DISSERTATION TITLED

"A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"

Submitted in partial fulfilment of

Requirements for

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BRANCH-I GENERAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"** is a bonafide work done by **DR. PAKKEER KANNU SYED FAHRUDEEN MUNNAVER**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2011- 2014.

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I solemnly declare that the dissertation entitled **"A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"** is done by me at Madras Medical College, Chennai-3 during July 2013to December 2013 under the guidance and supervision of Prof. K.S. CHENTHIL, M.D., to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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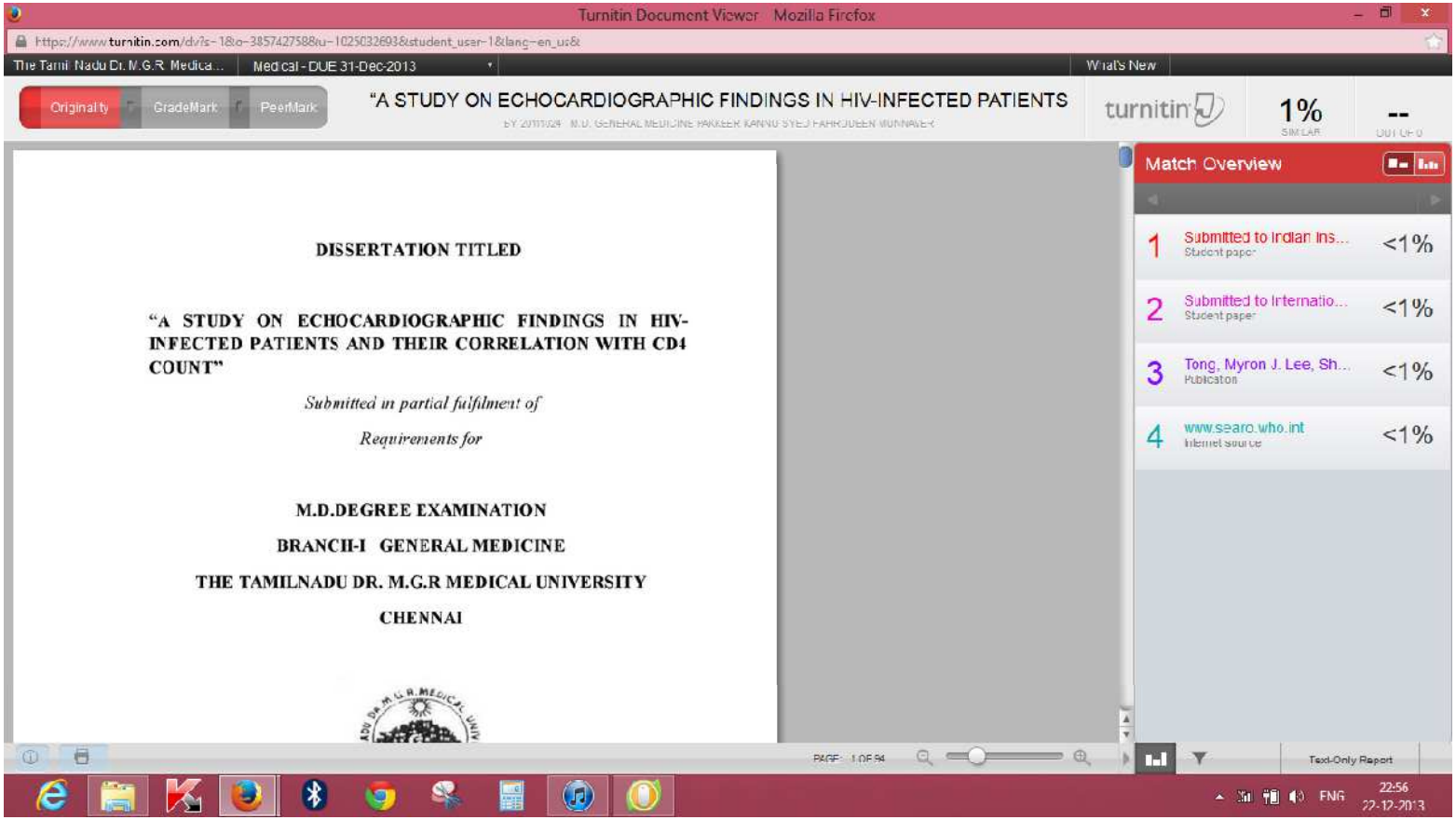
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ABBREVIATIONS

AIDS	:	Acquired Immunodeficiency Syndrome
HIV	:	Human Immunodeficiency Virus
ART	:	Antiretroviral Therapy
HAART	:	Highly Active Antiretroviral Therapy
CD4	:	T–lymphocyte cell bearing CD4 receptor.
NACO	:	National Aids Control Organization
ARV	:	Antiretroviral (Drug)
CDC	:	Centre for Disease Control and Prevention
PE	:	Pericardial effusion
LVDD	:	Left ventricle diastolic dysfunction
ELISA	:	Enzyme-Linked Immunosorbent Assay
HBsAg	:	Hepatitis B Surface Antigen
HBV	:	Hepatitis B Virus
HCV	:	Hepatitis C Virus

RTI	:	Reverse-Transcriptase Inhibitor
NNRTI	:	Non-Nucleoside Reverse-Transcriptase Inhibitor
NRTI	:	Nucleoside Reverse-Transcriptase Inhibitor
PCR	:	Polymerase Chain Reaction
PI	:	Protease Inhibitor
PCP	:	Pneumocystis (Jirovecii) Pneumonia
RNA	:	Ribonucleic Acid
ECG	:	Electrocardiogram
ECHO	:	Echocardiography
RVSP	:	Right ventricle systolic pressure
EF	:	Ejection Fraction
DCM	:	Dilated Cardiomyopathy
DNA	:	Deoxy ribonucleic acid

CONTENTS

ABSTRACT

A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT

Background and Purpose With advances in the management of patients with HIV and AIDS, not only survival has increased but manifestations of late stage HIV infection are encountered more often including cardiovascular complications. Cardiovascular disease has been reported as one of the leading causes of death in HIV-infected patients. In the present study our purpose was to study echocardiographic findings in HIV-infected patients and to correlate with CD4 count.

Methods We included 100 patients with HIV infection irrespective of the ART status.CD4 count was estimated for all the patients and all of them were subjected to Echocardiographic examination**.**

Results When CD4 count was compared within the age group it was not statistically significant($p=0.098$) and so was the comparison between the two sexes($p=0.529$).The comparison of the CD4 count and ART status was statistically significant($p<0.001$) and so was the comparison of LVDD among the study group($p<0.001$). The comparison of CD4 count with presence of Pericardial effusion was statistically significant ($p=0.013$) and so was the comparison of EF and PAH among the study group ($p<0.001$ for both).The comparison of CD4 with DCM was statistically insignificant($p=0.314$).

Conclusions Cardiovascular manifestations are common in HIV infected patients and often subclinical. Echocardiography is used for their early recognition and CD4 count correlates well with Echocardiographic findings.

Key Words HIV -infection, AIDS, Antiretroviral Therapy,CD4 cell count ,Echocardiography.

INTRODUCTION

Cardiovascular disease has been reported as one of the leading causes of death in HIV-infected patients. As the clinical presentation of HIV infection is still dominated by opportunistic infections, heart disease can be easily overlooked in these individuals. Moreover symptoms of breathlessness, fatigue and poor exercise tolerance are frequently ascribed to other conditions associated with HIV infection.

Echocardiographic abnormalities are frequent in HIV-infected patients who do not have detectable clinical manifestations. Echocardiography is very helpful in detecting cardiac dysfunction at an early stage much before overt clinical manifestations and treatment of cardiac dysfunction in such patients.

Most frequent echocardiographic abnormalities are reduced ejection fraction, pericardial effusion, dilated cardiomyopathy, diastolic dysfunction, regional wall motion abnormalities, pulmonary artery hypertension and others.

In this present study I aim to analyze whether the echocardiographic abnormalities have any correlation with CD4 count.

AIMS AND OBJECTIVES

- To study echocardiographic findings in HIV-infected patients.
- To evaluate their correlation with CD4 count.

REVIEW OF LITERATURE

HIV INFECTION AND AIDS:

Human immunodeficiency virus (HIV) was unknown till the early 1980's but since has infected millions of people in a worldwide pandemic.AIDS was first recognized in the United States in 1981, when the U.S. Centers for Disease Control and Prevention (CDC) reported the unexplained occurrence of Pneumocystis jiroveci pneumonia in five hitherto healthy homosexual men in Los Angeles and of Kaposi's sarcoma (KS) in 26 hitherto healthy homosexual men in New York and Los Angeles.

In 1983, human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy, and by 1984 it was demonstrated clearly to be the causative agent of AIDS. In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed. Since then it has served as the basis for developing improvements in diagnosis.

In India the first cases of HIV infection were documented among female sex workers in Chennai, Tamil Nadu in the year 1986.

The result of HIV infection is devastation of the immune system leading to onset of the acquired immunodeficiency syndrome (AIDS). All

HIV-infected persons are at risk for illness and death from opportunistic infections and neoplastic complications because of the unavoidable manifestations of AIDS.

In addition, therapy was dramatically changed with the introduction of antiretroviral drugs in 1987 and revolutionized by combination treatment, known as highly active antiretroviral therapy (HAART), in 1996. Three years after introducing HAART, mortality, AIDS, AIDS-defining diagnoses, and hospitalizations all decreased 60 to 80 percent. The EuroSIDA study, comparing this early HAART period to pre-HAART and later HAART (1998 to 2002) treatment periods, found a sustained decrease in mortality and progression to AIDS with ongoing HAART. Despite the absence of a cure, the natural history of the disease was radically changed.

EPIDEMIOLOGY

Global summary of the AIDS epidemics as on December 2009 [1]

Number of people living with HIV in December 2009

- Total 33.3 million (31.4 – 35.3 million)
- Adults 32.8 million (30.9 – 34.7 million)
- Women 22.5 million (20.9 – 24.2.million)

People newly infected with HIV in 2009

- Total 2.6 million (2.3. – 2.8 million)
- Adults 2.2 million (2.1 – 2.3 million)

AIDS deaths in 2009

- Total 1.8 million (1.6. – 2.1 million)
- Adults 2.2 million (1.4 – 1.7 million)

Summary of AIDS Epidemic in India[2]

Number of people living with HIV Infection

- Total 2.40 million (1.9-3.0 million)
- Males 61%
- Females 39%
- Children 3.5%

Prevalence among Adults

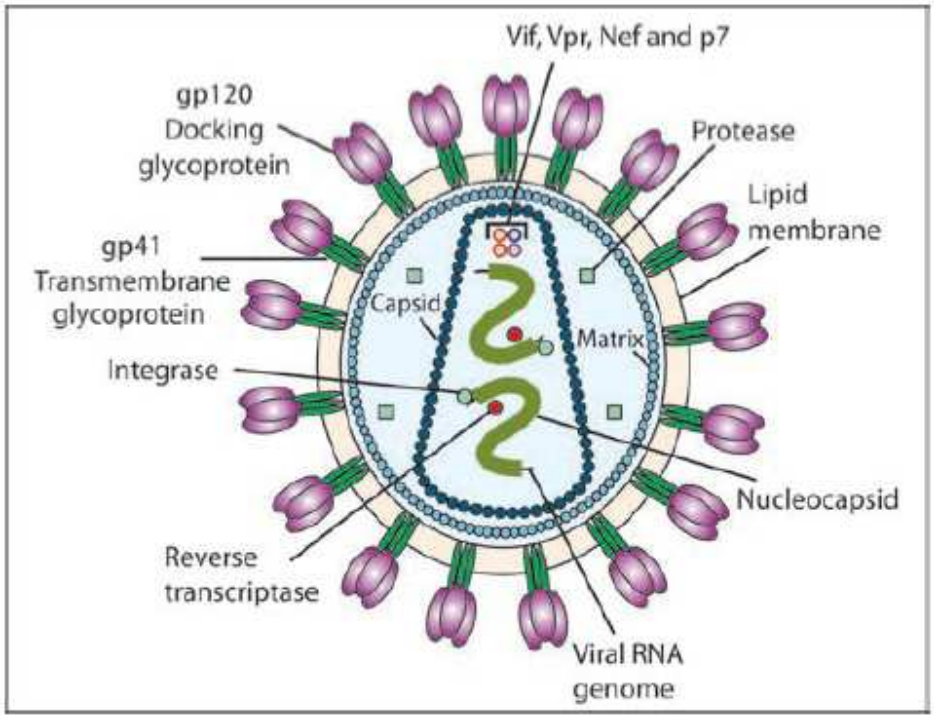
- Overall 0.31%
- Males 0.44%
- Females 0.23%

ETIOLOGIC AGENT:

HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. This subfamily has two types HIV-1 and HIV-2. The most common cause of HIV disease throughout the world is HIV-1, which includes several subtypes with different geographic distributions.HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa.

The newly defined groups of HIV-1 (M, N, O, P) and the HIV-2 groups A through G each are likely transferred to humans from a nonhuman primate reservoir. HIV-1 viruses likely came from chimpanzees and/or gorillas, and HIV-2 from sooty mangabeys. The AIDS pandemic is primarily caused by the HIV-1 M group viruses[21].

HIV STRUCTURE:



In electron microscopy the HIV virion shows an icosahedral .Structure. HIV is an enveloped positive stranded RNA virus that measures 120 nm in diameter and has a lipid bilayer with uniformly arranged 72 spikes of glycoprotein – gp 120 and gp 41 (HIV-1)/gp 36 (HIV-2). The virion gp120 which is located on the virus surface contains the binding site for cellular receptor(s). The two plus stranded RNA molecules are enclosed in a protein capsid (p24) together with certain viral enzymes (viral RNA-dependent DNA polymerase (Pol, also called the reverse transcriptase, RT (p66, p51) and nucleocapsid proteins (p9, p7). The capsid (p24) is

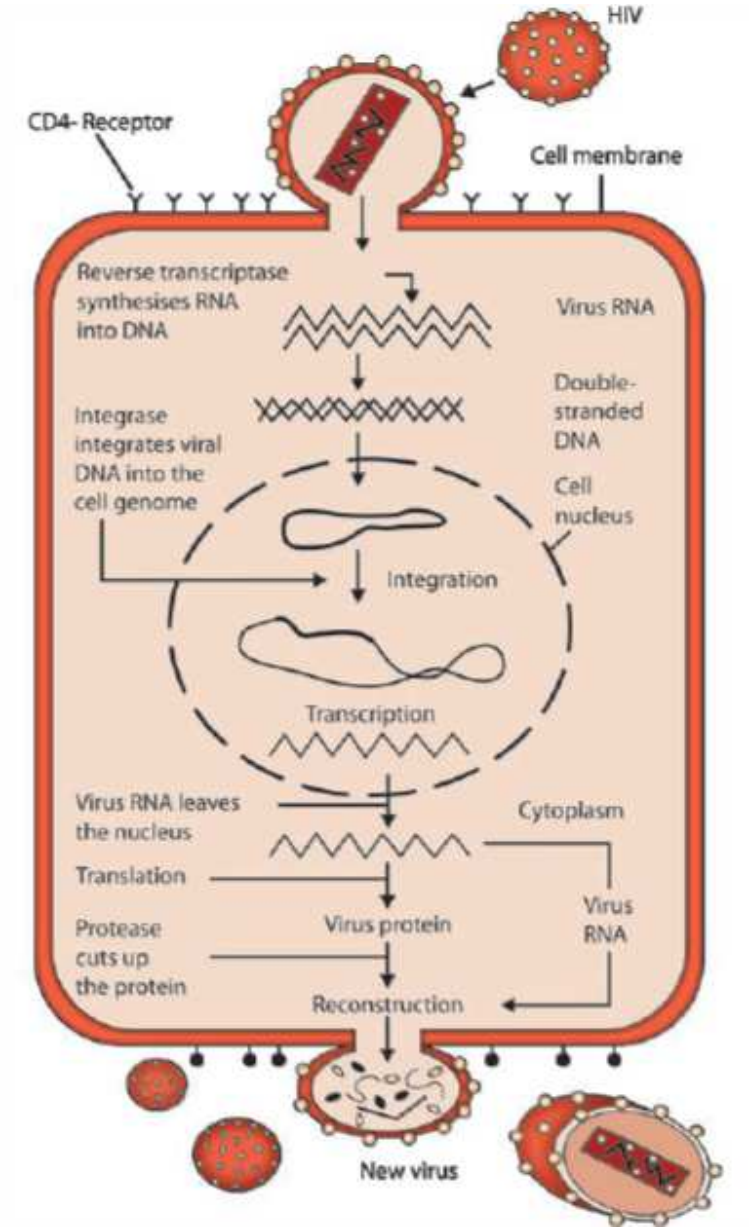
surrounded by a matrix layer (p17) that in turn is embedded in lipid bi-layer, the envelope.

REPLICATION CYCLE OF HIV:

HIV enters the body when a person comes in contact with infected blood, semen or vaginal secretions. The CD4 receptor is the principal target site for HIV, however specific chemokine receptors appear to be an important secondary cellular receptors for HIV. HIV-1 strains have been classified into

T-tropic (preferring to replicate in T-lymphocytes) and M-tropic (macrophages) viruses.

The chemokine receptor usage is distinct for each of these viruses, with T-tropic viruses making use of CD4 and CXCR4 (or fusin, the receptor for SDF-1), and M-tropic viruses making use of CD4 and CCR5 (receptor forRANTES). After attachment of CD4, gp120 is displaced leading to uncovering of domains on the envelope gp41 needed for virus cell fusion. Gp41 is involved in infectivity as well as syncytium formation.



After the viral capsid enters the cell, an enzyme called reverse transcriptase liberates the single-stranded RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA). The cDNA

and its complement form a double-stranded viral DNA which is then transported into the cell nucleus where it is integrated into the host cell's genome by the enzyme called integrase.

During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the proteins. The final step of the viral cycle, assembly of new HIV-1 virion, begins at the plasma membrane of the host cell where the various structural components then assemble to produce a mature HIV virion. This cleavage step can be inhibited by protease inhibitors. The mature virus is then able to infect another cell.

DEFINITION:

THE CDC CLASSIFICATION:

The current CDC classification system for HIV-infected adolescents and adults classify persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts.

The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is depicted by a matrix of nine mutually exclusive categories.

Using this system, any HIV-infected individual with a CD4+ T cell count of <200/μL has AIDS by definition, irrespective of the presence of symptoms or opportunistic diseases. Once individuals have had a clinical condition in category B, their disease classification cannot be reverted back to category A, even if the condition resolves; the same for category C in relation to category B.

	Clinical Categories		
CD4+ T Cell Categories	A Asymptomatic, Acute (Primary) HIV or PGL	B Symptomatic, Not A or C Conditions	C AIDS-Indicator Conditions
>500/μL	A1	B1	C1
200–499/μL	A2	B2	C2
<200/μL	A3	B3	C3

Category A:

Conditions listed in categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (Primary) HIV infection with accompanying illness or history of acute HIV infection.

Category B:

Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and meet at least one of the following criteria:

1. The conditions are attributed to HIV infection or are of a defect in cell-mediated immunity; or
2. The conditions are considered by physicians to have a clinical course or to require management and complicated by HIV infection. Examples
   - Bacilliary angiomatosis
   - Candidiasis, oropharyngeal (thrush)
   - Candidiasis, vulvovaginal; persistent, frequent, or poorly response to therapy.
   - Cervical dysplasia (moderate or severe)/cervical carcinoma in situ.
   - Constitutional symptoms, such as diarrhea lasting >1month or fever (38.5°C).
   - Hairy leukoplakia,
   - Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome.

- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, if complicated by tuboovarian abscess.
- Peripheral neuropathy

Category C:

- Candidiasis of bronchi, trachea, lungs or esophagus
- Cervical cancer invasive
- Coccidioidomycosis disseminated or extra pulmonary
- Extra pulmonary Cryptococcosis ,
- Cryptosporidiosis- intestinal (>1 month)
- Cytomegalovirus disease other than spleen, liver, or node
- HIV encephalopathy
- Herpes simplex, chronic (>1 month), or bronchitis, pneumonia, or esophagitis.
- Histoplasmosis, disseminated or extra pulmonary
- Isosporiasis - intestinal (>1 month)
- Kaposi sarcoma
- Lymphoma (Burkitt's primary CNS)
- MAC disseminated or extra pulmonary

- M. tuberculosis - any site
- Pneumocystis carinii pneumonia
- Pneumonia- recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis- brain
- Wasting syndrome - HIV

Case Definition - India (above 12 years of Age)

1. Two positive tests for HIV infection by ERS test (Elisa/Rapid/Simple) AND
2. Any one -criteria:
    a. Significant weight loss (>10% of body weight) within last 1 month/cachexia (rather than HIV infection). AND Chronic diarrhea (intermittent or continuous) >one month duration or prolonged fever (intermittent or continuous) >one month duration.
    a. Tuberculosis: Extensive pulmonary, disseminated, milliary,extra-pulmonary tuberculosis.

b. Neurological impairment preventing independent daily activities, not known to be due to the conditions unrelated to HIV infection (e.g. trauma)
c. Candidiasis of the oesophagus (diagnosable by oral candidiasis by odynophagia)
d. Clinically diagnosed life threatening or multiple episodes of pneumonia, with or without etiological confirmation.
e. Kaposi Sarcoma
f. Other conditions:
    i. Cryptococcal meningitis
    ii. Neuro Toxoplasmosis
    iii. CMV retinitis
    iv. P.marneffei
    v. Recurrent Herpes Zoster or multi-dermatomal herpes infection
    vi. Disseminated molluscum

TRANSMISSION:

The major routes for HIV transmission are:

- Unprotected sexual intercourse with an HIV-infected partner.
- Through transfusion of contaminated blood or blood products.
- Among injection drug users via sharing of contaminated needles and syringes.
- Intrapartum or perinatally from mother to infant; or via breast milk.

There is no evidence that the virus can be transmitted through casual or family contact or by insects such as mosquitoes.

There is a definite, though small, occupational risk of infection for laboratory personnel who work with HIV-infected specimens and for health care workers. The chances of transmission of HIV from an infected health care worker to his or her patients through invasive procedures is extremely low.

RISKFACTORS:

- **Viral load**[11]-The mean viral load was significantly higher in those who transmitted HIV to their partner.The importance of viral load is that a large proportion of HIV infections may be transmitted by

individuals with primary infection. This is due to the high levels of viremia that are seen in the setting of acute infection.

- **Sexually transmitted diseases**[14]-The presence of sexually transmitted diseases also increases the risk of HIV transmission.The probability of transmission was nearly four times higher in patients with genital ulceration compared to those without.
- **Sexual risk** -risk factors for HIV seroconversion included history of a multiple sexual partners, unprotected receptive anal sex with a partner with an unknown HIV serostatus, and use of nitrate inhalants.
- **Lack of circumcision**[10]-Lack of circumcision is associated with risk of HIV transmission in groups of heterosexual couples and MSM.
- **Genetic background**- Similarity of HLA-class-I alleles between HIV discordant couples may affect the risk of transmission, by selecting for viral strains that are more likely to escape the immune containment of the seronegative partner

PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS:

The distinctive characteristic of HIV disease is a profound immunodeficiency resulting from a progressive quantitative and also qualitative deficiency of the subset of T lymphocytes referred to as helper T cells. This subset of T cells is defined phenotypically by the expression on

the cell surface of the CD4 molecule, which serves as the primary cellular receptor for HIV.

A co-receptor must be present with CD4 for efficient entry of HIV -1 into target cells. The two major co-receptors for HIV-1 are the chemokine receptors CCRS and CXCR4. The CD4+ T lymphocyte and CD4+ monocyte lineage are the principal cellular targets of HIV.

Primary Infection:

After initial transmission, the virus infects CD4+ cells, probably T lymphocytes, monocytes, or bone marrow-derived dendritic cells. Both during this initial stage and later in infection, the lymphoid system is a important site for the establishment and propagation of HIV infection. The gut-associated lymphoid tissue (GALT) plays a major role in the establishment of infection and in the early depletion of memory CD4+ T cells.

Basically allpatients undergo a viremic stage during primary infection; in some patients this is associated with the "acute retroviral syndrome:' a mononucleosis-like illness. This phase is important in disseminating virus to lymphoid and other organs throughout the body, and it is ultimately

contained partially by the development of an HIV-specific immune response.

Establishment of Chronic and Persistent Infection:

Despite the powerful immune response that is mounted following primary infection, the virus is not cleared from the body. Instead, a chronic infection develops that persists for a median period of 10 years before the untreated patient becomes clinically ill. During this period of what appears to be clinical latency, the number of CD4+ T cells gradually declines, but few, if any, clinical signs and symptoms may be apparent. However, active viral replication can almost always be detected by measurable plasma viremia and the demonstration of virus replication in lymphoid tissue.

The level of steady-state viremia at -6 months to 1 year postinfection has important prognostic implications for the progression of HIV disease; individuals with a low viral set point at 6 months to 1 year after infection progress to AIDS more slowly than do those whose set point is very high at this time.

Advanced HIV Disease:

In untreated patients or in patients in whom therapy has not controlled viral replication, after some period of time CD4+ T cell counts

will fall below a critical level (~200/flL) and patients become highly susceptible to opportunistic disease. The presence of a CD4+ T cell count of <200/flL or an AIDS-defining opportunistic disease establishes a diagnosis of AIDS.

Control of plasma viremia by successful antiretroviral therapy, particularly maintaining the plasma viral load consistently at <50 copies of RNA per mL, even in individuals with low CD4+ T cell counts, has increased survival in these patients dramatically, including those whose CD4+ T cell counts may not increase significantly as a result of therapy .

IMMUNE ABNORMALITIES IN HIV DISEASE:

A wide range of immune abnormalities has been documented in HIV infected patients, resulting in different degrees of immunodeficiency. These include both quantitative and qualitative defects in lymphocytes, and qualitative defects in monocyte/macrophage and natural killer (NK) cell function. Autoimmune phenomena also have been observed in HIV-infected individuals.

IMMUNE RESPONSE TO HIV INFECTION:

Both humoral and cellular immune responses to HIV develop soon after primary infection.

Humoral immunity includes:

- Binding antibodies
- Neutralizing antibodies
    - Type specific
    - Group specific
- Antibodies participating in antibody-dependent cellular cytotoxicity (ADCC)
    - Protective
    - Pathogenic (bystander killing)
- Enhancing antibodies
- Complement.

Cell-mediated immunityincludes:

- Helper CD4+ T lymphocytes
- Class I MHC–restricted cytotoxic CD8+ T lymphocytes
- CD8+ T cell–mediated inhibition (noncytolytic)
- ADCC
- Natural killer cells.

CLINICAL MANIFESTATIONS:[4]

The clinical outcome of HIV infection include a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. HIV disease begins at the time of primary infection and progresses through various stages.

Active virus replication and progressive immunologic impairment occur throughout the course of HIV infection in most patients. With the exception of the rare, long-term nonprogressors HIV disease in untreated patients inevitably progresses even during the clinically latent stage.

THE ACUTE HIV SYNDROME:

It is estimated that 50–70% of individuals with HIV infection experience an acute clinical syndrome ~3–6 weeks after primary infection.It can have multiple clinical features, lasts 1-2 weeks, and resolves spontaneously as an immune response to HIV develops and the viral load declines from its peak levels. Most patient after that enter a phase of clinical latency.

Approximately 10% of patients can manifest a fulminant course of immunologic and clinical deterioration after primary infection, which can occur even after the disappearance of initial symptoms.

Clinical findings in the acute HIV syndrome are:

General

- Fever
- Pharyngitis
- Lymphadenopathy
- Headache
- Retroorbital pain
- Arthralgia
- Myalgia
- Lethargy
- Malaise
- Anorexia
- Weight loss
- Nausea
- Vomiting
- Diarrhea

Neurologic:

- Meningitis
- Encephalitis
- Peripheral neuropathy
- Myelopathy

Dermatologic:

- Erythematous maculopapular rash
- Mucocutaneous ulceration

THE ASYMPTOMATIC STAGE—CLINICAL LATENCY:

The length of time between the initial HIV infection and development of disease in untreated individuals varies greatly, but the median time is estimated to be 10 years. HIV disease with active viral replication usually progresses during this asymptomatic period, and CD4+ T cell counts fall.

The rate of disease progression is directly correlated with plasma HIV RNA levels. Patients with high levels of HIV RNA progress to symptomatic disease faster than patient with low levels of HIV RNA.

Some patients referred to as long-term nonprogressors show little if any decline in CD4+ T cell counts over extended periods of time. These patients generally have extremely low levels of HIV RNA; a subset, referred to as elite nonprogressors, exhibits HIV RNA levels <50 copies per milliliter.

SYMPTOMATIC DISEASE:

Symptoms of HIV disease can manifest at any time during the course of HIV infection. In general, the spectrum of illness changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in patient with CD4+ T cell counts <200/f.IL. Overall, the clinical spectrum of HIV disease is constantly changing as patient live longer and new and better treatment approaches and prophylaxis of opportunistic infections are developed.

In addition, a variety of neurologic, cardiovascular, renal, metabolic, and hepatic problems are increasingly seen in patient with HIV infection and may be a direct consequence of HIV infection. The key element to treating symptomatic complications of HIV disease, whether primary or secondary, is achieving good control of HIV replication through the use of combination

antiretroviral therapy and starting primary and secondary prophylaxis as indicated.

Major clinical syndromes are summarized below:

CARDIOVASCULAR MANIFESTATIONS:

- Coronary heart disease-myocardial infarction
- HIV-associated cardiomyopathy
- Myocarditis-Kaposi sarcoma, cryptococcosis, Chagas' disease, and toxoplasmosis
- Pericardial effusions, Cardiac tamponade
- Malignant lymphoma
- Diastolic dysfunction, systolic dysfunction
- Right ventricular hypertrophy
- Pulmonary arterial hypertension
- Non-bacterial thrombotic endocarditis.

PULMONARY MANIFESTATIONS:

- Acute bronchitis and sinusitis
- Bacterial pneumonia
- Pneumocystis pneumonia (PCP)
- Mycobacterium tuberculosis

- Atypical mycobacterial infections
- Idiopathic interstitial pneumonia: lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP).

GASTROINTESTINAL MANIFESTATIONS:

- Thrush
- Hairy leukoplakia
- Aphthous ulcers
- Esophagitis
- Diarrhea
- HIV enteropathy

HEPATOBILIARY MANIFESTATIONS:[19.]

- Co-infection with hepatitis B, C
- AIDS cholangiopathy
- Granulomatous hepatitis

NEUROLOGICAL MANIFESTATIONS:

- Neoplasms

Primary CNS lymphoma

Kaposi's sarcoma

- HIV encephalopathy
- Myelopathy

Vacuolar myelopathy

Pure sensory ataxia

Paresthesia/dysesthesia

- Peripheral neuropathy

Guillain-Barré syndrome

Mononeuritis multiplex

RENAL MANIFESTATIONS:

- HIV-associated nephropathy

HAEMATOLOGICAL MANIFESTATIONS:

- Anemia
- Persistent generalised lymphadenopathy
- Leukopenia,
- Thrombocytopenia

RHEUMATOLOGICAL MANIFESTATIONS:

- Reiter's syndrome,
- Non-specific reactive arthritis
- Septic arthritis.
- Diffuse infiltrative lymphocytosis syndrome
- Myopathy,
- Vasculitis
- AIDS-associated arthropathy

ENDOCRINE AND METABOLIC DISORDERS:

- Hypogonadism
- Hypothyroidism
- Hyperthyroidism
- HIV-Associated Wasting

NEOPLASTIC DISEASES:

- Kaposi's sarcoma (cutaneous and visceral, more fulminant course than in non-HIV-infected patients).
- Lymphoma (primarily B cell, may be CNS or systemic).

OPPORTUNISTIC INFECTION:

- P. jiroveci (pneumonia)
- CMV (chorioretinitis, colitis, pneumonitis, adrenalitis)
- Candida albicans (oral thrush, esophagitis)
- M. avium intracellulare (localized or disseminated infection)
- M. disseminated disease)
- Toxoplasma gondii (encephalitis, intracerebral mass lesion)
- Herpes simplex virus (severe mucocutaneous lesions, esophagitis)
- Diarrhea due to Cryptosporidium spp. or Isospora belli (diarrhea)
- JC virus (progressive multifocal leukoencephalopathy)
- Bacterial pathogens (pneumonia, sinusitis, skin).
- Tuberculosis (pulmonary or disseminated),
- Cryptococcus neoformans (meningitis,disseminated disease),

LABORATORY DIAGNOSIS OF HIV INFECTION:[3]

Diagnosis of HIV infection can be achieved by the detection of:

(a) antibodies in blood and body fluids

(b) antigen in blood and body fluids

(c) viral nucleic acid by polymerase chain reaction (PCR)

(d) virus isolation from blood and tissues.

According to NACO, a three-tiered strategy is adopted for diagnosis of HIV infection in clinical settings. Initially, a sample is tested by an ELISA/rapid test. If it is found reactive it is subjected to second and third ELISA/rapid assay using different antigen or principle of testing.

If all three tests are reactive, the samples are considered positive for antibodies against HIV. Samples that are negative in the first and second levels of testing are considered negative while samples that are positive in the two tests and negative in the third are considered equivocal and subjected to western blot for confirmation.

Detection of HIV Specific Antibodies[5]:

Immunoassays for the detection of a serological response to HIV-1 infection were developed in a series of stages, called generations. The first generation assays were very sensitive but not specific and the technology was later improved by using recombinant and synthetic peptides as antigens (2nd and 3rd generation kits). More recently, 4th generation ELISA tests have been developed that detect both antibodyand p24 antigen simultaneously.

The different HIV-1 antibody detection tests currently available are ELISA, rapid immunoassays such as HIV spot tests, immuno Combs' tests, dot blot immunoassays and agglutination assay (Capillus). Antibodies to HIV-2 in clinical samples were detected by ELISA with synthetic gp36 (TM portion of the HIV-2 envelope) antigens

Detection of Viral Antigen in Blood and Body Fluids:

The p24 antigen assay detects the viral capsid p24 protein in blood which is detected earlier than HIV antibody during acute infection. The most commonly used HIV p24 antigen test procedure is a basic antibody-sandwich ELISA. This test is of limited diagnostic potential because antigenaemia is restricted to two stages of HIV infection: early in the illness

during the latter half of the window period and late in the illness (end-stages) when immune collapse has set in.

Detection of Viral Nucleic Acid:

Detection of HIV nucleic acid in plasma/serum is used for diagnosis of HIV infection in children aged less than 18 months (early infant diagnosis or EID) and estimation of viral loads. The detection of HIV nucleic acid can be achieved by either polymerase chain reaction (PCR), nucleic acid sequence based amplification (NASBA) or branched DNA (bDNA) technique.

However, the most widely used test is the polymerase chain reaction (PCR). For EID, the NACO recommends the use of a HIV DNA PCR using dried blood spot specimens.

TREATMENT

Following a diagnosis of HIV infection, there are severalexaminations and laboratory studies that should be performed to help determine the extent of disease and provide baselinestandards for future reference.

- History and physical examination
- Routine chemistry and hematology

- AST, ALT, direct and indirect bilirubin
- Lipid profile and fasting glucose
- CD4+ count
- Two plasma HIV RNA levels
- HIV resistance testing
- HLA-B5701 screening
- RPR or VDRL test
- Anti-Toxoplasma antibody titer
- PPD skin test
- Mini-Mental Status Examination
- Serologies for hepatitis A, hepatitis B, and hepatitis C
- Immunization with pneumococcal polysaccharide; influenza as indicated
- Immunization with hepatitis A and hepatitis B if seronegative.

ANTIRETROVIRAL THERAPY:

The cornerstone of medical management of HIV infection is combination antiretroviral therapy, (cART) or highly active antiretroviral therapy (HAART).[20]

Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life of patients with HIV infection.

However, several important questions related to the treatment of HIV disease lack definitive answers. Among them are questions regarding when antiretroviral therapy should be started, what the best cART regimen is, when a given regimen should be changed, and which drugs in a regimen should be changed when a change is made.

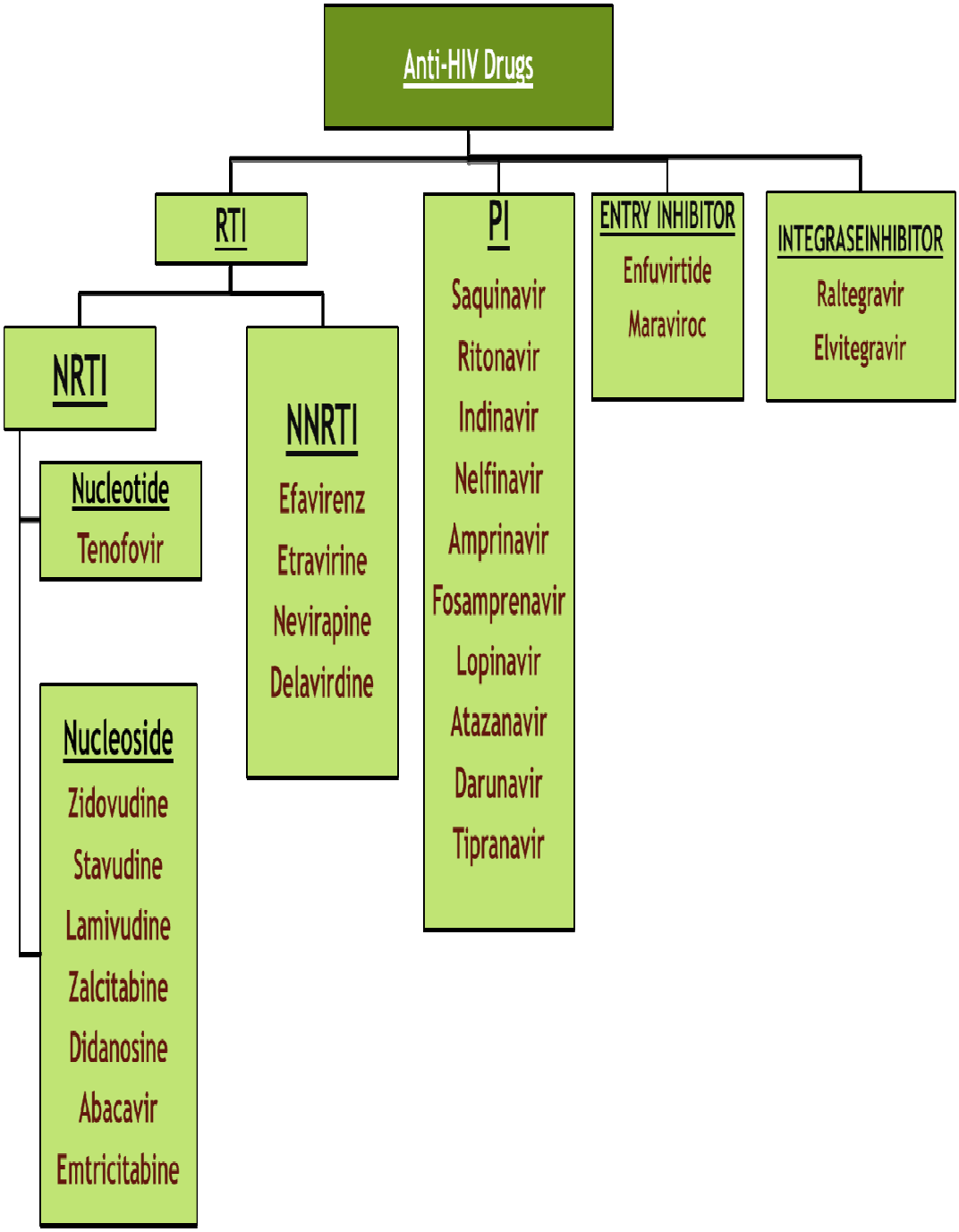
Antiretroviral therapy can also be used to reduce the risk of vertical transmission.

The ARVs can be used after exposure to HIV too, as in cases of accidental needle stick injury, and in cases of sexual assault and rape. It is called post-exposure prophylaxis (PEP).

HAART:

These drugs fall into four main categories:

1. Drugs that inhibit the viral reverse transcriptase enzyme,
2. Drugs that inhibit the viral protease enzyme,
3. Drugs that inhibit viral entry, and
4. Drugs that inhibit the viral integrase


Anti-HIV Drugs
RTI
PI
ENTRY INHIBITOR
INTEGRASEINHIBITOR
NRTI
NNRTI
Nucleotide
Tenofovir
Nucleoside
Zidovudine
Stavudine
Lamivudine
Zalcitabine
Didanosine
Abacavir
Emtricitabine
Efavirenz
Etravirine
Nevirapine
Delavirdine
Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprinavir
Fosamprenavir
Lopinavir
Atazanavir
Darunavir
Tipranavir
Enfuvirtide
Maraviroc
Raltegravir
Elvitegravir

Mechanism of Drug Action:

1. Nucleoside/Nucleotide Analogues These agents act by causing premature DNA-chain termination during the reverse transcription of viralRNA to proviral DNA and should be used in combination with otherantiretroviral drugs. The most common usage is combination with another nucleoside/nucleotide analogue and a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor.

2. Nonnucleoside Reverse Transcriptase Inhibitors These agents interfere with the function of HIV-1 reverse transcriptase by binding to regionsoutside the active site and causing conformational changes in theenzyme that render it inactive. These agents are very potent; however,when they are used as monotherapy, they result in the rapid emergenceof drug-resistant mutants.

3. Protease Inhibitors These drugs are potent and selective inhibitors of the HIV-1 protease enzyme and are active in the nanomolar range.

rapid emergence of resistant isolates when these drugs are used as monotherapy. Thus,the protease inhibitors should be used only in combination with other antiretroviral drugs.

4. HIV Entry Inhibitors These agents act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion. A variety of small molecules that bind to HIV-1 co-receptors are currently in clinical trials.

5. HIV lntegrase Inhibitors These drugs interfere with the integration of proviral DNA into the host cell genome. The first agent in this class,raltegravir, was approved in 2007 for use in treatment-experienced patients.

CLASS SPECIFIC TOXICITIES

1. **NRTIs :**
    - Hepatotoxicity
    - Lactic acidosis
    - Peripheral neuropathy
    - Pancreatitis
2. **NNRTIs:**
    - Rash
    - Hepatitis

3. Protease Inhibitors

- Hyperglycemia
- Fat maldistribution (Lipodystrophy)
- Hyperlipidemia
- Increased bleeding episodes in patients with hemophilia
- A vascular necrosis
- G.I. intolerance and hepatitis

INDICATIONS TO START ANTIRETROVIRAL THERAPY

Table – Indications for the initiation of ART[6,7,8.]
I. Acute infection syndrome
II. Chronic infection a. Symptomatic state (including HIV-associated nephropathy) b. Asymptomatic state 1. CD4+ count <500/L 2. Pregnancy
III. Postexposure prophylaxis

According to NACO Guidelines

ClinicalCD4 count available

Stage I or II ART if CD4 <350/mm3

Stage III and IV ART regardless of CD4.

At present, a reasonable course of action is to initiate HAARTin anyone with the acute HIV syndrome; all pregnant women;patients with an AIDS-defining illness; patients with HIVassociatednephropathy; patients with hepatitis B infectionwhen treatment for hepatitis B is indicated, and patients with asymptomatic disease with CD4+ T cell counts <500mm$^{3.}$

The two options for initial therapy most commonly in use today are

(1) Two nucleoside/nucleotide analogues (one of which is usually tenofovir or abacavir, and the other of which is usually lamivudine or emtricitabine) combined with a protease inhibitor; or

(2) two nucleoside/nucleotide analogues and a nonnucleoside reverse transcriptase inhibitor.

INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV INFECTION

- Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy
- A reproducible significant increase (defined as 3-fold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
- Persistently declining CD4+ T cell numbers
- Clinical deterioration
- Side effects

ECHOCARDIOGRAPHY[18]

EVALUATION OF SYSTOLIC FUNCTION:

Several parameters are used for evaluation of systolic function of the heart. These parameters are LVEF, stroke volume and cardiac index, systolic tissue velocity of the mitral annulus and myocardium, strain, and regional wall motion analysis.

LEFT VENTRICULAR EJECTION FRACTION:

The most well accepted expression of global LV function is LVEF. In clinical practice, LVEF is usually determined by visual assessment of two-dimensional echocardiographic images of the left ventricle.

LVEF should be measured more objectively whenever possible, using volumetric measurements as described by the following equation:

$$LVEF = (LVEDV - LVESV) / LVEDV$$

Where LVEDV and LVESV are LV end-diastolic volume and end-systolic volume, respectively.

LVEF can also be calculated from LV dimensions measured with M-mode or two-dimensional echocardiography. M-mode or two -dimensional echocardiographic measurement of LV dimensions from the mid-ventricular level is used to calculate LVEF as follows:

$$LVEF = (LVEDD2 - LVESD2) / LVEDD2$$

where LVEDD and LVESD are end-diastolic dimension and endsystolic dimension, respectively.

Grading of systolic dysfunction (American Society of Echocardiography):

Ejection fractionsystolic dysfunction

>55% normal

45% - 54% mild systolic dysfunction

30% - 44% moderate systolic dysfunction

<30% severe systolic dysfunction

ASSESSMENT OF DIASTOLIC FUNCTION:

Assessment of diastolic function should be an integral part of an evaluation of cardiac evaluation because about 50% of patients with heart failure have preserved LVEF.

Assessment of diastolic function requires an understanding of diastology and various means to evaluate diastolic function. Currently, echocardiography is the best noninvasive way to evaluate diastolic function and to estimate filling pressures.

LV diastolic filling consists of a series of events that are affected by numerous factors, including myocardial relaxation, compliance, cardiac rhythm, and pericardial compliance.

Normal diastolic function ensures adequate filling of the ventricles during rest and exercise without an abnormal increase in diastolic pressure or pulmonary venous congestion. The initial diastolic event that happens is myocardial relaxation, an active energy-dependent process that causes LV pressure to decrease rapidly after the end of contraction. When LV pressure falls below LA pressure, the mitral valve opens, and rapid early diastolic filling begins.

The proportion of LV filling during the early and late diastolic phases depends on elastic recoil , rate of myocardial relaxation, chamber compliance, LA pressure, and heart rate.

Several parameters are used for grading of diastolic dysfunction. In most cardiac diseases, the initial diastolic abnormality is impaired relaxation. With further progression of disease and a mild to moderate increase in LA pressure, the mitral inflow velocity pattern appears similar to a normal filling pattern (pseudonormalized). With further decrease in LV compliance and increase in LA pressure, diastolic filling becomes restrictive.

Most patients with restrictive filling are symptomatic and have a poor prognosis unless the restrictive filling can be reversed by treatment. However, restrictive filling may be irreversible and represent the end stage of diastolic heart failure.

Grading of diastolic dysfunction:

GRADE	**diastolicdysfunction**
0	normal
1	(mild dysfunction): impaired relaxation with normal filling pressure .
2	(moderate dysfunction): pseudonormalized mitral inflow pattern.
3	(severe reversible dysfunction): reversible restrictive (high filling pressure)
4	(severe irreversible dysfunction): irreversible restrictive (high filling pressure) .

DILATED CARDIOMYOPATHY:

This is basically characterised by enlarged LV cavity and global systolic function is decreased.

End-diastolic and end-systolic dimensions and volumes are increased, and systolic function is decreased. With gradual dilation, the LV cavity which becomes more spherical, with a sphericity index (short-axis dimension/long-axis dimension) nearing the value of 1 (normally, ≥1.5).

LV mass is uniformly increased (eccentric hypertrophy), and wall thickness is typically within normal limits. Ventricular contractility usually is globally reduced, but regional wall motion abnormalities can be present.

Secondary features may be identified by echocardiography in patients with dilated cardiomyopathy. These include dilated mitral annulus with incomplete mitral leaflet coaptation causing functional MR, evidence of low cardiac output (decreased excursion of mitral leaflets), enlarged atrial cavities, RV enlargement, and occasionally apical mural thrombus.

Echocardiography also plays a role in assessing the prognosis. Some of the determining prognostic factors are[22.]

(a) degree of cardiomegaly;

(b) degree of LV dysfunction;

(c) extent of wall thickness of ventricles;

(d) pulmonary hypertension;

(e) restrictive filling pattern as assessed by mitral inflow Doppler; and

(f) some tissue Doppler imaging parameters.

PERICARDIAL EFFUSION:

Echocardiography is the diagnostic modality of choice for detecting, quantifying, and assessing the hemodynamic impact of pericardial effusions and can often provide additional information about the pericardial contents.

A separation of pericardial fluid between the visceral and parietal layers of the pericardium that persists through diastole as well as systole represents a small effusion. Small effusions tend to pool at the baseof the heart.

Moderate-sized effusions are visible circumferentially as echo-free regions anterior to the right ventricular (RV) free wall and posterior to the

left ventricle. As an effusion enlarges, it extends apically, laterally and then anteriorly becoming circumferential.

PULMONARY ARTERY HYPERTENSION:

Echocardiography usually demonstrates enlargement of the right atrium and ventricle, normal or small left ventricular dimensions, and a thickened interventricular septum.

Right ventricular dysfunction is difficult to measure echocardiographically, but the position and curvature of the intraventricular septum provide an indication of right ventricular afterload.

Echocardiographic findings that indicate a poor prognosis include pericardial effusion and a markedly diminished left ventricular cavity. Doppler echocardiographic estimates of right ventricular systolic pressures can be obtained by measuring the velocity of the tricuspid regurgitant jet and by using the Bernoulli formula.

Grading Pulmonary hypertension

< 31	Normal:
31–35	Borderline
36–40	Mild

41–50	Moderate
>50	Severe.

CD4 CELL COUNT

CD4 T-cell laboratory testing through flow cytometry is considered an essential part of HIV care, since this parameter is used to stage disease and guide clinical management. Certain CD4 T cell thresholds are used as reference to either initiate prophylaxis against opportunistic infections (OIs) and/or to begin antiretroviral therapy. The CD4 cell count is also a relatively consistent indicator of treatment response.

CD4 and CD8 T cells:[15].

Human T lymphocytes can be functionally divided into cells that provide help for other immune cells and those that mediate cellular cytotoxicity. Helper T lymphocytes express CD4 ,whereas cytotoxic T cells express CD8. The CD4 and CD8 molecules are members of the immunoglobulin superfamily and mediate adhesion to major histocompatibility complex class II and class I molecules, respectively.

A CD4:CD8 ratio is calculated by dividing the number of CD4+ T cells by the number of CD8+ T cells; this ratio is usually greater than 1 in

immunocompetent individuals. However, in HIV infection, the CD4:CD8 ratio is less than 1. This reflects increasing numbers of CD8+ T cells and depletion of CD4+ T cells in chronic infection. This ratio usually increases with the initiation of antiretroviral therapy.

HIV and CD4 Cells:

CD4 cells are reduced precipitously in acute HIV infection, but usually rebound over several weeks as HIV-specific CD8 T cells help to lower plasma viremia. In the untreated patient, CD4 T cells subsequently decline over several years.

Subsequently, the CD4 cell count declines at an average yearly rate of approximately 50 cells/mm3. Significant depletion of CD4 T cells can lead to opportunistic infections and mortality in the untreated patient.

Treatment with ART leads to viral suppression and immunologic improvement; the extent of the immune recovery is dependent on the degree of immune compromise prior to treatment. Incomplete immunologic recovery among patients with advanced disease may be related to collagen formation in the gut and lymphoid tissues leading to disruption of normal architecture.

Normal CD4 cell count:

The normal adult CD4 count for most laboratories falls in a range of 800 to 1050 cells/mm3.When considering laboratory variations of two standard deviations, the normal CD4 cell count range falls within 500 to 1400 cells/mm3. This broad range in normal values reflects the fact that the CD4 cell count is the product of three variables: the white blood cell count, the percentage of lymphocytes, and the percentage of lymphocytes that bears the CD4 receptor.

Condition that affect CD4 count:

- Infection
- Medications
- Alcohol abuse[17.]
- Chronic conditions
- Pregnancy.

CD4 T CELL RESPONSE TO ANTIRETROVIRAL THERAPY:[16.]

With antiretroviral therapy and effective viral suppression, the expected CD4 cell response is an increase of 100 to 150 cells/mm3 at one year and an additional 20 to 50 cells/mm3 annually for the next three to five years. When ART is discontinued there is generally a rapid viral load

rebound and sharp decline in CD4 count up to 100 to 150 cells/mL in three to four months.

Factors that correlate with reduced CD4 recovery:

- Older age,
- Male sex, and
- Type of ART used.

ECHOCARDIOGRAPHIC FINDINGS IN PATIENTS WITH HIV INFECTION[18].

In HIV-infected patients, concurrent pulmonary infections, pulmonary hypertension, anemia, portal hypertension, malnutrition, or malignancy can alter or confuse the characteristic signs that may be seen in heart failure in other populations. Thus, patients with left ventricular systolic dysfunction can present asymptomatic or can present with New York Heart Association Class III or IV heart failure.

Echocardiography is useful for assessing left ventricular systolic function in this population and, in addition to diagnosing left ventricular dysfunction, often reveals low to normal wall thickness or left ventricular hypertrophy and a dilated left ventricle.

Echocardiography should be performed in any patient at elevated cardiovascular risk, with any clinical manifestations of cardiovascular disease, or with unexplained or persistent pulmonary symptoms or viral coinfections at baseline and every 1 to 2 years thereafter, or as clinically indicated.

Dilated cardiomyopathy was strongly associated with a CD4 count lower than 100 cells/mL.

Clinical and echocardiographic findings suggest that diastolic dysfunction is relatively common in long-term survivors of HIV infection.

HIV-infected patients with pericardial effusions often have a lower CD4 count than those without effusions, indicating more advanced disease. Effusions are generally small and asymptomatic.Screening echocardiography is recommended for HIV-infected individuals, irrespective of the stage of Disease.

The CD4 count has been independently associated with survival in HIV PAH patients, and pulmonary hypertension was the direct cause of death in these patients.

MATERIAL AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, ART Centre and Madras Medical College.

ETHICAL COMMITTEE APPROVAL:

Obtained.

STUDY DURATION:

This study was conducted over a period of six months.

STUDY POPULATION:

Patients admitted with HIV infection at medical wards, Institute of Internal medicine.

SAMPLE SIZE:

100 cases

TYPE OF STUDY

Cross sectional study.

INCLUSION CRITERION:

- HIV infected adults with CD4 count < 500

EXCLUSION CRITERIA:

- Structural Heart Disease
- Coronary Artery Disease
- Systemic Hypertension
- Diabetes mellitus
- Thyroid disorders
- Dyslipidemia

DATA COLLECTION AND METHODS: Informed consent was obtained from each patient or the relative.

Patients had their history taken according to a Questionnaire and were subjected to clinical examination.

Patients are subjected to routine blood investigations like complete blood count, renal function tests, liver function tests; Fasting lipid profile, Thyroid function test,ECG, echocardiography and CD4 count will be done

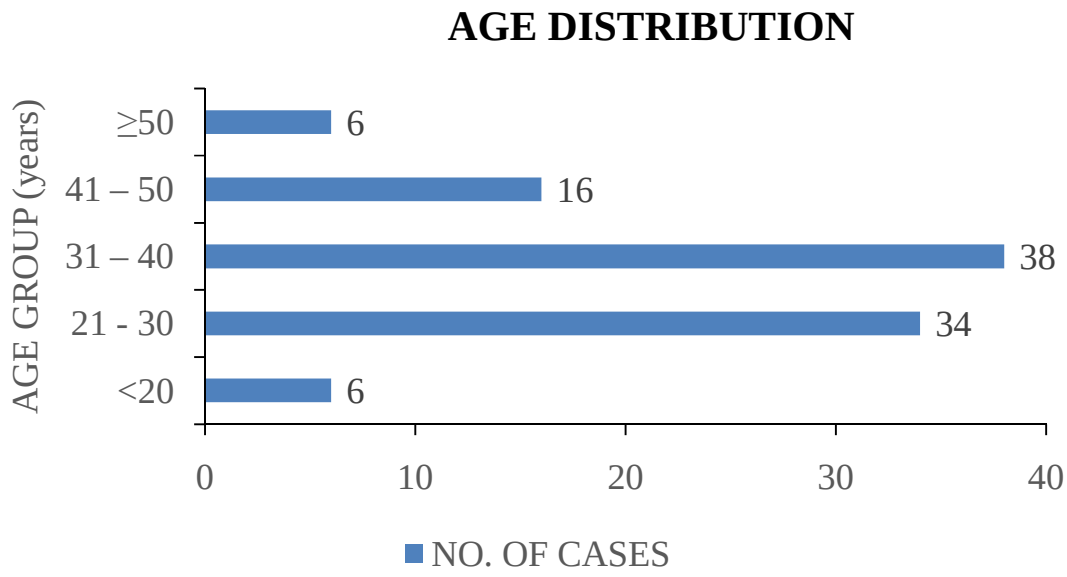
All the data were entered in the proforma (enclosed).

Data were analyzed using SPSS package and ANOVA.

OBSERVATION AND RESULTS

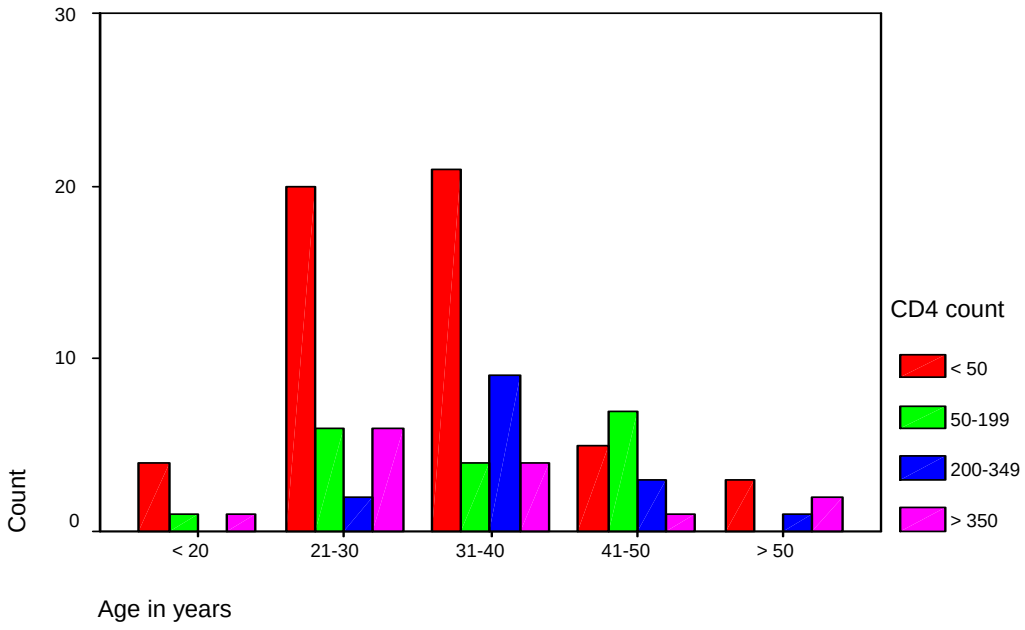
AGE DISTRIBUTION:

AGE GROUP (years)	NO. OF CASES
<20	6
21 - 30	34
31 – 40	38
41 – 50	16
≥50	6



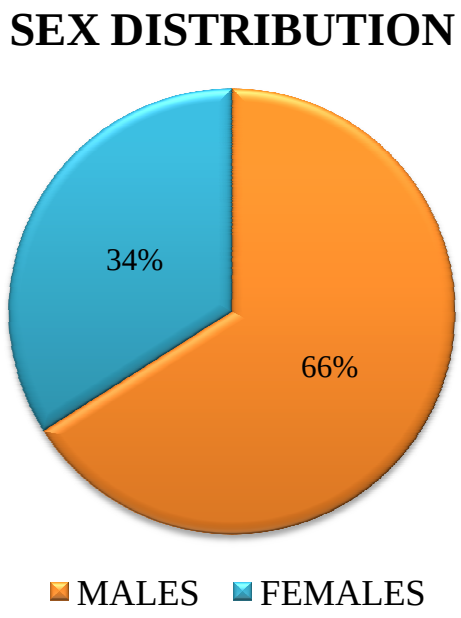
AGE AND CD4 COUNT:

Age in years	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
< 20	4	1	0	1	
21-30	20	6	2	6	
31-40	21	4	9	4	p value 0.098
41-50	5	7	3	1	
≥50	3	0	1	2	



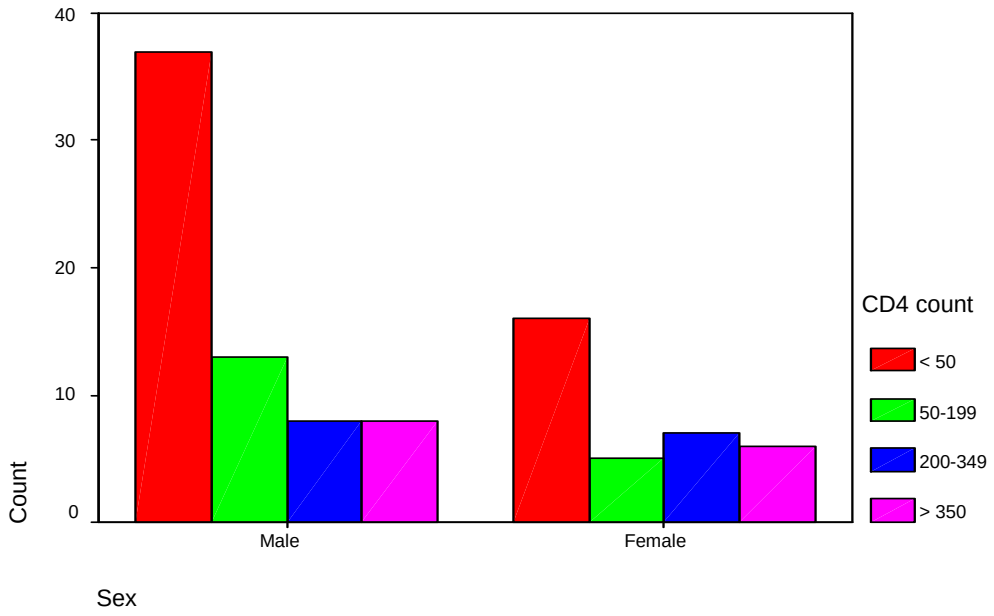
SEX DISTRIBUTION:

SEX	NO. OF CASES
MALE	66
FEMALE	34



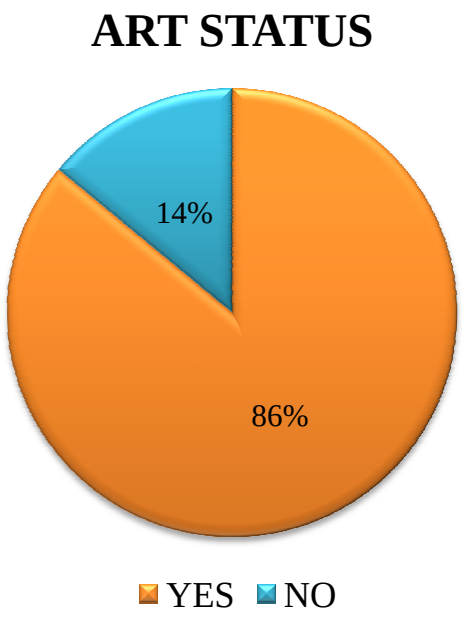
SEX AND CD4 COUNT:

Sex	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
Male	37	13	8	8	p value
Female	16	5	7	6	0.529



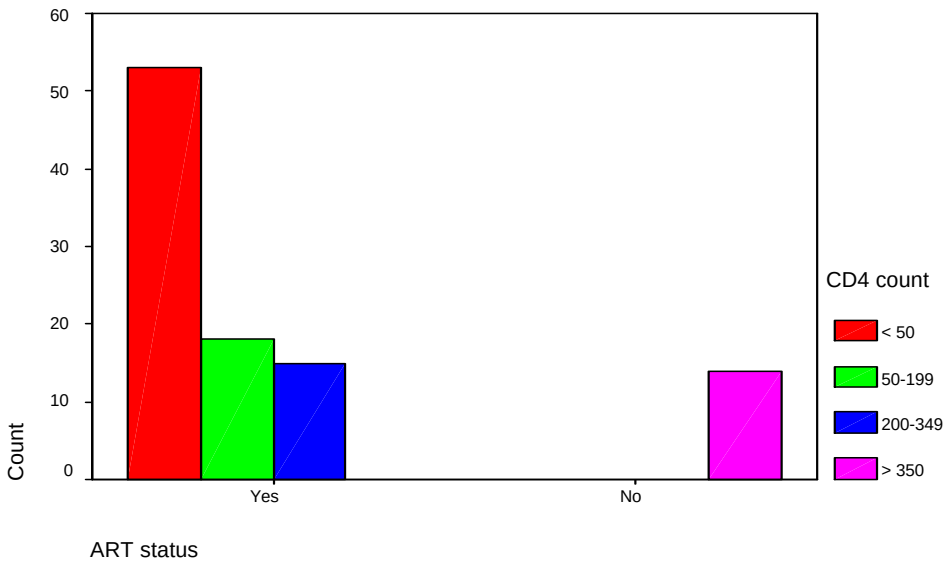
ART STATUS:

ART STATUS	NO. OF CASES
YES	86
NO	14



ART STATUS AND CD4 COUNT:

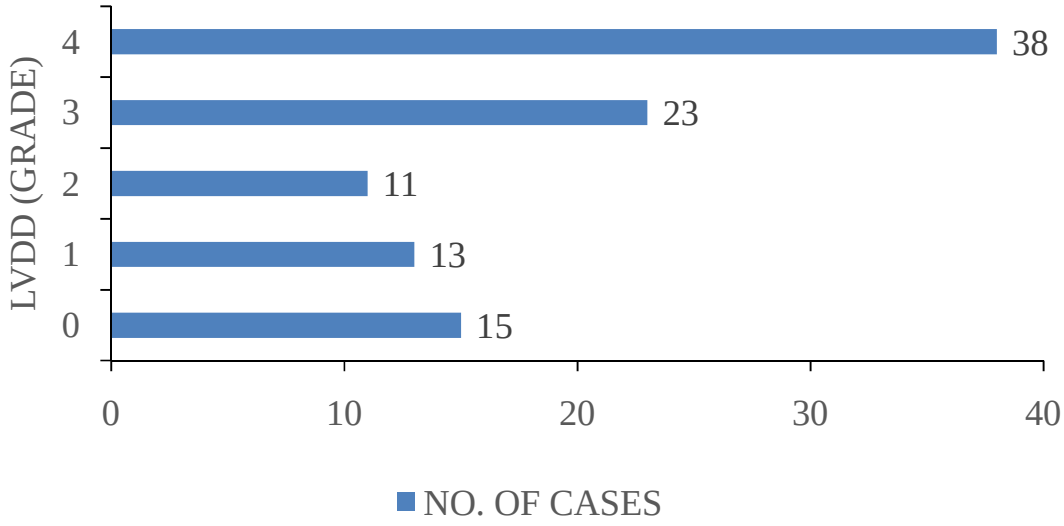
ART STATUS	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
YES	53	18	15	0	
NO	0	0	0	14	**p value <0.001**



LVDD AMONG THE STUDY GROUP:

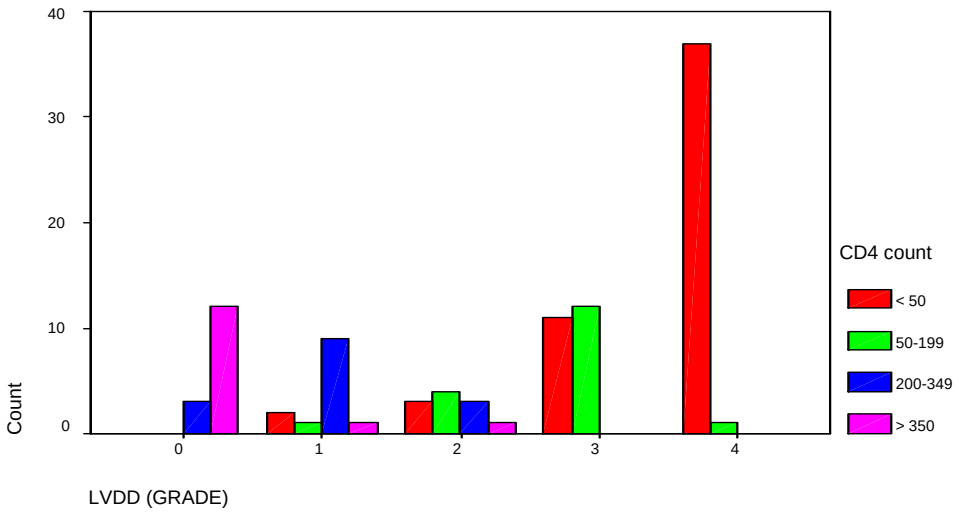
LVDD (GRADE)	NO. OF CASES
0	15
1	13
2	11
3	23
4	38

LVDD AMONG THE STUDY GROUP



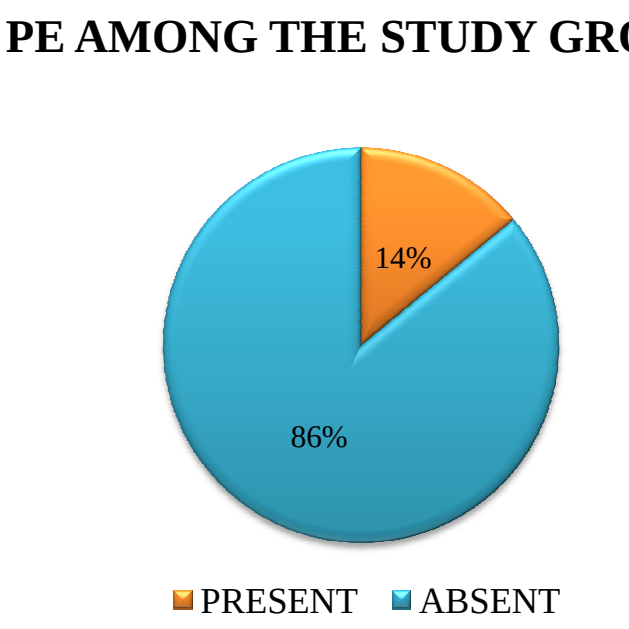
LVDD AND CD4 COUNT:

LVDD (GRADE)	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
0	0	0	3	12	
1	2	1	9	1	p value
2	3	4	3	1	**<0.001**
3	11	12	0	0	
4	37	1	0	0	



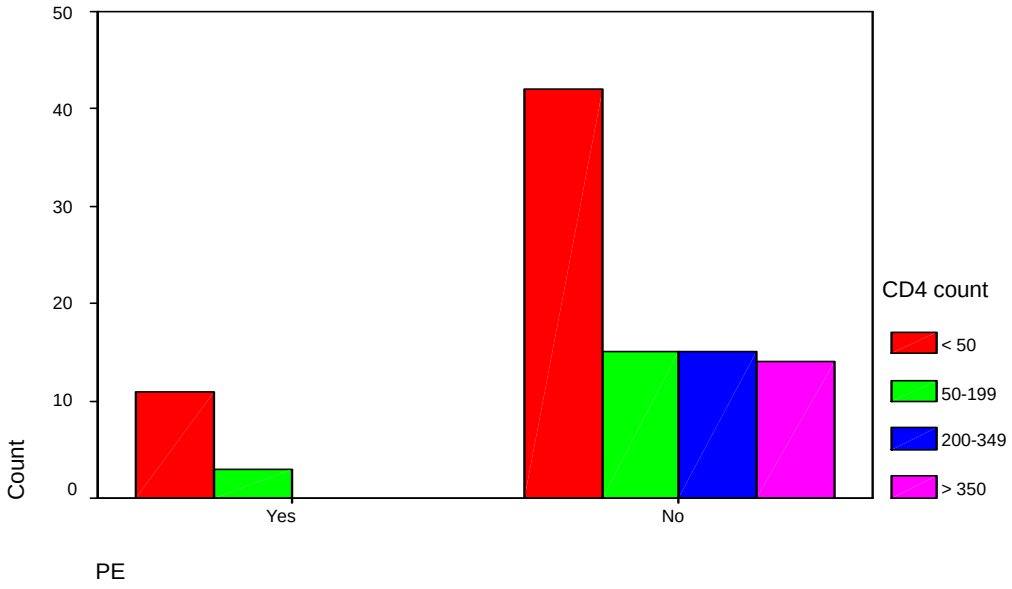
PE AMONG THE STUDY GROUP:

PERICARDIAL EFFUSION	NO. OF CASES
PRESENT	14
ABSENT	86



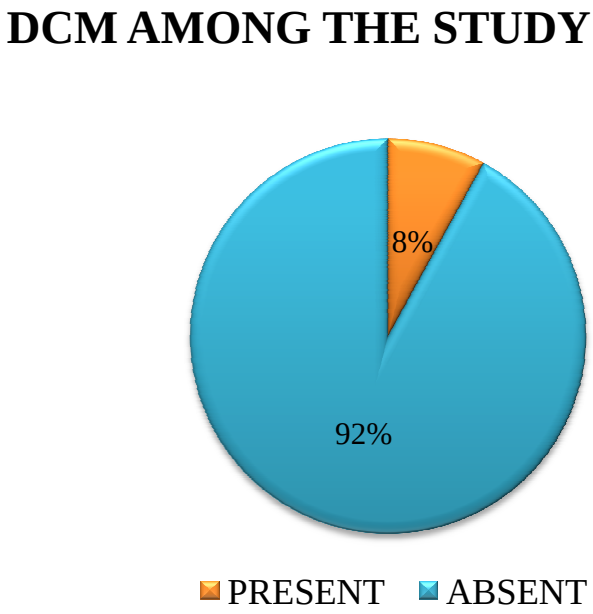
PEAND CD4 COUNT:

PERICARDIAL EFFUSION	No. of patients with CD4 count (cells/mm^3)				p value
	< 50	**50-199**	**200-349**	> 350	
PRESENT	11	3	0	0	**0.013**
ABSENT	42	15	15	14	



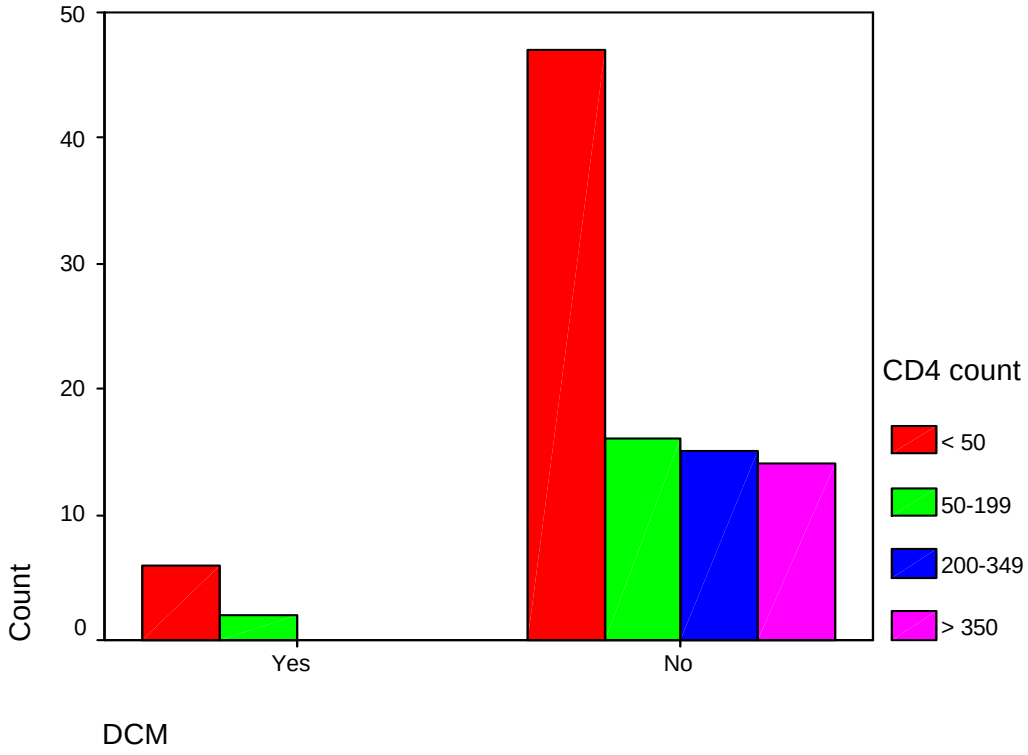
DCM AMONG THE STUDY GROUP:

DILATED CARDIOMYOPATHY	NO. OF CASES
PRESENT	8
ABSENT	92



DCMAND CD4 COUNT:

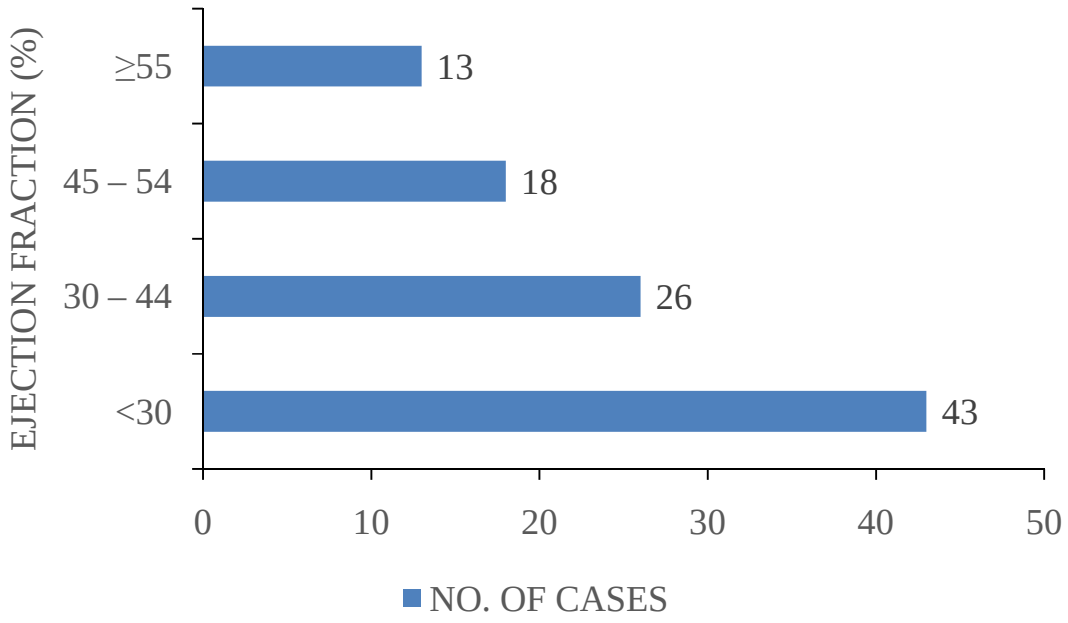
DILATED CARDIOMYOPATHY	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
PRESENT	6	2	0	0	p value 0.314
ABSENT	47	16	15	14	



EF AMONG THE STUDY GROUP:

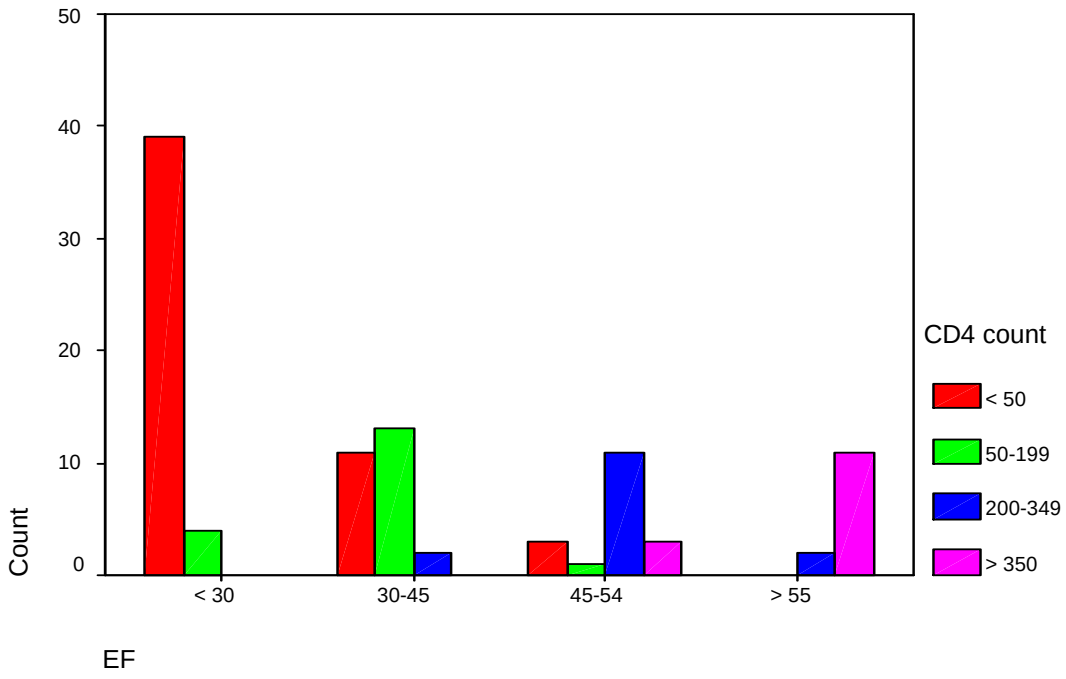
EJECTION FRACTION (%)	NO. OF CASES
<30	43
30 – 44	26
45 – 54	18
≥55	13

EF AMONG THE STUDY GROUP



EFAND CD4 COUNT:

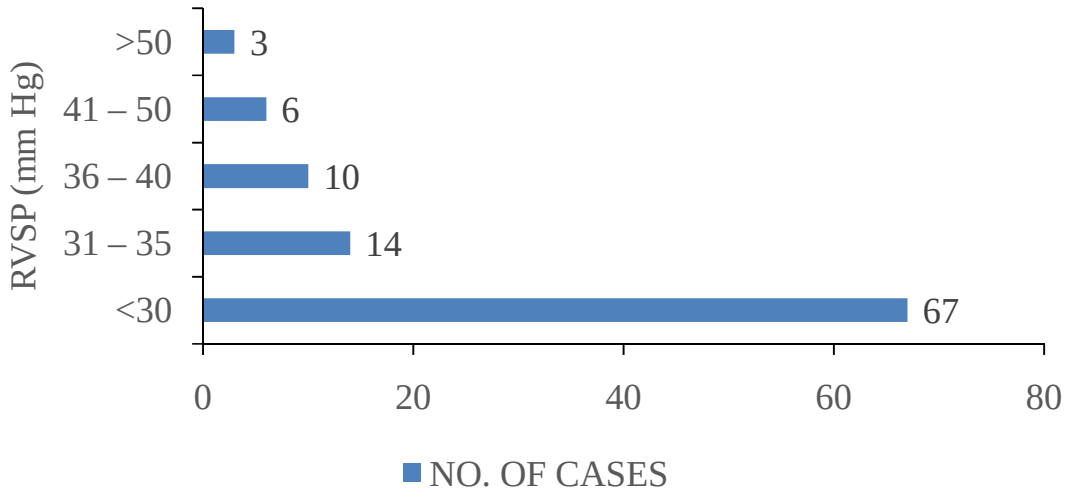
EF (%)	No. of patients with CD4 count (cells/mm^3)				
	< 50	**50-199**	**200-349**	**> 350**	
<30	39	4	0	0	
30 – 44	11	13	2	0	p value
45 – 54	3	1	11	3	**<0.001**
≥55	0	0	2	11	



PAH AMONG THE STUDY GROUP:

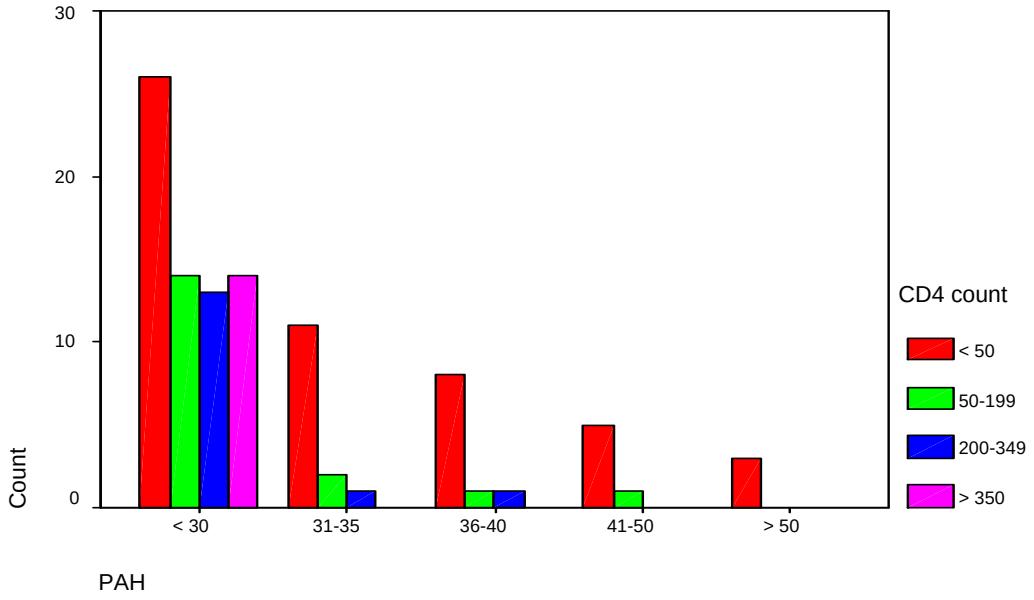
RVSP (mm Hg)	NO. OF CASES
<30	67
31 – 35	14
36 – 40	10
41 – 50	6
>50	3

PAH AMONG THE STUDY GROUP



PAHAND CD4 COUNT:

RVSP (mm Hg)	No. of patients with CD4 count (cells/mm^3)				
	< 50	50-199	200-349	> 350	
<30	26	14	13	14	
31 – 35	11	2	1	0	p value
36 – 40	8	1	1	0	**<0.001**
41 – 50	5	1	0	0	
>50	3	0	0	0	



RESULTS

Age distribution:

In this present study about 6% were in the age group <20years, 34% were in the age group of 21-30 years, 38% were in the age group of 31-40 years and16% were in the group of 41-50 years and 6% were in the age group of >50 years.

Age and CD4 count:

In this present study, 66.7% of the patientsin the age group of <20years had a CD4 count of <50, 16.7% had a CD4 count between 50-199,none had aCD4 countbetween 200-349 and 16.7% had a CD4 count of>350. 58.8% of the patients in the age group of 21-30 years had a CD4 count of <50, 17.6% had a CD4 count between 50-199, 5.9% had aCD4 count between 200-349 and 17.6% had a CD4 count of >350. 55.3% of the patients in the age group of 31-40years had a CD4 count of <50, 10.5% had a CD4 count between 50-199, 23.7% had aCD4 count between 200-349 and 10.5% had a CD4 count of >350. 31.3% of the patients in the age group of 41-50years had a CD4 count of <50, 43.8% had a CD4 count between 50-199, 18.8% had aCD4 count between 200-349 and 6.3% had a CD4 count of >350. 50.0% of the patients in the age group of >50years had a CD4 count

of <50, none had a CD4 count between 50-199, 16.7% had aCD4 count between 200-349 and 33.3% had a CD4 count of >350. Their comparison was not statistically significant (p value = 0.119).

Sex distribution:

In our study about 66% were males and 34% were females.

Sex and CD4 count:

In this present study, 56.1% of the males had a CD4 count of <50, 19.7% had a CD4 count between 50-199, 12.1% had aCD4 count between 200-349 and 12.1% had a CD4 count of >350. 47.1% of the females had a CD4 count of <50, 14.7% had a CD4 count between 50-199, 20.6% had aCD4 count between 200-349 and 17.6% had a CD4 count of >350.Their comparison was not statistically significant (p value = 0.529).

ART status:

Among the 100 patients enrolled in this study, 86 were on ART and 14 were ART naïve.

ART status and CD4 count:

Among the 86 patients who were on ART, 61.6% had a CD4 count of <50, 20.9% had a CD4 count between 50-199, 17.4% had a CD4 count

between 200-349 and none had a CD4 count of >350. All the 14 patients who were ART naïve had a CD4 count of >350. Their comparison was statistically significant (**p value <0.001**).

LVDD:

Among the 100 patients, 15 had grade 0 LVDD; 13 had grade 1; 11, 23 and 38 had grade 2, 3 and 4 LVDD respectively.

LVDD and CD4 count:

Among the 15 patients with grade 0 LVDD, 20% had a CD4 count between 200-349 and 80% had a CD4 count of >350. Among the 13 patients with grade 1 LVDD, 15.4% had a CD4 count of <50, 7.7% had a CD4 count between 50-199, 69.2% % had a CD4 count between 200-349 and 7.7% had a CD4 count of >350. Among the 11 patients with grade 2 LVDD, 27.3% had a CD4 count of <50, 36.4% had a CD4 count between 50-199, 27.3% had a CD4 count between 200-349 and 9.1% had a CD4 count of >350. Among the 23 patients with grade 3 LVDD, 47.8% had a CD4 count of <50 and 52.2% had a CD4 count between 50-199. Among the 38 patients with grade 4 LVDD, 97.4% had a CD4 count of <50 and 2.6% had a CD4 count between 50-199. Their comparison was statistically significant (**p value < 0.001**).

PE:

Among the 100 patients, 14 had PE.

PE and CD4 count:

Among the 14 patients, 78.6% had a CD4 count of <50 and 21.4% had a CD4 count between 50-199. Their comparison was statistically significant (**p value = 0.014**).

DCM:

Among the 100 patients, 8 had DCM.

DCM and CD4 count:

Among the 8 patients, 75% had a CD4 count of <50 and 25% had a CD4 count between 50-199. Their comparison was not statistically significant (p value = 0.086).

EF:

Among the 100 patients, 43 had EF <30%; 26, 18 and 13 had EF of 30-44%, 45-54% and ≥55% respectively.

EF and CD4 count:

Among the 43 patients with EF < 30%, 90.7% had a CD4 count of <50 and 9.3% had a CD4 count between 50-199. Among the 26 patients with EF 30-44%, 42.3% had a CD4 count of <50; 50% had a CD4 count between 50-199 and 7.7% had a CD4 count between 200-349. Among the 18 patients with EF 45-54%, 16.7% had a CD4 count of <50; 5.6% had a CD4 count between 50-199; 61.1% had a CD4 count between 200-349 and 16.7% had a CD4 count of >350. Among the 13 patients with EF ≥55%, 15.4% had a CD4 count between 200-349 and 84.6% had a CD4 count of >350. Their comparison was statistically significant (**p value < 0.001**).

PAH:

Among the 100 patients, 67 had RVSP <30mmHg; 14, 10, 6 and 3 had RVSP of 31-35mmHg, 36-40mmHg, 41-50mmHg and >50mmHg respectively.

PAH and CD4 count:

Among the 67 patients who had a RVSP <30mmHg, 38.8% had a CD4 count of <50; 20.9% had a CD4 count between 50-199; 19.4% had aCD4 count between 200-349 and 20.9% had a CD4 count of >350. Among the 14 patients with RVSP 31-35mmHg, 78.6% had a CD4 count of <50;

14.3% had a CD4 count between 50-199 and 7.1% had a CD4 count between 200-349. Among the 10 patients with RVSP 36-40mmHg, 80% had a CD4 count of <50; 10% had a CD4 count between 50-199 and 10% had a CD4 count between 200-349. Among the 6 patients with RVSP 41-50mmHg, 83.3% had a CD4 count of <50 and 16.7% had a CD4 count between 50-199. All the 3 patients with RVSP >50mmHg had a CD4 count of <50. Their comparison was statistically significant (**p value < 0.001**).

DISCUSSION

Number of patients taken up for study :

Study groups	Total number of cases
Ayaskanta Singh et al[12]	70
Mondy et al[13]	656
Reinsh et al[9]	803
Present study	100

But no controls were used in this present study.

AGE:

Mean age of patients in various studies

Ayaskanta Singhet al Males 38.87±8.71 years

Females 33.38±7.73 years

Reinsh et al Males 44.2± 10.3 years

Females 40.3±9.2 years

Present study 33±9.1 years

The mean age of patients in this present study was lower than that of previous studies.

GENDER:

Sex distribution of patients in various studies:

Ayaskanta et alMales 45 (64.3%)

Females 25 (35.7%)

Mondy et al Males 501(76%)

Females 155(24%)

Present study Males 66(66%)

Females 34(34%)

The male female ratio is comparable to other studies.

CD4 COUNT:

The Mean CD4 count was

Reinsh et al 509±301cells/mm^3

Present study 149.53±147.53cell/mm^3

In this present study mean CD4 count is lower than the previous studies.

Median CD4 count was

Mondy et al 462 (326-661)cell/mm^3

Present study 48(24-491)cell/mm^3

Our study has low median CD4 count.

ART status:

Patients who were on ART

Mondy et al 478(73%)

Present study 86(86%)

EF:

Mondy et al found 533(82%) cases with EF >55% and 1(<1%) case with EF<35%.In our study we found 13(13%) cases with EF>55% and 43(43%) cases with EF<30%.In comparison our study had patients with significant reduction in EF.

EF and CD4 count:

Ayaskanta singh et al studied patients with EF<50% and foundCD4 count <50 and CD4 count 50-199 were present in 9(56.2%) and 6(37.5%) cases respectively.In our present study we studied patients with EF<30% and observed CD4 count <50 and CD4 count 50-199 in 39(90.7%) and 4(9.3%) cases respectively.In the former study EF was not stratified below <50%.

LVDD:

Mondy et al found 477(74%) cases with GR 0 and 61(9%) cases with GR 3 LVDD.In our study we found 15(15%) cases with GR 0 and 38(38%) cases with GR 4 LVDD .In comparison our study had patients with significant LVDD.

LVDD and CD4Count:

Ayaskanta singh et al studied patients with LVDD and found CD4 count <50 and CD4 count 50-199 were present in 3 (50%) and 2 (33.3%) cases respectively.In our present study we studied patients with LVDD GR 4 and observed CD4 count <50 and CD4 count 50-199 in 37(97.4 %) and 1(2.6%) cases respectively. In the former study LVDD was not stratified with grading.

PAH:

Mondy et al found 139(43%) cases with RVSP <31mmHg and 5(2%) cases with RVSP≥50.In our study we found 67(67%) cases with RVSP <31 and 3(3%) cases with RVSP ≥50.In comparison our study had patients with significant PAH.

PAH and CD4:

Ayaskanta singh et al studied patients with PAH and observed CD4 count <50 and CD4 count 50-199 in 3(37.5%) and 4(50%) cases respectively. In our present study we found RVSP ≥50 and CD4 count <50 in 3(100%) cases.In the former study PAH was not graded according to RVSP mm Hg.

DCM and CD4 count:

Ayaskanta singh et al studied patients with DCMand found CD4 count <50 and CD4 count 50-199 were present in 5(83.3%) and 1(16.7%) cases respectively. In our present study we had patients with DCM and observed CD4 count <50 and CD4 count 50-199 in 6(75%) and 2(25%) cases respectively. Our study results were comparable to the former study.

PE and CD4:

Ayaskanta singh et al studied patients with PE and found CD4 count <50 and CD4 count 50-199 in 8 (66.7%) and 2 (16.7%) cases respectively. In our present study we had patients with DCM and CD4 count <50 and CD4 count 50-199 in 11(78.6 %) and 3(21.4 %) cases respectively.

LIMITATIONS OF STUDY

- One limitation of this study was less number of patients.
- As this study was a cross-sectional study follow up of patients could not be done to assess the clinical improvement resulting from HAART.
- This study did not include a suitable HIV-seronegative control group.

CONCLUSION

- Cardiovascular manifestations are common in HIV infected patients and often subclinical.
- Echocardiography is a useful technique for the early recognition and treatment of cardiac abnormalities.
- CD4 count correlates well with Echocardiographic findings.

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PROFORMA

A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4COUNT

Name : Patient ID No:

Age/Sex :

IP No :

Presenting complaints			
☐	Dyspnea	☐	Oliguria
☐	Orthopnea	☐	Abdominal distension
☐	PND	☐	Swelling of legs
☐	Chest pain	☐	Others

Past history	
☐ Diabetes mellitus	☐ Coronary artery disease
☐ Hypertension	☐ Other comorbid illnesses

Personal history	
☐ Smoking	☐ Alcoholism

ART status	
☐ Yes – duration:	☐ No

CLINICAL PARAMETERS			
Pulse		**Blood Pressure**	

General examination

Systemic examination	
CVS:	**RS:**
P/A:	**CNS:**

Investigations

RFT			**LFT**		
Glucose (F)		mg/dl	Total bilirubin		mg/dl
(PP)		mg/dl			
Urea		mg/dl	Direct bilirubin		mg/dl
Creatinine		mg/dl	SGOT		U/l
Na+		mEq/l	SGPT		U/l
K+		mEq/l	ALP		U/l
			Total protein		g/dl
			Albumin		g/dl

Hemogram			**Lipid profile**		
TC		cells/mm^3	Total cholesterol		mg/dl
DC			LDL		mg/dl
ESR		mm/hr	HDL		mg/dl
Hb		g/dl	Triglycerides		mg/dl
PCV		%	**Thyroid function test**		
Platelets		lakhs/mm^3	T_3		ng/dL

RBCs		million/mm^3	T_4		μg/dL
			TSH		μIU/mL
CD4 count					

Chest X-ray:

ECG:

Echocardiography:

PATIENT CONSENT FORM

Study Detail : **"A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted ❑

in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests. ❑

Signature/thumb impression Signature of Investigator

Patient's Name and Address: Study Investigator's Name:

DR. PAKKEER KANNU SYED FAHRUDEEN MUNNAVER

S. NO	AGE	SEX	ART status	CD4 count	EF	LVDD (GRADE)	PAH	PE	DCM
1	21	F	Y	88	29	4	48	Y	N
2	31	M	Y	262	38	2	26	N	N
3	22	F	N	422	58	0	24	N	N
4	30	M	Y	132	38	3	28	N	N
5	31	F	Y	41	42	3	30	N	N
6	21	M	Y	33	29	4	46	N	N
7	41	F	Y	124	38	3	30	N	N
8	41	M	Y	340	58	1	24	N	N
9	32	F	N	486	60	0	26	N	N
10	42	M	Y	311	48	2	26	N	N
11	32	M	Y	28	27	4	61	Y	N
12	19	F	Y	24	28	4	55	Y	N
13	22	M	Y	31	25	4	44	N	N
14	51	M	Y	44	40	3	28	N	Y
15	33	F	Y	322	50	1	26	N	N
16	23	F	N	472	62	0	25	N	N
17	19	M	Y	152	37	3	26	N	N
18	23	M	Y	46	52	1	30	N	N
19	33	M	Y	44	39	2	28	N	N
20	24	M	Y	37	28	4	38	N	N
21	34	F	Y	40	43	3	30	N	N
22	52	M	Y	48	51	2	28	N	N
23	29	M	Y	167	40	2	28	N	N
24	34	M	Y	288	49	1	26	N	N
25	53	M	N	388	60	0	26	N	N
26	35	M	Y	47	38	3	30	N	N
27	54	M	Y	28	25	4	62	Y	N
28	24	F	Y	35	27	4	48	N	N
29	36	M	Y	37	28	4	46	N	N
30	25	M	Y	99	38	3	34	N	N
31	28	M	Y	264	47	1	38	N	N
32	35	F	N	416	56	0	25	N	N
33	43	M	Y	149	36	3	28	N	N
34	37	M	Y	39	29	4	37	N	N
35	42	F	Y	40	29	4	39	N	Y
36	25	F	Y	45	39	3	28	N	N
37	48	M	Y	117	37	3	30	Y	N
38	38	M	Y	238	47	1	34	N	N
39	51	F	N	449	61	0	26	N	N
40	26	M	Y	138	38	3	26	N	N
41	36	F	Y	49	43	3	30	Y	N
42	20	M	Y	40	28	3	36	N	N
43	44	M	Y	175	43	3	30	N	N

44	39	M	Y	337	60	0	28	N	N
45	27	M	N	377	53	1	24	N	N
46	40	M	Y	71	28	3	38	N	Y
47	37	F	Y	41	28	3	30	Y	N
48	27	M	Y	39	27	4	38	N	N
49	26	F	Y	35	26	4	39	N	N
50	31	M	Y	43	41	2	28	N	N
51	49	M	Y	37	28	4	30	N	Y
52	32	M	Y	39	26	4	28	N	N
53	27	F	Y	47	41	3	30	N	N
54	28	M	Y	43	29	4	28	N	N
55	50	M	Y	188	52	2	28	Y	N
56	38	F	Y	289	49	1	26	N	N
57	33	M	N	408	51	2	25	N	N
58	21	M	Y	42	26	4	34	N	N
59	31	M	Y	40	28	4	30	N	N
60	45	M	Y	37	25	4	38	N	N
61	34	M	Y	33	24	4	48	N	N
62	39	F	Y	331	52	1	26	N	N
63	19	M	N	434	58	0	26	N	N
64	43	F	Y	151	29	3	26	N	N
65	28	F	Y	31	24	4	32	N	N
66	29	M	Y	38	29	4	33	N	N
67	35	M	Y	48	29	4	32	N	N
68	26	M	Y	45	29	4	34	N	N
69	41	M	Y	41	28	4	33	Y	Y
70	40	F	Y	40	28	4	35	N	N
71	36	M	Y	35	25	4	38	Y	N
72	31	F	Y	172	42	3	26	N	N
73	29	F	N	461	60	0	25	N	N
74	37	M	Y	74	28	3	33	N	Y
75	25	M	Y	48	29	4	30	N	N
76	32	F	Y	38	28	4	30	N	N
77	38	M	Y	33	27	4	28	Y	Y
78	30	F	Y	325	51	1	26	N	N
79	46	M	Y	29	24	4	30	Y	N
80	30	M	Y	41	29	4	28	N	N
81	33	F	Y	223	50	1	28	N	N
82	42	M	N	491	60	0	25	N	N
83	39	M	Y	171	41	2	26	N	N
84	24	M	Y	38	28	4	30	N	N
85	20	M	Y	47	50	1	28	N	N
86	34	F	Y	48	41	3	35	N	N
87	40	M	Y	34	28	4	34	Y	N

88	52	F	Y	316	51	0	26	N	N
89	22	M	N	372	52	0	25	N	N
90	44	F	Y	113	40	2	28	N	N
91	23	M	Y	33	25	4	33	N	N
92	30	F	Y	49	43	3	30	N	N
93	35	F	Y	262	49	0	26	N	N
94	32	M	N	456	63	0	24	N	N
95	22	M	Y	129	38	1	28	N	N
96	20	M	Y	44	29	4	32	N	N
97	23	M	Y	47	29	4	28	N	N
98	36	F	Y	40	28	4	30	Y	Y
99	47	M	Y	241	39	2	28	N	N
100	21	M	N	463	61	0	24	N	N

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

EC RegNo.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.P.Syed Fahrudeen Munnaver,
PG in MD General medicine
Madras Medical College, Chennai-3.

.

Dear P.Syed Fahrudeen Munnaver

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A study of echocardio graphic findings in HIV- Infected Patients and their correlation with CD4 count" No.24072013.

The following members of Ethics Committee were present in the meeting held on 02.07.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.G.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. Kalai Selvi -- Member
   Prof of Pharmacology, MMC, Ch-3
6. Prof. Siva Subramanian, -- Member
   Director, Instt. of Internal Medicine, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandhini 12/7/13

Member Secretary, Ethics Committee

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Assignment title	Medical
Author	20111024 . M.d. General Medicine PAKKEER KANNU SYED FAHRUDEEN MUNNAVER
E-mail	syedfm@gmail.com
Submission time	22-Dec-2013 09:47PM
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First 100 words of your submission

DISSERTATION TITLED "A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV- INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT" Submitted in partial fulfilment of Requirements for M.D.DEGREE EXAMINATION BRANCH-I GENERAL MEDICINE THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY CHENNAI INSTITUTE OF INTERNAL MEDICINE MADRAS MEDICAL COLLEGE CHENNAI - 600003. APRIL 2014 CERTIFICATE This is to certify that the dissertation entitled "A STUDY ON ECHOCARDIOGRAPHIC FINDINGS IN HIV-INFECTED PATIENTS AND THEIR CORRELATION WITH CD4 COUNT" is a bonafide work done by DR. PAKKEER KANNU SYED FAHRUDEEN MUNNAVER, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial...