e., the odds of DCM was 3.2 in those in lower BMI group compared to the groups with normal or higher BMI. HIV infection profoundly affects nutritional status because it is associated with poor appetite, impaired nutrition absorption, increased basal metabolic rate and OIs. Under nutrition in HIV patients is manifested by weight loss, loss of lean body mass and micronutrient deficiencies, esp., selenium. Cardiac function can be affected by nutrition and can affect nutritional status(18).

Prevalence of clinically symptomatic DCM is estimated between 1 and 5% but there was no association between symptoms of heart failure and this abnormality in our study. Thus reliance on clinical symptoms of heart failure only, will fail to identify patients who might benefit from treatment (2).

We found the prevalence of pericardial effusion ~2.5% which is nearer to Iranian study~5.22% but much lower than other studies with prevalence of 8%,11%,and 22%(8,8,5),respectively. The discrepancies in the figures could be due to research designs in that some of the studies included inpatients. These studies have shown significant association with lower CD4 count and not starting on ART, the latter is true in our study, too. ($p<0.014$).Before effective ARVs were available, pericardial effusion was the most frequent cardiac manifestation. The majority of HIV associated pericardial effusions were asymptomatic which is true in our case as there was no significant association between symptoms and the condition under study. Pericardial diseases can be caused by HIV itselfis(TBc, cryptococcosis), and neoplasms(Kaposi sarcoma, lymphoma). Tuberculosis is the leading cause of pericardial effusion in Sub Saharan Africa (1, 3).

PHTN was found in 1.4% of patients which is higher than the Italian study~0.4%(14), but is in the range with those from Zimbabwe~0.6-5%.It is much lower than Iranian and Indian figures,20% and 12.68%,respectively (16).

It was only chest pain that was associated with this disease($p<0.044$) in our study which is in contrast to studies elsewhere which were associated with shortness of breath, body swelling in addition to chest pain. (14).This could be, again, some studies have been done on inpatients which possibly have advanced disease. The pathogenesis of PHTN in HIV is multifactorial and poorly understood(3).HIV infection itself, infections (esp.P.jirovei), thromboembolism are reported as causes(3,14).It occurs in the early and late stages of HIV infection and does not seem to be related to the degree of immunodeficiency(17) which is infact true in our study. More favorable outcome has been seen with specific treatment of PHTN than with ARVs, but ART could delay the development of PAHTN in HIV infected patients and is recommended irrespective of CD4 counts (14).

We found CAD in 3.9% of the HIV infected individuals. Different literatures came up with conflicting results. But most would agree that CAD risk and CV event risk increases in those who are HIV infected compared to HIV negative individuals(1, 3,20). ART has also carries small but significant risk for CAD. In our study no significant association was found between all indicators and CAD. The reason could be most of the study subjects are young(76.8%) to accumulate the classic risk factors and though we didn't look into the type of ART regimen used and the prevalence of dyslipidemia, this can have effect on the abnormality under discussion. Most of the studies are inpatient studies and more focused on CV mortality (20), so it poses some challenge to compare with our study.

CHAPTER SEVEN - Conclusion and Recommendations

7.1 Conclusion

This study has came up withan original information on high prevalence(42.1%) of cardiac abnormalities and the pattern of cardiac diseases in HIV infected patients .The most common abnormalities were Diastolic dysfunction and LVH. It has also shown the prevalence of DCM and its association with lower CD4 counts, not starting on ART and ,lower BMI ; prevalence of pericardial effusion and its association with not starting on Antiretroviral therapy. In this study, PHTN was associated with chest pain, but CAD was not associated with any of the variables evaluated. The study also came up with incidental echocardiographic abnormalities (CRHD, VSD, and HCM).

7.2 Recommendation

The study shaded light on the pattern and abnormalities of cardiac diseases in HIV patients in JUSH ART clinic. In addition, asymptomatic cardiac disease is the commonest presentation. So, physicians caring for these patients should be vigilant not to overlook cardiac abnormalities even in the absence of cardiac symptoms. Hence, routine evaluation of these patients with echocardiography at least yearly is needed.

The study also came up with significant effect of ART on DCM , and due to the fact that lower CD4 is associated with increased risk of DCM, we recommend starting ART earlier with less cardiotoxic drugs . Early initiation of cART reduces the risk of developing pericarditis.

Routine assessment of nutritional status in the form of BMI and nutritional supplementation is mandatory in HIV patients with lower BMI. In addition factors that compromise intake and absorption of food should be sought thoroughly and treated accordingly.

We also recommend the MOH to update HIV/AIDS guidelines towards earlier start of cART and incorporate routine evaluation and treatment of cardiac abnormalities in HIV patients along with the care which is being given.

This paper may be used as bench mark for further studies in the country and in Africa at large

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ANNEX I CONSENT FORM

Jimma University College of Public Health and Medical Sciences, Jimma University.

Questionnaire for assessing pattern of cardiac diseases in HIV-infected patients at JUSH ART clinic.

A).INFORMATION TO THE PARTICIPANT

Interview code no _____

Greeting and self introductionand consent

Greeting: - Good morning/afternoon.

My name is_____.We are conducting a scientific research on prevalence and patterns of cardiac diseases among HIV/AIDS patients who have follow up at JUSH ART clinic. Therefore, I am happy to inform you that you are one of the potential participants in this study. Your participation is only determined by you. If you feel you will not participate in this study, your decision will be much respected from the outset. It is only if you are willing I will proceed to ask you some information.

Data will be collected with interview and Portable echocardiography. The echocardiographic procedure will be conducted after you lied on left lateral recumbent position on a bed.The procedure will take around 30minutes and there will be no risk imposed to you during the procedure.

The information gathered will be used for writing a proposal for partial fulfillment of a specialty certificate in Internal Medicine at Jimma University. Here, I want to assure you that any information obtained from you will remain confidential and even there is no need of writing your names or any personally identifiable information.

B) CERTIFICATE OF CONSENT

Do you wish to participate in the study?

f the participant agrees to participate in the study, proceed with interview and the echocardiographic interrogation after the patient has signed the consent.

I have adequate information about the research and I have decided to participate in the study.

Signature ----------

If the participant says “No, I don’t want to participate in the study”, thank him(her) and stop .

Thank you!

Name of interviewer_____

ANNEX II: INFORMED CONSENT

A) In Amharic

፩ ለተሳታፊው የሚሰጥ የጥናት ውል ማስገነዘቢያ

□ኔ ዶ/ር ኤልሳ ተገኔ የተባልኩ □□ስጥ ደዌ ህክምና ት/ት ክፍል የመጨረሻ አመት ሬዚደንት የመመረቂያ ፅሁፌን ለመስራት ለሚያስፈልገኝ ጥናት እርስዎ መመረጥዎን ሳሳውቅዎት በታላቅ ደስታ ነው::

ጥናቱ የሚካሂደው በቃል መጠይቅና በልብ መመርመርያ መሳሪያ ሲሆን በርሶ ላይ ምንም አይነት ጉዳት አይደርስም::

□ልብ ምርመራው የሚካሂደው የመመርመሪያ አልጋ ላይ በግራ በኩል በእንግላል ተኝተው ሲሆን እስከ 30:00 ደቂቃ □□□ል ::

ከጥናቱ መውጣት ከፈለጉ በማንኛውም ሰዓት አቋርጠው መውጣት ይችላሉ:: ይህም በማድረግዎ ምንም ተጽእኖ አይደርስብዎትም::

ከጥናቱ የሚገኘው ውጤት ወደፊት የሚካሂዱ ሌሎች ጥናቶች መነሻ ከመሆኑም ባሻገር የተፈለገው ጥናት በዞናችን ምን እንደሚመስል ያስገነዝባል::

የርሶ ስምና ሊሎች የርሶን ማንነት የሚያመለክቱ ነገሮች በጥናቱ ላይ አይገቡም::

አመሰግናለሁ

፪ □ተሳ□□□ □ቃ□ኛነት ማረጋገጫ ቅፅ

ስለጥናቱ በቂ እውቀት ስላገኘሁ በሙሉ □ቃ□ ለመሳተ□ □ስኛለሁ::

□ርማ ____

ተሳታፊው በጥናቱ ለመሳተፍ ካልፈለገ አመስግነው ያሰናብቷቸው::

□□□ቂ□ ሰም ----------

ቀን----------

A) AfaanOromotin

I) OddeffanooQoratamaafkenamu

Ani ----------

yoonta'u,Karorabarrefamaeebbaairratihirmaataaakkanaaftaatankabajaanisingaafadha. Qorannoonkanadeemsiifamugaaffiifimeeshaaittinonneilaalaniinyoota'u , rakkoontokkoyuuisiinitihingahu.

Sireeirratigarabitaatigaragaltanieegaciistanboodameeshaaonneeittiqorattanitilaalamtu.Qorrannoon kun deqiiqaa 30 fudhata.Ooddeffanoonqorranookanarraaargamuhoojjiifundurraafadeemsamuufgargaarsaguddaakenna. Qorrannookeessaayeroobarbaadanitibahuunkandanda'amuyoota'u, kuniimmotajaajilaisiiniikeennamuirratidhiibbaahoommayyuhinqabu.

II) MallattooMirkanessaa

Qo'annairratiqoodafudhachuufyoowaligaltanbakkaarmaangaddiiirratimallattonmirkenessa.

Galatoomaa

Mallattoo----------

Maqaa –Qorratagoodhuu----------

Guyyaa----------

Yooqo'annairratiqoodafudachuuhinbarbaadnetaanan, Isaangeleteessaatidhiisaa.

Annex III: Questionnaire designed to assess cardiac diseases in HIV-infected patients at JUSH ART clinic, Sept-Nov/2012

Part I – Identification, Sociodemographiccharacteristics and anthropometric measurements of the study participants

1. Card no.----------,wt(kg)-----, ht(cm)-----
2. Gender □M □F
3. Age ---------
4. Marital status □married □single □divorced □widowed
5. Occupation □farmer □house wife □employee □student
   □merchant □ others (specify) ----------
6. Literacy status □illiterate □semi-literate □literate
7. Annual Income (birr) □ <3000 □3000-6000 □>6000
8. Living area
   □Urban
   □ Rural

Part II: HIV disease status and other clinical characteristics of the study participants

1) duration since diagnosis of HIV----------
2) Nadir CD4 count----------
3) WHO clinical stage----------
4) Which of the following symptoms do you have now or recent past?

□shortness of breath on exertion □palpitation □body/leg swelling

□chest pain □other symptoms (specify)----------

Part –III

Transthoracic Echocardiographic report format

Linear dimensions	Normal Range, mm	Result	Hemodynamic variables		NL range	result
Aortic root diameter	20-37		E/A ratio		1-2	
Left atrial diameter	20-40					
LV diastolic diameter	35-57					
LV systolic diameter	20-40		TR velocity		<2.5m/s	
IVSd	6-11		PASP			
LV posterior wall	6-11		Systolic function		NL range	result
Main pulmonary artery	15-21		LV ejection fraction		≥55%	
Mid-RV	27-33		TAPSE*		≥1.5	
Pericardial fluid	<5mm		Wall motion	Nl	Regional hypokinesis	Global hypokinesis

Ref:Feigenbaum's, The Echo manual,Otto&Braunwald's

TAPSE: tricuspid annular plane systolic excursion

Diagnosis: ----------