"A STUDY OF LEFT VENTRICULAR DYSFUNCTION BY ECHOCARDIOGRAPHY IN HIV INFECTED PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR PRABHAKAR KORE HOSPITAL, BELGAUM"

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This is to certify that the dissertation entitled **"A STUDY OF LEFT VENTRICULAR DYSFUNCTION BY ECHOCARDIOGRAPHY IN HIV INFECTED PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR PRABHAKAR KORE HOSPITAL, BELGAUM"** is a bonafide research work done by **REG. NO. BG0115004**

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LIST OF ABBREVIATIONS USED

%	-	Percentage
3TC	-	Lamivudine
AIDS	-	Acquired Immunodeficiency Syndrome
ART	-	Antiretroviral therapy
ARV	-	Antiretroviral
AZT	-	Zidovudine
CAD	-	Coronary Artery Disease
cART	-	Combination antiretroviral therapy
CCR	-	Chemokine receptor
CDC	-	Centers for Disease Control
CMV	-	Cytomegalovirus
CNS	-	Central nervous system
CVD	-	Cardiovascular disease
DNA	-	Deoxyribonucleic acid
ECG	-	Electrocardiography
EFV	-	Efavirenz
EIA	-	Enzyme immunoassay
ELISA	-	Enzyme-linked immunosorbent assay
FDA	-	Food and Drug Administration
FTC	-	Emtricitabine
HAART	-	Highly active antiretroviral therapy
HIV	-	Human Immunodeficiency Virus
HSV	-	Herpes simplex virus
KS	-	Kaposi sarcoma

LVEF	-	Left ventricular ejection fracton
mg/dL	-	Milligrams per deciliter
mmHg	-	Millimeters of mercury
MTCT	-	Mother-to-Child transmission
NACO	-	National AIDS Control Organization
NK	-	Natural killer
NNRTIs	-	*Non-nucleoside reverse-transcriptase inhibitors*
NRTIs	-	Nucleoside reverse transcriptase inhibitors
NVP	-	Nevirapine
PAH	-	Pulmonary arterial hypertension
PI	-	Protease inhibitor
PLHA	-	Person living with HIV and AIDS
POC	-	Point of care
RNA	-	Ribonucleic acid
STD	-	Sexually transmitted disease
TB	-	Tuberculosis
TC	-	Total count
TDF	-	Tenofovir
TNF	-	Tumor necrosis factor
U.S.	-	United States
UNAIDS	-	United Nations Programme on HIV and AIDS
WHO	-	World Health Organization

ABSTRACT

Background and objectives

The advances in diagnosis, treatment, monitoring of HIV infection and the availability of antiretroviral drugs have lead to improved survival of patients but this has resulted in manifestations of late stage disease which includes cardiac involvement. This study was intended to find the association of Left Ventricular dysfunction in HIV infected patients.

Methodology

This one-year study was done from January 2016 to December 2016 in the Department of Medicine of a tertiary care hospital in North Karnataka. Prior to the commencement, ethical clearance was obtained. A total of 100 consecutive patients of HIV infection presenting to the medicine department were included. Patients were subjected to complete blood count. Electrocardiography and Echocardiography was performed on these patients to assess the cardiac involvement.

Results

Majority of the patients were males (76%) and the commonest age group involved was those between 40-49 years. In 73 patients (73%) duration of HIV infection was between 1 to 10 years. In this study, 79 patients (79%) were on treatment with Anti-Retroviral drugs. Cardiac manifestations were observed in 62% of the patients. Sinus tachycardia (29%) was found to be the most common cardiac manifestation on ECG. Diastolic dysfunction was present in 35 patients (35%) and systolic dysfunction was present in 49 patients (49%).

Conclusion and interpretation

Patients with HIV infection are at higher risk of developing Left Ventricular dysfunction.

Keywords

Human Immunodeficiency Virus, Left Ventricular Dysfunction, Acquired Immunodeficiency Syndrome.

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INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), emerging from HIV infection, was first identified in 1981 when a common pattern of symptoms was recognized among a small number of homosexual men in the USA. AIDS cases were soon noted in other groups, including intravenous drug users and haemophiliacs. In 1983, as Anglaret X reported, the French physician and virologist Luc Montagnier discovered the retrovirus that causes AIDS in humans, which was initially termed lymphadenopathy-associated virus (LAV), and later, in 1986, received the international designation of human immunodeficiency virus (HIV).[1]

Having claimed more than 35 million lives so far, HIV persists to be a major global public health issue. 1 million people were lost to HIV-related causes globally in 2016. By the end of 2016, there were approximately 36.7 million people living with HIV (PLHIV) with 1.8 million people being newly infected. As per the India HIV Estimation 2015 report, National adult (15–49 years) HIV prevalence in India is estimated at 0.26% (0.22% – 0.32%) in 2015. In 2015, adult HIV prevalence is estimated to be around 0.30% among males and about 0.22% among Females. Among the States, in 2015, Manipur showed the highest estimated adult HIV prevalence of 1.15%, followed by Mizoram (0.80%), Nagaland (0.78%), Andhra Pradesh & Telangana (0.66%), Karnataka (0.45%), Gujarat (0.42%) and Goa (0.40%). The total number of PLHIV in India is estimated at 21.17 lakhs (17.11 lakhs–26.49 lakhs) in 2015 compared with 22.26 lakhs (18.00 lakhs-27.85 lakhs) in 2007. Undivided Andhra Pradesh and Telangana have the highest estimated number of PLHIV (3.95 lakhs) followed by Maharashtra (3.01 lakhs), Karnataka (1.99 lakhs), Gujarat (1.66 lakhs), Bihar (1.51 lakhs) and Uttar Pradesh (1.50 lakhs). These seven States together

account for two thirds (64.4%) of total estimated PLHIV. Since 2007, when the number of AIDS related deaths (ARD) began to show a declining trend, the annual number of AIDS related deaths declined by 54%. In 2015 an estimated 67.6 (46.4 – 106.0) thousand people died of AIDS-related causes nationally.[2]

AIDS is characterized by an acquired, profound, inevitable immune suppression that predisposes the patient to multiple opportunistic infections, malignant neoplasms and a progressive dysfunction of multiple organ systems. Of a large armamentarium of anti-retroviral drugs and recent advances in the diagnosis, treatment and monitoring of persons living with HIV and AIDS (PLHA), there has been a noticeable improvement in the survival of such patients. Due to the longer survival of PLHA, the manifestations of late stage HIV infection are now being met with more frequently than before, which includes HIV related cardiac diseases.[3]

Successful long-term HAART results in a steady recovery of CD4 T-cell numbers and an improvement of immune responses and T-cell repertoire (previously lost antigen responses may be restored). The peripheral T-cell counts initially rise after therapy is initiated, but this represents a redistribution of activated T cells from the viral replication centres in the lymph nodes rather than a true increase in total-body CD4 T-cell counts.

As of 2016, 19.5 million [17.2 million–20.3 million] PLHIV were accessing antiretroviral therapy, up from 17.1 million [15.1 million–17.8 million] in 2015 and 7.7 million [6.8 million–8.0 million] in 2010. In 2016, around 53% [39–65%] of all PLHIV had access to treatment. Since 2010, new HIV infections among adults declined by an estimated 11%, from 1.9 million [1.6 million–2.1million] to 1.7 million [1.4 million–1.9 million] in 2016. In 2016, 1 million [830 000–1.2 million]

people died from AIDS-related illnesses worldwide, compared to 1.9 million [1.7 million–2.2 million] in 2005 and 1.5 million [1.3 million–1.7 million] in 2010.[4]

Prior the advent of ART, studies showed a relationship between HIV and left ventricular (LV) dysfunction. Various terms were used to describe the syndrome, including HIV-associated cardiomyopathy, HIV-associated HF, and HIV-associated LV dysfunction. As initially described, HIV- associated HF was associated with severe immune system compromise, had no specific therapy, and had a median survival of 101 days after diagnosis. Concurrent shifts in epidemiological patterns of HIV treatment and cardiovascular diseases produced a complex and evolving relationship between HF and HIV that requires a contemporary review. Most studies related to HF are focused on high-income countries and are misaligned with the global predominance of HIV in low and middle-income countries (LMICs).[5]

The prevalence of cardiac involvement in AIDS patients has been reported to range between 28% and 73%.[3] The cardiac diseases found to be associated to HIV infections include pericardial effusion, left ventricular dysfunction, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, malignant neoplasm, coronary artery disease and drug related cardiotoxicity.[3]

Experts say that the introduction of HAART is associated with cardiovascular complications such as the development of the metabolic syndrome, with a predisposition for developing hyperlipidaemia and coronary atherosclerosis. Hruz *et al*., in their studies, have shown that the clinical use of HIV protease inhibitors is associated with insulin resistance and other metabolic changes that prevent the uptake of glucose by the heart muscle and increase the long-term cardiovascular risk. Studies have shown that exposure to ritonavir, atazanavir and lopinavir precipitated acute

heart failure and death of mice with acute pulmonary oedema in transgenic mouse models with dilated cardiac chambers. Overexposure of the cardiac muscle to the action of the enzyme Cre-recombinase was responsible for cardiac dysfunction. These studies prove that HIV protease inhibitors affect glucose transport and induce acute heart failure.[1]

Mayosi, in epidemiologic studies of cardiac dysfunction in sub-Saharan Africa, states that it is mainly due to non-ischemic causes such as hypertension, pericarditis, rheumatic carditis and cardiomyopathy. The two endemic diseases that are responsible most for LVD in Africa are cardiomyopathy and pericarditis. The most common forms are dilated cardiomyopathy (DCM), peripartum cardiomyopathy and endomyocardial fibrosis. DCM is more commonly associated with HIV patients and has increased with immunosuppressive therapy in patients with HIV who suffer from pericarditis, which is associated with a large pericardial effusion and tuberculosis.[1]

Advanced cases of HIV infection are associated with nutritional deficiencies. Malabsorption and diarrhoea episodes lead to electrolyte disturbances as well as elemental nutrient deficiencies. Selenium deficiency escalates the virulence of the Coxsackie viruses in the cardiac tissue. Treatment with selenium causes reversal of the cardiomyopathy and normalizes the function of the left ventricle (LV) in nutritionally depleted patients. The levels of vitamin B12, carnitine, and thyroid and growth hormones can also be altered in patients with HIV infection, which may be associated with LVD.[1]

Among PLHIV with HF, Left Ventricular Systolic Dysfunction (LVSD) is currently less common in high-income countries. Diastolic dysfunction, however, is

present in up to 64% of asymptomatic PLHIV taking ART in high-income countries and appears to be independent of traditional risk factors including age and hypertension. Often, early stage diastolic dysfunction is the only echocardiographic abnormality found in asymptomatic PLHIV. Asymptomatic PLHIV have higher LV mass than HIV-uninfected subjects, and higher LV mass is inversely proportional to nadir CD4T-cell count. The mechanisms of diastolic dysfunction in PLHIV isn't known yet but may involve direct myocardial effects of HIV.[5]

Echocardiography is very helpful in detecting cardiac dysfunction at an early stage, much before overt clinical manifestations develop. Common signs of cardiac involvement are impairment of LV fractional shortening. This could be explained by a reduction of cardiac contractility. Hence, early detection of cardiac involvement in HIV cases in pre-AIDS or AIDS phase of the disease is important to prevent significant morbidity from cardiac involvement.[6]

OBJECTIVE

The objective of the present study is to study the left ventricular dysfunction (Systolic and Diastolic) in HIV infected patients.

REVIEW OF LITERATURE

Human Immunodeficiency Virus

HIV belongs to the family of Retroviridae and subfamily of lentiviruses. HIV is transmitted primarily by sexual contact, by blood and blood products and by infected mothers to the infants intrapartum, perinatally or via breast milk. After 30 years of investigations, there is no evidence that HIV is transmitted through casual contact or via insects such as mosquito bite.[3]

HIV-1 and HIV-2 are the two subtypes of HIV. HIV-1 is the most common cause of HIV in the world. HIV-1 is divided into four groups M, N, O and P of which group M (major) is responsible for most of the infections in the world and is further diversified into subtypes and intersubtype recombinant forms.[3]

The chimpanzee subspecies Pan troglodytes troglodytes has been established to be the natural reservoir of the HIV-1 M and N groups. The M group comprises of nine subtypes or clades, designated A, B, C, D, F, G, H, J and K as well as more than 60 known circulating recombinant forms.[3]

The most common subtype worldwide is subtype C viruses and accounts for almost 50% of the infections worldwide and in India >95% of the infections.[3]

In the late 1970s, subtype B was seeded in the United States and Europe.[3]

The extraordinary diversity of HIV, reflected by the presence of multiple subtypes, circulating recombinant forms, and continuous viral expansion, has implications for possible differential rates of transmission, rates of progression, responses to therapy, and the development of resistance to antiretroviral drugs.[3]

HIV-2 is found mainly in West Africa. Compared with HIV-1, HIV-2 infections are defined by low viral loads, slow rates of clinical progression by low rates of transmission and unique treatment recommendations due to innate resistance to NNRTI's. HIV-2 is divided into groups A to H.[3]

History

1900s Researchers believe that sometime in the early 1900s a form of simian immunodeficiency virus, SIV, was transmitted to humans in central Africa.[7]

1959 The first known case of HIV in a human occurs in a man who died in Congo, later confirmed as having HIV infection. The authors of the study did not sequence a full virus from his samples, writing that "attempts to amplify HIV-1 fragments of >300 base pairs were fruitless. However, after many attempts, four shorter sequences were acquired"; these defined small portions of two of the six genes of the complete HIV genome.

[7] June 28, in New York City, Ardouin Antonio, a 49-year-old Jamaican-American shipping clerk died of Pneumocystis carinii pneumonia, a disease closely linked to AIDS. Gordon Hennigar, who carried out the post-mortem examination of the man's body, found "the first reported instance of unassociated *Pneumocystis carinii* disease in an adult" to be so unusual that he preserved Ardouin's lungs for later study. The case was published in two medical journals at the time, and Hennigar has been quoted in various publications saying that he believes Ardouin probably had AIDS.[7]

1960s HIV-2, a viral variant found in West Africa, is thought to have transferred from sooty mangabey monkeys to people in Guinea-Bissau.[7]

1964 Jerome Horwitz of Barbara Ann Karmanos Cancer Institute and Wayne State University School of Medicine synthesize AZT under a grant from the US National Institutes of Health (NIH). AZT was formerly intended as an anticancer drug.[7]

1965 Genetic studies of the virus prove that, in or about 1966, HIV first arrived in America, infecting one person in Haiti. At this time, many Haitians were working in Congo, providing the opportunity for infection.[7]

1969 A St. Louis teenager, named Robert Rayford, dies of an illness that baffles his doctors. Eighteen years later, molecular biologists at Tulane University in New Orleans test samples of his remains and find evidence of HIV.[7]

1975 Wasting and other symptoms were first reported among residents of Africa, that was later determined to be AIDS.[7]

1976 Arvid Noe, a Norwegian sailor dies; it is later determined that he contracted HIV/AIDS in Africa during the early 1960s.[7]

1977 Grethe Rask, a Danish physician dies of AIDS contracted in Africa.[7] A San Francisco prostitute gives life to the first of three children who were later diagnosed with AIDS. The children's blood was tested after their deaths and was confirmed to be HIV infected. The mother succumbed to AIDS in May. Investigation results prove she was infected no later than 1977.[7]

1978 Senhor José, a Portuguese man died; he was later confirmed as the first known infection of HIV-2. It is understood that he was exposed to the disease in Guinea-Bissau.[7]

1979 A primal case of AIDS in the United States was a female baby born in New Jersey in 1973 or 1974. She was born to a sixteen-year-old girl, who was an identified drug-injector, who previously was known to have had multiple male

sexual partners. The baby expired in 1979 at the age of five. Subsequent testing on her stored tissues confirmed that she had acquired HIV-1.[7] Herbert Heinrich was a bisexual German concert violinist who died in 1979. Tests in 1989 found that he was HIV-positive, and there had been contemplation that he was infected by a prostitute who was infected by Roed.[7]

1980 A thirty-year-old woman from the Dominican Republic died at Mount Sinai Medical Centre in New York City secondary to CMV infection.[7]

AZT (zidovudine), the first antiretroviral drug, becomes available to treat HIV.[7]

In April, Western blot test was approved by the FDA as a more precise test for the presence of HIV antibodies than the ELISA test.[7]

1988 December 1, The first World AIDS Day took place.[7]

1992 The first combination drug therapies for HIV were introduced. Such "cocktails" were more effective than AZT alone and slowed down the development of drug resistance.[7]

2007 The first case of someone being cured of HIV is reported. Timothy Ray Brown, a San Francisco man, suffering from leukemia and HIV, is cured of HIV through a bone marrow transplant in Germany. The first CCR5 receptor antagonist, Maraviroc is approved by the FDA as an antiviral drug for the treatment of AIDS.[7]

2015 New, aggressive strain of HIV discovered in Cuba Researchers at the University of Leuven in Belgium say the HIV strain CRF19 can develop into

AIDS within two to three years of exposure to the virus.[7] Usually, HIV takes approximately 10 years to develop into AIDS. Patients with CRF19 may begin to get sick before they even know they've been infected, which ultimately means there's a significantly shorter time span to stop the disease's progression.[7]

Epidemiology

HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2016, 1.0 million people were lost to HIV-related causes globally. There were roughly 36.7 million PLHIV at the end of 2016 with 1.8 million people becoming newly infected in 2016 globally.[12]

54% of adults and 43% of children living with HIV are currently receiving lifelong ART. 19.5 million people were consuming antiretroviral therapy in 2016. 1 million [830 000–1.2 million] people expired due to AIDS-related illnesses in 2016. 76.1 million [65.2 million–88.0 million] people have become infected with HIV since the beginning of the epidemic. 35.0 million [28.9 million–41.5 million] people were lost to AIDS-related illnesses since the start of the epidemic.[12]

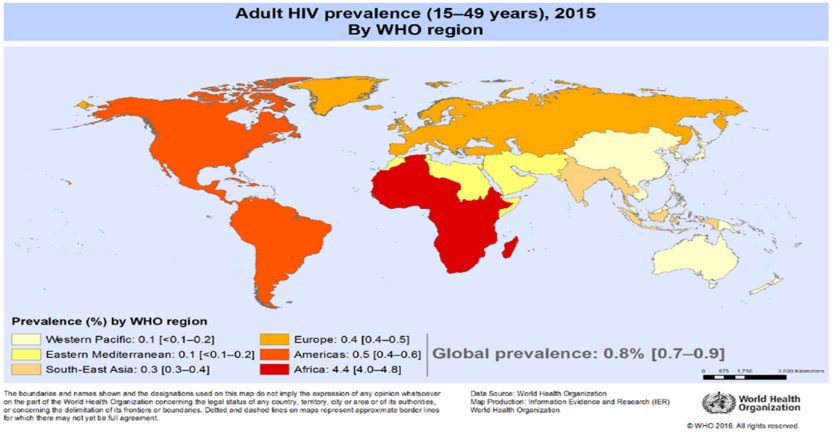


Figure: 1 Adult HIV Prevalence in the world

International statistics

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), globally in 2008, approximately 33.4 million people (1% of the global adult population aged 15-49 years) were infected with HIV, a decline from 2006 (39.5 million reported at that time). UNAIDS estimates that 2.7 million people were newly infected with HIV and that 2 million people died from AIDS in 2008, both statistics showed a slight drop over time.[12]

The vast majority of infections remain in sub-Saharan Africa, where 5.2% of the population is believed to be infected. Between 2004 and 2006, the prevalence of HIV infection in central and eastern Asia and Eastern Europe rose by 21%. During this period, the number of new HIV infections in persons aged 15 to 64 years increased by 70% in Eastern Europe and central Asia.[12]

The infection rates in many developed countries remain constant, and some developing countries have achieved significant gains in controlling and even reversing the effects of the HIV epidemic. However, this is partly due to deaths in HIV-infected people, together with simultaneous prevention of new infections. For example, India has used a national prevention campaign focusing on high-risk populations that may have prevented 100,000 new HIV infections over the 5 years it has been implemented, with increasing results seen in areas with higher levels of investment.[12]

The mortality rate in some countries has considerably increased. In South Africa, the all-cause HIV-associated mortality rate rose by 79% between 1997 and 2004.[12]

Racial, sexual, and age-related differences in incidence

In the United States, the percentage of HIV infection is maximum in blacks (83.7 cases per 100,000 population). The prevalence is also maximum among Hispanic people (29.3 per 100,000 population). These increased rates are due to socioeconomic factors rather than genetic predisposition.[12]

HIV infection is greater among males. In 2009, males were estimated as 76% of all diagnosed of HIV infection among adults and adolescents in the US. Among heterosexuals, females are more inclined to acquire HIV infection from an infected male than a male would from an infected female, but a large proportion of infections in males are due to homosexual contact, with or without injection drug use. Injection drug use alone is more likely to cause HIV in males.[12]

Prior to the initiation of universal testing of blood supply, males were more prone to acquire HIV infection through contaminated blood products for the treatment of haemophilia. The risk of HIV exposure from factor VIII concentrates has been virtually eliminated by viricidal treatment of plasma-derived factor VIII concentrates, as well as the introduction of recombinant factor VIII concentrates and the gradual elimination of albumin from the production process used for these products.[12]

In the developing world, HIV infection is equally common in males and females. In the developing world, heterosexual contact is the primary route of HIV transmission.[12]

Young adults tend to be at greater risk of acquiring HIV, typically through high-risk activities such as unprotected sexual intercourse or intravenous drug use. In 2009 in the US, the maximum percentage (15% of all diagnoses) and the maximum

rate (36.9 per 100,000 population) were among people aged 20–24 years. Children may become infected through transplacental transmission or even by breastfeeding. Rare cases have been reported, wherein children were infected after sexual abuse by HIV-infected adults.[12]

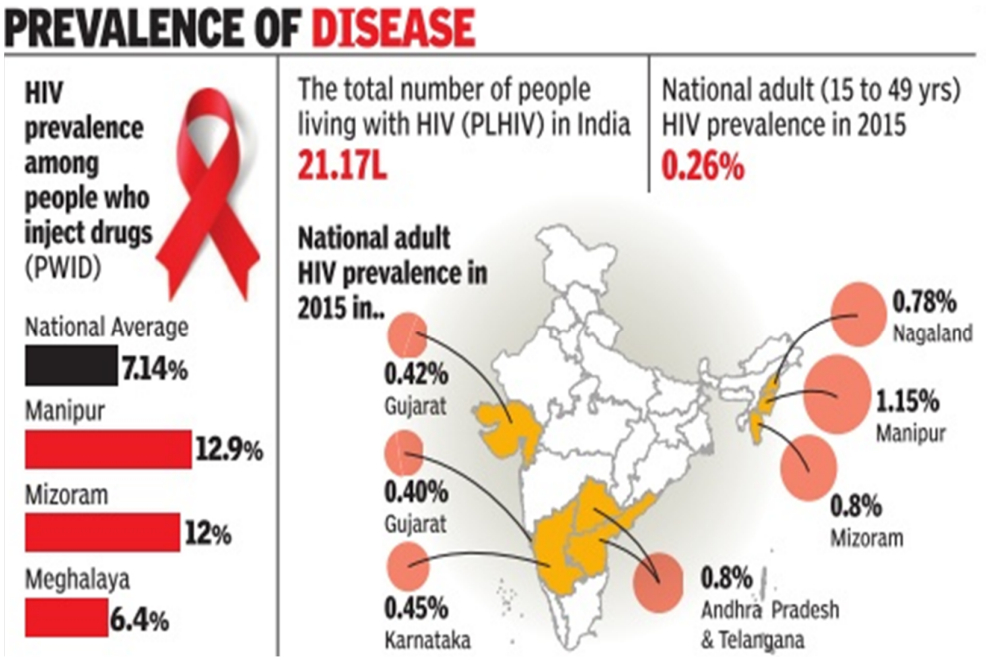


Figure: 2 HIV in India

TRANSMISSION

Due to diversities in transmission rates and virulence, HIV-1 is a pandemic, with increasing prevalence rates in developing countries, while HIV-2 is more endemic, with constant prevalence rate in most countries (Remy, 1998). HIV-2 appears to be transmitted by the same routes as HIV-1; however, the frequency of transmission is lower, probably due to a very low virus load in many asymptomatic individuals (Adjorlolo-Johnson *et al.*, 1994; Berry *et al.*, 1998; Cavaco-Silva *et al.*, 1998; Kanki *et al.*, 1994; O'Donovan *et al.*, 2000). For instance, sexual and vertical

transmissions of HIV-2 are around 5 to 9 fold and 10 to 20 fold lesser than HIV-1, respectively.[16]

HIV can be transmitted through certain body fluids such as blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk from a person who has HIV. These fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream for transmission to occur.[16]

Risk factors include the following:

- Unprotected sexual intercourse, especially anal intercourse has an 8-fold increase in transmission risk
- Multiple sexual partners
- Sexually transmitted diseases (STDs): Gonorrhea and chlamydia infections hike the risk by 3-fold, syphilis increases the risk by 7-fold, and herpes genitalis increases the risk up to 25-fold.
- Sharing of intravenous drug
- Receipt of blood transfusions prior to 1985
- Mucosal contact with infected blood or needle-stick injuries[11]

The modes to decrease the risk of transmission at birth include caesarean delivery and prenatal ART in the mother and ART in the new-born immediately after birth.[11]

VIROLOGY

The retrovirus genome consists of two similar copies of single-stranded RNA molecules and is defined by the presence of structural genes *gag, pol, env*. HIV-1 and HIV-2 viruses differ in the arrangement of their genome, although the fundamental structure (*i.e.* the presence of the three structural genes, *gag, pol* and *env*) is the same as for all retroviruses. In fact, in addition to having these three genes, the genomes present a complex combination of other regulatory/accessory genes.[17]

Both viruses potentially lead to AIDS, although the involvement of the central nervous system may be more frequent in HIV-2 infection. In addition, HIV-2 infection takes longer to advance to AIDS and appears less virulent than HIV-1.[17]

Similar, to other retroviruses, the *gag* gene encodes for the structural proteins of the core (p24, p7, p6) and matrix (p17) and the *env* gene encodes for the viral envelope glycoproteins gp120 and gp41, which identify cell surface receptors. The enzymes crucial for viral replication are encoded by the *pol* gene, which is the reverse transcriptase which converts viral RNA into DNA, the integrase that integrates the viral DNA into host chromosomal DNA (the provirus) and the protease that cleaves large Gag and Pol protein precursors into their components.[17]

HIV viral particles are contained in a lipid rich membrane and have a diameter of 100 nm. Each viral particle membrane contains glycoprotein heterodimer complexes composed of trimers of the external surface gp120 and the transmembrane spanning gp41 glycoproteins bound together. The binding between gp120 and gp41 is not covalent hence the gp120 may be shed spontaneously within the local environment and detected in the serum, as well as within the lymphatic tissue of HIV-infected patients. During the process of budding from the infected cell, the virus may

also integrate into its membrane different proteins from the host cell membrane, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may aid the adhesion to other target cells. A matrix protein (p17) is attached to the inside of the viral lipoprotein membrane. Virus membrane and the matrix protein contain the capsid composed of polymers of the core antigen, p24. The capsid contains two copies of HIV RNA combined with a nucleoprotein and the enzymes reverse transcriptase, integrase and protease.[17]

HIV viruses are described by other accessory/ regulatory genes that play key roles in modulating virus replication. The *tat* gene encodes for the Tat protein that is expressed very early after infection and promotes the expression of HIV genes. The *rev* gene which encodes for Rev protein ensures the export from the nucleus to the cytoplasm of the correctly processed messenger and genomic RNA. The function of the other accessory HIV proteins is less well understood; the Vpr protein is involved in the arrest of the cell cycle. This protein also enables the reverse transcribed DNA to gain access to the nucleus in non-dividing cells such as macrophages, a function that is performed by Vpx in HIV-2.

Vpu is a protein essential for the correct release of the virus particle, whereas the *vif* gene codes for a small protein (Vif) that enhances the infectiveness of progeny virus particles.[17]

Finally, the Nef protein has many functions including cellular signal transduction and the down regulation of the CD4 receptor on the cell surface to allow virus budding in the late stages of the virus replication cycle.[17]

The HIV replication cycle consists of six steps; 1) binding and entry; 2) uncoating; 3) reverse transcription; 4) provirus integration; 5) virus protein synthesis and assembly and 6) budding.[17]

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* occurring in a setting of polyclonal immune activation. The helper subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule which serves as the primary cellular receptor for HIV. A co-receptor must also be present together with CD4 for efficient binding, fusion and entry of HIV-1 into the target cells. HIV uses two major co-receptors, CCR5 and CXCR4, for fusion and entry, these co-receptors are termed *chemokines.* Patients with CD4+T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases.[17]

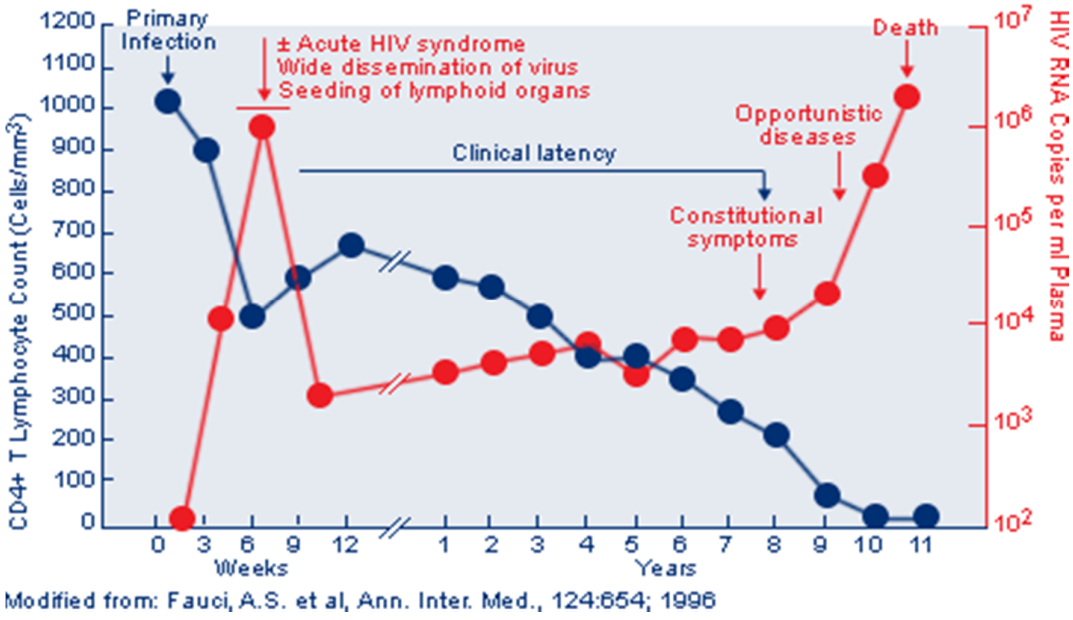


Figure: 3 Timeline of CD4 T-cell and viral-load changes over time in untreated human immunodeficiency virus infection

PATHOGENESIS OF HIV

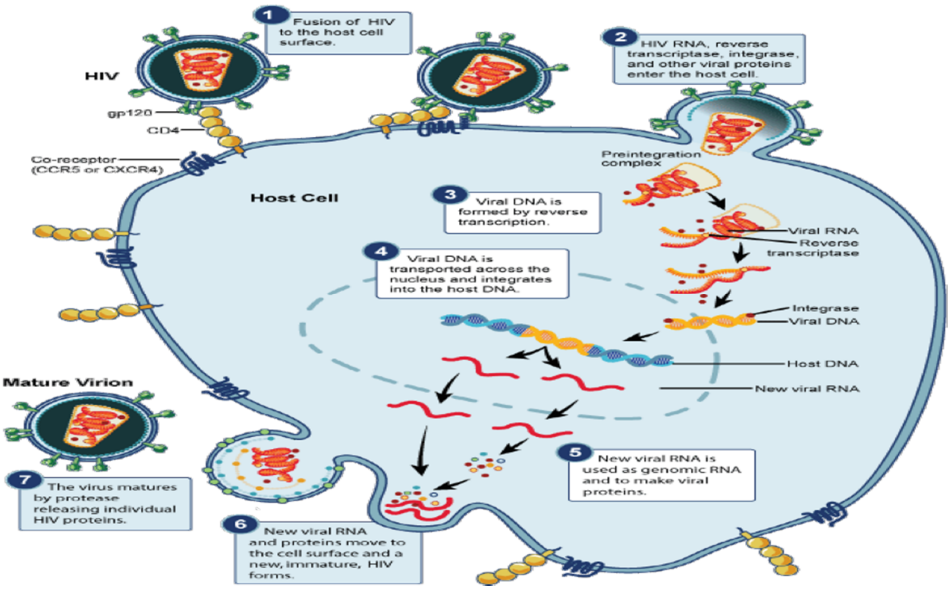


Figure: 4 HIV life cycle

The pathogenesis of HIV infection and the progression to AIDS are a result of the properties of the infecting virus isolate and the host's immune response to the virus. The balance between the effectiveness of these two components determines the different outcome of the infection, from the development of AIDS to long-term survival.[17]

HIV cannot survive outside the bloodstream or lymphatic tissue. Moreover, the virus is easily inactivated by the exposure to common detergents and disinfectants. Thus, virus transmission requires the directed exposition to infected blood or secretions in the presence of skin damage, *i.e.* by needles or sharp tools, or abrasions in mucosal tissues within sexual intercourses. Transmission of HIV is highly dependent on the biologic properties of the virus isolate, its concentration in the infected body fluid and host susceptibility.[17]

HIV is frequently integrated or replicating into the infected cells, which are the main vehicles of virus transmission. In fact, HIV-infected cells can transfer the virus to cells of the local immune system (*e.g.*, T-cells, macrophages, dendritic cells), as well as those lining vaginal or anorectal mucosae. The cervix mucosa is the first tissue to be infected in the case of infection acquired through heterosexual intercourse. The dendritic cells and CD4+ lymphocytes can be infected through receptor-dependent mechanisms and allow virus spreading to regional lymph nodes and finally into the bloodstream.[17]

Viral replication within the lymphatic tissue of infected mucosae and regional lymph nodes is already protracted in the early stages of the infection. In particular, virus particles can be found within follicular dendritic cells (FDC), macrophages, and activated CD4+ T-cells, which are the main targets of infection. Infected cells particularly in macrophages and resting CD4+ T cells, which are permanent viral reservoirs, can undergo lysis or allow the establishment of latent infection. This represents a great hindrance in the complete eradication of the infection since it allows virus persistence also in the presence of effective regimens of HAART.[17]

After 10-12 days from infection, virus RNA is detectable in the blood by RT-PCR amplification methods. The onset of viremia in plasma is a critical time point in the natural history of HIV infection because it indicates that infected individual has acquired the potential of transmitting the infection and provides the first chance to diagnose the infection in the blood sample.[17]

HIV RNA plasma viremia levels rapidly and predictably rise up to a peak level over 100 million copies per cubic centimetre, approximately in the phase of antibody seroconversion.[17]

These high levels of HIV-1 viremia are usually short-lived since the host generates humoral and cellular immune responses which partly control viral replication. Over the subsequent weeks, viremia declines by several orders of magnitude until it reaches a lower steady level (viral set point) or drops under detection level. Several factors associated with innate and acquired antiviral immunity can influence viral replication and the establishment of a viral set point during this phase of infection (often referred as "acute infection").[17]

However, the role of the virus specific cell-mediated immune response, in particular, of the specific CD8+ T-cell cytotoxic activity, seems to be central in the initial control of virus replication at this stage of the infection, before the appearance of anti-HIV binding and/or neutralising antibodies.[17]

The time of appearance of first HIV specific antibodies (seroconversion) has been estimated by detecting their presence in sequential samples from patients with accurate information on the time of HIV infection, starting from the first day of exposure. Using commercially available third generation tests, seroconversion has been observed to occur in a period ranging from 3 to 5 weeks, with an average of 22 days.[17]

Thus, the time period in which the infection is present, but antibodies are not detectable, yet, can be referred as the serological "window period". However, in rare occasions infected individuals could result seronegative over 3 months after virus transmission, indicating that in some circumstances the generation of HIV specific antibodies may require a longer period.[17]

Ranging from few days to few weeks since exposure to HIV, most of the infected individuals present symptoms resembling flu-like or mononucleosis-like

illness, as fever, maculopapular rash, oral ulcers, lymphadenopathy, arthralgia, pharyngitis, malaise, weight loss and myalgia. These clinical features are quite heterogeneous and it has been reported that individuals who display more severe and durable symptoms in the course of acute infection tend to progress more rapidly to AIDS.[17]

The symptomatic phase of acute HIV-1 infection lasts between 7 and 10 days, and rarely longer than 14 days. During acute HIV-1 infection, the number of CD4+ T-cells dramatically declines, in association with high viremia levels, before the onset of antiviral immune response. When a specific immune response has been evoked, HIV viremia drops and CD4+ T- cells raise again, although to levels lower than those present before infection, suggesting the persistence of virus-associated pathogenic effects. In addition, qualitative functional impairment of immune responses to HIV and other antigens can be detected, indicating that the virus induces, very early after infection, a dysfunction of CD4+ T- cells and of other cells of the immune system.[17]

Few weeks after the onset of acute infection, most of the infected individuals enter into a clinical asymptomatic period, generally associated with the drop of HIV viremia levels and absence of symptoms. This event reflects primarily the antiviral action exerted by both innate and adaptive immune responses.[17]

In particular, antibodies specifically bind to HIV antigens, determining the prevention of cell infection (neutralization of infectivity), or favouring the elimination of infected cells by a mechanism known as Antibody- Dependent Cellular Cytotoxicity (ADCC), mediated by T-lymphocytes and natural killer cells. In addition, HIV-specific T-lymphocytes recognize virus antigens on the surface of

infected cells and promote their elimination by antigen-specific cytotoxic mechanisms.[17]

Undoubtedly, in the course of asymptomatic phase, HIV continuously replicates in the body compartments, counteracting antiviral immunity and producing a state of chronic systemic inflammation. There are several reasons why anti-viral immunity is not able to eradicate the infection.[17]

Among them, the persistence of the integrated virus in lymphoid compartments (reservoir), with low expression of virus antigens and the high frequency of mutations within virus genome, which leads to escape from the immune system, are the most effective mechanisms. Hence, virus replication keeps occurring in the lymphoid compartment, and momentary peaks of HIV-viremia can be detected in plasma even in absence of symptoms related to the infection. In some infected individuals, HIV viremia is not detectable for many years, indicating the occurrence of an efficient control of the infection. Individuals displaying this condition have been termed as elite "controllers".[17]

In the course of the asymptomatic period, HIV associated pathogenic effects persist and induce a slow but progressive loss of CD4+ lymphocytes and impairment of the immune system. The progression of the disease is characterized by the destruction of the lymphoid tissue architecture, which is a consequence of the virus replication and of the chronic activation of the cells of immune system. This leads to an increase of virus diffusion to surrounding CD4+ T-cells and assists in HIV-1 spread within local, regional and whole lymphoid environment. Particularly at this stage, HIV infection is associated with an extensive replication in the gut lamina

propria and submucosa and in draining lymph nodes, with local depletion of CD4+ T-cells.[17]

The further progression of the disease depends on the capacity of the host to contain virus replication and to reconstitute the pool of memory T- cells within the mucosa associated lymphoid tissue or lymph nodes. In absence of virus containment, the destruction of the lymphoid system proceeds and CD4+ T-cell number continues to drop to levels (< 200 cells/µl) which determine the risk of onset of opportunistic infections by bacteria, viruses, fungi and parasites, and tumours, as a consequence of a serious impairment of the immune system.[17]

The most common opportunistic infections, which define the AIDS stage, are caused by *Microcystis carinii, Candida albicans, Cytomegalovirus, Herpes zoster* or enteropathic parasites (*Cryptosporidium and Giardia* species, *Isospora belli*), which can determine life-threatening diseases. This phase is usually characterized by diffuse lymph node swelling, severe reduction of body weight, fever and respiratory and gastrointestinal symptoms.[17]

A progressive encephalopathy, induced by HIV or other opportunistic infections, is also associated with a severe invalidation and increased risk of mortality. Neoplastic diseases, as Kaposis Sarcoma and lymphomas, most likely emerging as a consequence of the immunodeficiency status, also severely weaken the organism, worsening the clinical course of the disease.[17]

During the AIDS phase, the number of CD4+ T-cells continues to decrease and anaemia and marked lymphopenia are frequently detected. Based on the latest evidence, UNAIDS/WHO estimate that, in the absence of treatment, the mean time from the infection onset to AIDS-related death, is approximately 11 years. Of course,

the progression of the disease is extremely variable, depending on the infecting virus isolate and the antiviral response of the host.[17]

Immunologic control of HIV

The primary mechanism for immunologic control of HIV appears to be CD8+ cytotoxic T-cells. T-cell responses are correlated with the steady-state viral load and hence, the rate of progression.[18] Cellular immunity is apparently responsible for some multiply-exposed, but uninfected individuals.[19]

Although antibodies against HIV can be detected, it is clear that they are not sufficiently neutralizing to assist with immunologic control of the infection.

The role of NK (Natural Killer) cells may be necessary in the initial control of HIV. Escape mutations have been detected, signifying that immunologic pressure on HIV exists from NK cells.[20]

WHO clinical staging system for HIV infection[21]

Primary HIV Infection	• Asymptomatic • Acute retroviral syndrome
Stage 1	• Asymptomatic • Persistent generalized lymphadenopathy
Stage 2	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infections
Stage 3	• Unexplained severe weight loss (>10% of presumed or measured) • Unexplained chronic diarrhoea for longer than one month • Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month) • Persistent oral candidiasis • Oral hairy leukoplakia • PulmonaryTB(current) • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre) or chronic thrombocytopaenia (<50 × 109 per litre)

Stage 4	• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Disseminated mycosis (coccidiomycosis or histoplasmosis) • Recurrent non-typhoidal Salmonella bacteraemia • Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV associated tumours • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV associated nephropathy or symptomatic HIV associated cardiomyopathy

DIAGNOSIS

Screening for HIV infection

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians should screen for HIV in all adults and adolescents at all increased risk for HIV infection including all pregnant women.[22]

The Centres for Disease Control (CDC) recommends HIV screening for patients in all health- care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening). The CDC recommends that persons at high risk for HIV infection to screened for HIV atleast annually.[23]

Citing the benefits of early diagnosis and treatment and the failure of risk based screening to identify a substantial proportion of HIV-infected patients early in the disease, the American College of Physicians recommends that clinicians shall adapt to routine screening for HIV and encourage patients to be tested.[24]

HIV testing and counselling[31]

People access HIV treatment and prevention through the gateway of HIV testing and counselling. It is currently estimated globally that about half of the PLHIV do not know their HIV status.[31]

The people who do not know often test late meaning that many people start treatment when they are already significantly immune compromised resulting in poor health outcomes and ongoing HIV transmission.[31]

WHO recommends all forms of HIV testing should be performed voluntarily and should adhere to the five C's: Consent, Counselling, Correct test results and

Connections to core treatment and prevention.[31]

Standard HIV test[27]

Standard serological test consists of screening EIA (Enzyme Linked Assay) performed in the lab with whole blood and is done as a rapid test at point of care (POC).

The EIA tests are screening test and require confirmatory western blot.

EIA screening for anti-HIV requires a repeatedly reactive test which is the criteria for western blot testing. Western blot detects antibodies to HIV 1 protein.

Western Blot should be coupled with EIA due to 2% rate of false positive EIA tests.

Standard serological assays (EIA and WB or IFA) show sensitivity in patients with established disease (>3months after transmission) of 99.5% and sensitivity of 99.994%.

A positive test should be confirmed with repeated testing or with collaborating clinical or laboratory data.

False negative result:

- Window period
- Seroconversion
    - Infants
    - Patients treated prior to Seroconversion
    - Patients with late stage disease

- Atypical host response
- Failure to mount immunologic response
- Rapid test
- Technical or clinical error

False positive:

Reported to range from 0.0004 to 0.0007%

- Autoantibodies
- Investigational HIV vaccines
- Factitious HIV infection
- False positive oral fluid ora quick test
- Influenza vaccine
- False positive rapid screening tests
- Technical error

Alternative HIV serological tests:

- IFA
    - Possible advantage- simple, less expensive, more rapid than western blot
    - Disadvantage- resource limited setting
- Home kits
- Saliva test
- Nucleic Acid Amplification Test
- Rapid test- Recommended for HIV screening as an alternative to EIA.

Useful where rapid results are important

- Occupational exposure
- Pregnant women in labour without testing
- Outreach clinics
- In emergency room/ STD clinics

CD4 cell count[27]

This is a standard test to assess:

- Prognosis for progression to AIDS to death
- Formulate differential diagnosis in a symptomatic patient
- To make a therapeutic decision regarding ART and prophylaxis for opportunistic infection.

Technique:

The standard technique uses flow cytology and hematology analysers.

Normal values- mean of 800-1050 with a range of two standard deviations of approximately 500-1400 cells/mm^3.

CD4 slope- It refers to the rate of decline of CD4 counts. Sequentially collected data for 8729 untreated HIV infected patients from 20 cohorts in Cascade showed the median CD4 count at about 8 months post seroconversion was approximately 610ceels/mm^3.

Response to ART[25,27]

CD4 count typically increases by >50 cells/mm^3 at four to eight weeks after viral suppression with ART and then increases at a rate that correlates with time, baseline CD4 count and virologic suppression. With good virologic response the increase at one year averages 100 to 150 cells/mm^3 at >5years it averages 20 to 50 cells/mm^3/year.

ANTIRETROVIRAL TREATMENT[110]

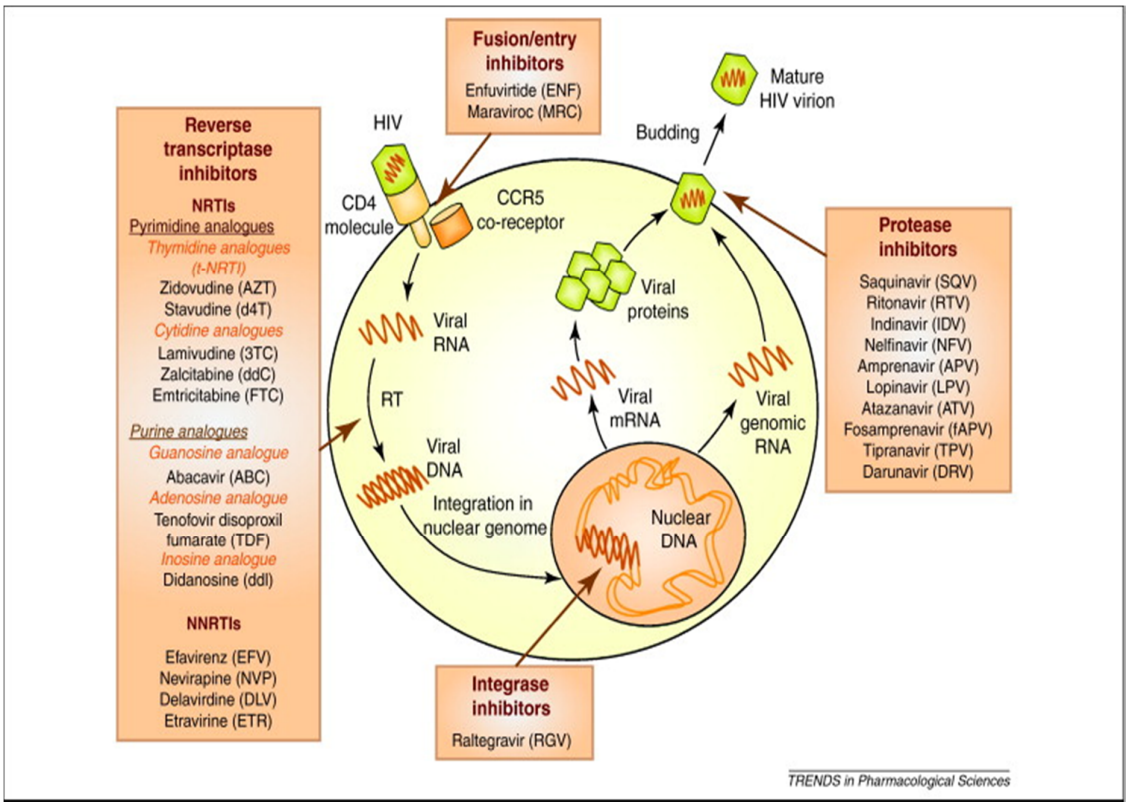


Figure: 5 Site of Action of Antiretroviral Drugs

NRTI/ NtRTI	NNRTI	PI	Integrase inhibitor	Fusion inhibitor	Entry inhibitor
Abacavir (Abacavir, ABC)	Delavirdine (delavirdine mesylate, DLV)	Atazanavir (Atazanavir sulfate, ATV)	Dolutegravir (DTG)	Enfuvirtide (T-20)	Maraviroc (MVC)
Didanosine (ddI)	Efavirenz (EFV)	Duranavir (Duranavir ethanolate,DRV)	Raltegravir (RAL)		
Emtricitabine (FTC)	Etravirine (ETR)	Fosamprenavir (Fosamprenavir calcium, FPV)			
Lamivudine (3TC)	Nevirapine (NVP)	Indinavir (Indinavir sulfate, IDV)			
Stavudine (d4T)	Rilpivirine (rilpivirine hydrochloride (RPV)	Nelfinavir (Nelfinavir mesylate, NFV)			
Tenofovir disoproxil fumerate (TDF)		Ritonavir (RTV)			
Zidovudine (Azidothymidine, AZT, ZDV)		Saquinavir (saquinavir mesylate, SQV)			
		Tipranavir (TPV)			
		Lopinavir (LPV)			

Since 1987, over 20 drugs have been accepted by the Food and Drug Association (FDA) for the clinical use against HIV infection (FDA 2013). Effective antiretroviral therapy (ART) can attain a persistent viral suppression and good immunological recovery (Thaker and Snow, 2003). There are six classes of antiretroviral drugs that are currently being used in the treatment of infections caused by HIV. These include nucleoside /nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs), fusion inhibitors (FIs) and entry inhibitors (FDA 2013).[110]

a) Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI and NtRTI)[110]

The NRTI interferes with the activities of the HIV reverse transcriptase enzyme. They are structurally similar to the nucleoside building blocks of nucleic acids (RNA, DNA), but devoid of the hydroxyl (-OH) group in the 3` position making them unable to form the 5` to 3` phosphodiester bond essential for DNA synthesis (Warnke et al., 2007).

To apply their antiviral activity, the NRTIs are first intracellularly phosphorylated by cellular kinases to their active 5` triphosphate forms. The activated 5` triphosphate competes with the natural deoxynucleotide triphosphates (dNTPs) for the incorporation by reverse transcriptase (RT) into the growing primer. Once the 5` triphosphate form is incorporated, it results in the termination of the elongation and synthesis of DNA, due to their lack of 3` hydroxyl group (Wanke et al., 2007, Maga et al., 2010, Esposito et al., 2012). The HIV reverse transcriptase recognizes the NRTIs substrate with a higher affinity than the cellular DNA polymerases, thus the NRTIs do not interfere with cellular polymerases (Esposito et al., 2012).

The NtRTIs are compounds that already possess a phosphate molecule in their structure and only requires two phosphorylation steps to be converted to their active triphosphate forms. Similar to NRTI, NtRTIs active forms compete with natural dNTPs for incorporation by RT into the growing primer, thereby terminating the viral DNA synthesis (Esposito et al., 2012). Currently, tenofovir is the available NtRTI compound.

b) Nonnucleoside reverse transcriptase inhibitors (NNRTIs)[110]

NNRTIs are diverse in their structure and chemical composition. They act by binding non- competitively to the same hydrophobic pocket (nonnucleoside inhibitor binding pocket, NNIBP) that is situated close to the polymerase catalytic active site within the palm domain of the p66 subunit of the RT (Sluis-Cremer and Tachedjian 2008, Maga et al., 2010).

The NNRTIs do not interfere with dNTP binding but alter the conformation and mobility of RT resulting in unproductive complexes (Maga et al., 2010). Unlike the NRTIs, NNRTIs do not require the involvement of cellular enzymes to apply their antiviral activity and are not effective against HIV-2 (Wanke et al., 2007, Esposito et al., 2012). Some NNRTIs also inhibit the late stages of HIV-1 life cycle by interfering with the Gag-Pol polyprotein processing. However, higher concentrations are needed to affect the late stage of HIV-1 replication, when compared to the concentrations that are required to block RT (Sluis-Cremer and Tachedjian 2008).

c) Protease inhibitors (PIs)[110]

PIs, interfere with the proteolytic maturation, a stage that is vital for the production of infectious HIV virus particles. The PIs inhibit the activity of the

protease subsequently blocking the cleavage of the large precursor polypeptide chain into smaller functional proteins. This results in the production of non-infectious virus particles (Warnke et al., 2007, Adamson 2012).

d) Integrase inhibitors (INIs)[110]

The integrase inhibitors interfere with the catalytic functions of HIV integrase during the strand transfer stages of viral integration. Thus the transfer of virally coded DNA into host chromosome is blocked (Temesgen and Siraj 2008, Hicks and Gulick 2009).

e) Fusion inhibitors (FIs)[110]

Fusion inhibitors are polypeptides that are homologous to the C-terminal hepta repeat (HR) region of glycoprotein 41 (gp 41). The fusion inhibitors act by competing with the C- terminal for binding to the N-terminal hepta repeat region of gp 41.

Once the fusion inhibitor binds to the N-terminal it prevents the formation of the hairpin-like structure that is responsible for the fusion of viral and cell membranes. Thus the viral genome is prevented from entering the CD4+ cells (De-Clercq 2009, Matos et al., 2010).

f) Entry Inhibitors[110]

The entry inhibitors (CCR5 antagonist) block the gp 120-CCR5 interaction by binding to the co-receptor (CCR5) and changing its shape such that gp120 cannot recognize it. The viral genome is prevented from entering the CD4+ cells (Britz et al 2006, De Clercq 2009).

CARDIAC MANIFESTATIONS IN HIV[32]

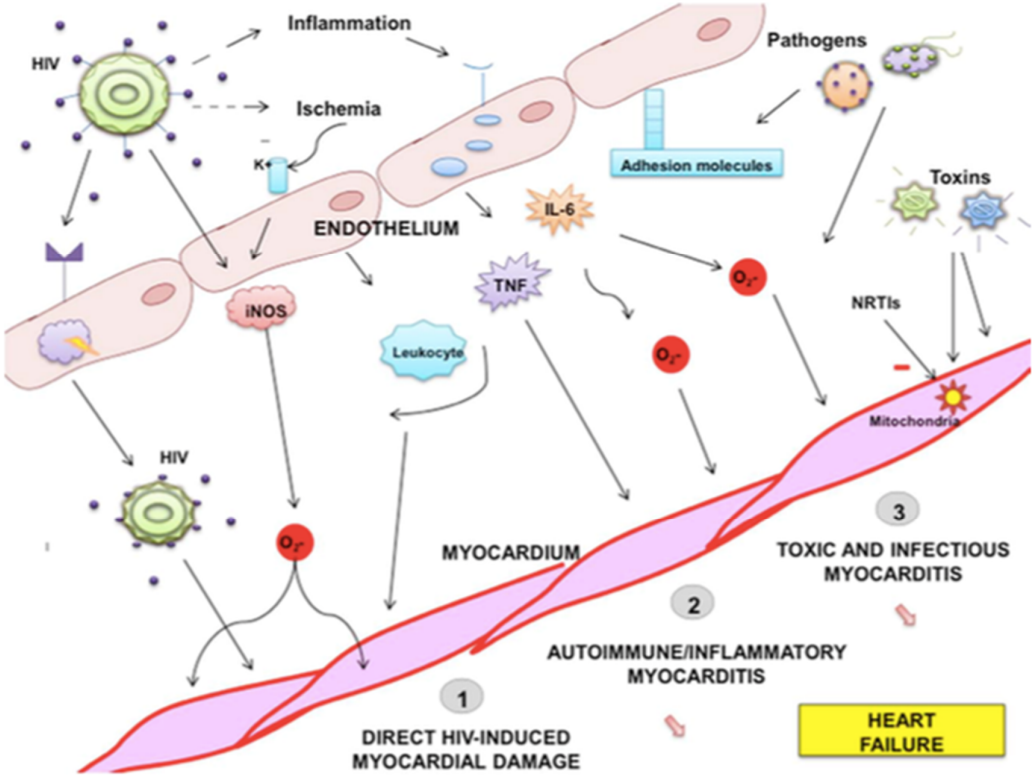


Figure: 6 Pathogenesis of HIV associated Heart Failure

Pathophysiology of human immunodeficiency virus (HIV)–associated heart failure. HIV causes damaged myocardium directly and also indirectly through inflammation and increased susceptibility to infections, toxins, and, eventually, ischemia. The endothelium serves as a reservoir of HIV and also acts to elaborate cytokines, such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), and free radicals in response to increased inflammation. Other causes of myocardial dysfunction among HIV-infected individuals include mitochondrial dam- age resulting from HIV therapy such as nucleoside reverse transcriptase inhibitors (NRTIs) and other toxins. iNOS indicates inducible nitric oxide synthase.

The actual aetiopathogenesis of cardiac injury in HIV infection is not clear. It is however generally agreed that several factors come into play either singly or in combination to produce cardiac pathology.[33]

There is an extensive range of hypotheses regarding the pathogenesis of HIV associated heart muscle disease. These include myocardial invasion with HIV itself, opportunistic infections, viral infections, an autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, endothelial dysfunction, autonomic dysfunction, and prolonged immunosuppression.[34]

1.Direct HIV myocardial invasion

HIV infection and the myocardial inflammatory process (myocarditis) related to it are the most studied causes of cardiomyopathy in HIV-infected patients.[35] Although it is clear that HIV can affect myocardial interstitial cells, the evidence that the virus can enter cardiac myocytes which do not possess CD4 receptors is less clear.[36]

Possibly, other cells such as the dendritic cells play a role not only as a reservoir but also as antigen-presenting cells in the context of the major histocompatibility complex and activities of progressive tissue injury mediated by cytokines.[37]

HIV was isolated in culture from an endomyocardial biopsy specimen from a patient with AIDS and dilated cardiomyopathy.[38]

Using immuno-cytochemical tests, the HIV-1 antigen has been found in endothelial cells from an endomyocardial biopsy specimen of a patient with left ventricular hypokinesia.[39]

HIV-1 virions seem to irregularly infect the myocardial cells, without any direct association between the qualitative presence of the virus and myocyte dysfunction. Necrosis of the myocardial fibres is usually minimal, with associated lymphocytic infiltrates.[40]

Additionally, the HIV nucleic acid sequences have been reported in the myocardium of HIV infected patients using in-situ hybridization.[41]

In that study, the distribution of the hybridization assay signal in heart tissue was sparse and did not correlate with any histopathologic or clinical evidence of heart disease.

However, HIV sequences might have been contaminants from other cells or from blood since PCR technique is very sensitive[38] and immunohistochemical studies have shown no evidence of group 120 or p24 antigen expression on the heart.[42]

It has however been shown through in vitro studies that newly developed human foetal cardiac myocyte cell line could ingest HIV-1 through a specific F_c receptor despite the absence of CD4 receptors on the myocytes.[43]

The evidence is accumulating that HIV gp120 may also play an important pathogenic role in HIV cardiomyopathy.[44]

The effects appear to involve changes in intracellular ionized free calcium and p38 mitogen activated protein (MAP) kinase[45,46] activation and these have been implicated in myocardial dysfunction.[47-49] The pathogenic role for p38 MAP kinase in myocardial dysfunction has been described both in animal models and in humans.[50,51]

A recent study implicated p38 MAP kinase activation in the negative inotropic effect of gp120 in adult rat ventricular myocytes.[52]

Similarly, prolonged and repeated activation of p38 MAP kinase in cardiac myocytes by gp120 could result in HIV cardiomyopathy in vulnerable individuals.

Adrenergic signalling is characteristically blunted in humans as well as animal models with myocardial depression, cardiomyopathy, and chronic heart failure from a variety of causes.[53]

A physiological role for p38 MAP kinase in adrenergic signalling in cardiac myocytes was recently suggested by an elegant study in a transgenic mice model lacking b1-adrenergic receptors.[54]

Magne et al[55] provided strong evidence for the regulation of b2-adrenergic signalling through a MAP kinase/cPLA$_2$ pathway. Human heart failure is associated with a relative decrease in b1- and an increase in b2-adrenergic receptors.[56]

Thus activation of p38 MAP kinase by HIV gp120 would lead to blunted autonomic responses typical of human cardiomyopathies and chronic heart failure.

The HIV-1 gp 120 has also been shown to damage mitochondria of cardiomyocytes and induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis.

The immunohistochemical data from human heart failure patients raise the interesting possibility that CXCR4 is the receptor responsible for the physiological effects of HIV gp120 on adult rat ventricular myocytes. This recently identified binding site has no previously known function in the heart.[57]

Controlling the activation and termination of this gp120 signalling pathway in myocytes has considerable potential clinical relevance. The basic mechanisms involved in p38 MAP kinase activation are relevant to chronic heart failure, ischemia, ischemic preconditioning, and adrenergic signalling in cardiac myocytes as well. This gp120 signalling pathway in cardiac myocytes may provide a novel therapeutic target for HIV as well as other cardiomyopathies.

2.Opportunistic infections

Since HIV infection results in profound suppression of T cell macrophage mediated immunity and since there are significant abnormalities in B cell lymphocytic function leading to abnormalities of humoral immunity, patients with HIV disease frequently face many life threatening infections.

Among patients with myocarditis, opportunistic bacterial, fungal, and protozoan pathogens can be identified in 10 to 15 percent of cases. Many organisms have been implicated in the development of myocarditis in HIV infected patients.

3.Cytokines

There is increasing evidence that immune cells especially T lymphocytes are activated to produce cytokines in HIV disease. Reservoir cells (e.g. dendritic cells) may play a pathogenic role in the interaction between HIV and the myocyte and in the activation of multifunctional cytokines (e.g. tumour necrosis factor-alpha [TNF-a], interleukin-1 [IL-1], interleukin-6, interleukin-10) that contribute to progressive late tissue damage and decreased myocardial function. Viral infection in the context of a nonspecific stimulator of monokines such as IL-1 or TNF-a is much more likely to lead to myocarditis and myocyte damage than viral infection alone.

TNF-a produces a negative inotropic effect by altering intracellular calcium homoeostasis and possibly by inducing nitric oxide synthesis, which likewise reduces myocyte contractility.

Proin inflammatory cytokines activate inducible nitric oxide synthase (iNOS), thus stimulating the production of NO, a sequence of events that may contribute to the association between dilated cardiomyopathy and encephalopathy in HIV disease.[57]

Increased levels of TNF-a and iNOS have been reported in patients with HIV associated dilated cardiomyopathy with iNOS staining intensity correlating with mortality and degree of immunosuppression.

The intensity of both TNF-a and inducible nitric oxide synthase staining has been reported much higher in myocardial biopsy samples from patients with HIV-associated cardiomyopathy specifically in those with a myocardial viral infection independently of anti- retroviral treatment than in those with idiopathic dilated cardiomyopathy.[58]

HIV may also inflict damage on myocytes by means of a mechanism of "innocent bystander destruction" proposed for neurological cell damage in AIDS associated subacute encephalitis.[59]

According to this hypothesis, the myocytes are damaged by the toxic enzymes and cytokines released through HIV replication in the interstitium and it may be particularly relevant to the myocardium since increased numbers of infected interstitial cells have been found in HIV positive subjects with active myocarditis.[60]

4.Autonomic dysfunction

HIV infection may be associated with abnormalities of the autonomic nervous system, particularly in advanced disease. Five to seventy-seven percent of patients suffered changes in cardiovascular autonomic reflexes according to the definition of the complication.

Cardiovascular autonomic reflexes may be profoundly affected causing postural hypotension, syncope, and cardiorespiratory arrest during invasive procedures. Patients with AIDS are subject to long term physiologic stress due to tragic implications of their disease; the pathway being mediated through prolonged and excessive secretion of catecholamines. This may, in turn, lead to intermittent microvascular spasm and focal[61] or widespread ischaemia, resulting in cardiac damage as seen in some cases of phaeochromocytoma.[62]

An autonomic imbalance may also be related to HIV induced neural pathway[63] damage or may be a result of direct beta – receptor stimulation by group 120 protein.[64]

These theories are yet to be explored, but they do offer a possible explanation for the presence of non-inflammatory myocardial necrosis associated with AIDS.

Takotsubo cardiomyopathy, a new syndrome, which is characterized by transient left ventricular dysfunction and by a typical left ventriculogram showing transient extensive akinesia of the apical and mid portions of the left ventricle with hypercontraction of the basal segment has been described in an HIV infected patient.[65]

Takotsubo cardiomyopathy seems to be a new type of acute heart failure, which generally has a good prognosis. Myocardial damage by catecholamine overload, adrenoceptor hypersensitivity, and changes of catecholamine dynamics due to stress may cause this condition.[66]

5.Nutritional deficiencies

Nutritional deficiencies are commonly observed in HIV infection, especially in more advanced stages of the disease. They make left ventricular dysfunction more probable.[67] In particular, recent reports have described abnormally low levels of serum selenium in paediatric AIDS patients[68] and in autopsy tissue samples of the adult myocardium.[69]

A selenium deficiency has been shown to exacerbate the virulence of agents that induce myocarditis.[67] In wasting patients, selenium replacement restores ventricular function and reverts cardiomyopathy.[67] A non-obstructive cardiomyopathy associated with selenium deficiency has been described in patients with advanced HIV disease. The patients improved with selenium repletion.

Malabsorption and diarrhoea promote fluid and electrolyte disorders and nutritional deficiencies.[70] Trace element deficiencies have been directly or indirectly related to cardiomyopathy.[70]

Other specific nutritional deficiencies include B group vitamins, folates and zinc and these could worsen immune function or contribute to cardiac dysfunction.[71,72]

6.Drugs and toxins

The advent of potent antiretroviral drugs in recent years has had an impressive impact on mortality and disease progression in HIV-infected patients, hence, issues related to long-term effects of drugs are of growing importance.[73]

Drug-induced cardiotoxicity in HIV-infected patients has been a highly controversial issue, especially due to the association between zidovudine and dilated cardiomyopathy.[73,74]

There is evidence that zidovudine is related to the diffuse destruction of ultra-structures and inhibition of mitochondrial DNA replication, resulting in lactic acidosis that contributes to myocardial dysfunction.

However, no direct clinical relationship has been proved connecting exposure to reverse transcriptase inhibitors and induction of ventricular dysfunction. Interferon alpha, an antineoplastic, antiviral and immunomodulator have been reported to have a variety of reversible cardiotoxic effects including cardiomyopathy and congestive cardiac failure.[75]

Doxorubicin used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin lymphoma has a dose-related effect on dilated cardiomyopathy[76], as does foscarnet sodium when used to treat cytomegalovirus (CMV) oesophagitis.[77]

Amphotericin B used for disseminated fungal infection has also been reported to cause reversible dilated cardiomyopathy.[78]

Among HIV-infected patients with cardiac abnormalities, the incidence of alcohol, cocaine and injection drug use is high. An abnormal diastolic function has

been demonstrated in patients with substance abuse at various stages of HIV infection and in a control group who were HIV negative.[79] The table shows drugs used in HIV infection and their effect on the myocardium:

Medications	Treatment	Cardiovascular effect
Amphotericin B	Antifungal	DCM, Hypertension and bradycardia
Doxorubicin	Kaposi sarcoma	Cardiomyopathy
Foscarnet	CMV	Cardiomyopathy
Ganciclovir	CMV	Ventricular tachycardia
HAART	Antiretroviral	Coronary Artery Disease
Interferon	Antineoplastic Antiviral Immunomodulator	Myocardial Ischemia or ischemic cardiomyopathy
Zidovudine	Antiretroviral	Myocarditis or dilated cardiomyopathy

7.Autoimmunity

There is a growing body of evidence to support autoimmunity as the main mechanism causing cardiomyopathy in HIV-infected patients.[80]

Compared to patients with idiopathic dilated cardiomyopathy whose inflammatory infiltrates indicate a preponderance of CD4+ T cells and B lymphocytes, HIV-infected patients with an echocardiographic diagnosis of dilated cardiomyopathy and histopathology compatible with myocarditis present more CD3+ and CD8+ T cells.[81]

The existence of an active immune process within the myocardium was suggested by findings of viral hybridization and increased expression of class I major histocompatibility complex molecules (MHC-I).[82] As for humoral immunity, myocardial specific anti-alpha-myosin antibodies were found in 15% of HIV-positive patients, compared to a prevalence of 3.5% in control groups.[83]

The HIV gene may provoke cell surface cardiac muscle protein resulting in induction of circulating cardiac auto antibodies which can trigger a progressively destructive autoimmune reaction.[84]

Another finding that supports the theoretical role played by autoimmunity in cardiomyopathy associated with HIV is the therapeutic response of patients with heart failure to immunoglobulins, which act by inhibiting cardiac antibodies, competing with Fc receptors and reducing the secretion and action of inflammatory cytokines.

8.Endothelial dysfunction

Dysfunction and activation of the vascular endothelium have been described in HIV infection. Circulating markers of endothelial activation such as blood pro-coagulants and cell adhesion molecules are found less often in these patients.

These findings occur because of the secretion of cytokines as a response to the activation of mononuclear cells or to a viral infection in the tunica adventitia or a response to the effects of the viral proteins gp 120 and Tat in the endothelium.

Endothelial cells that have been injured and activated can cause tissue damage, inflammation and remodelling, accelerating the development of cardiovascular disease. The same mechanism of endothelial dysfunction, changes in leukocyte adhesion and arteritis can stimulate atherogenesis and eventually ischemia and myocardial injury.

HIV-1 has been shown to cause vascular damage. HIV-1 may cause vasculitis and coronary arteritis through activation of cytokines and cell-adhesion molecules and alteration of major-histocompatibility-complex class I molecules on the surface of smooth-muscle cells. Infected cells may also generate reactive oxygen species with the activation of factors that induce apoptosis.[85,86]

Studies have shown that exposure to HAART increased intercellular adhesion molecule-1 (ICAM-1) gene expression and concomitant exposure to TNF-alpha further increased ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and endothelial-leukocyte adhesion molecule cell surface protein levels.[87]

These studies indicate that chronic HAART exposure increases oxidative stress in endothelial cells and induces mononuclear cell recruitment, which may

eventually precipitate the cardiovascular diseases observed in HIV-1 positive individuals on anti- retroviral therapy.[87]

HAART is associated with metabolic and somatic changes that may lead to an increased risk of coronary and cerebrovascular disease. Insulin resistance, impaired glucose tolerance and diabetes mellitus all occur with increased frequency in HIV-seropositive patients receiving protease inhibitors. Impaired glucose tolerance has been found in 16–46% of protease inhibitor recipients and diabetes mellitus in 7–13%.[88,89] In one study, HAART was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure.[90]

9.Myocardial involvement by AIDS-associated tumors

Kaposi sarcoma (KS) affects the myocardium usually as part of a disseminated process. The tumour plaques are localized to the epicardial space and typically do not involve the underlying myocardium or the overlying parietal pericardium, although concomitant myocardial infiltration with heart failure has been described.[91]

The incidence of Kaposi's sarcoma has declined by almost 40% annually since the advent of HAART and is now less than 10% of the reported incidence in 1994.[92] Primary lymphomas of the heart occur with increased frequency among patients with AIDS.[93] They are usually of the non-Hodgkin's type and of B-cell origin.

Echocardiography is the most sensitive test for cardiac involvement. Thickened myocardium or luminal tumour masses are found in 50% to 75% of patients.

The myocardium may appear speckled with disseminated nodular areas producing heterogenous echogenicity.[94]

TYPES OF HEART MUSCLE DISEASES IN HIV

1.Myocarditis

Myocarditis is defined histologically by the Dallas criteria, which require the presence of an inflammatory infiltration of the myocardium with adjacent myocyte necrosis or degeneration that is not typical of the ischaemic damage associated with coronary artery disease.[95]

Three histological patterns of myocarditis have been described in patients with AIDS:

- Lymphocytic infiltration with myocyte necrosis
- Lymphocytic infiltration without inflammation and
- Myocyte damage without evidence of inflammatory infiltrate

The prevalence of myocarditis in HIV infected patients has been difficult to establish with estimates ranging from 6%[96] to 52%.[97]

The virus itself may cause myocarditis in HIV infection, either directly or indirectly via autoimmune processes, or via one of many opportunistic organisms. No specific etiologic factor was found in more than 80% of cases of myocarditis in one series.

The diagnosis of myocarditis requires a high index of suspicion based on symptoms and/or compatible physical findings such as fever and signs of heart failure.

Non-specific ECG changes may occur such as sinus tachycardia, conduction defects and repolarisation abnormalities, and there may be radiological evidence of cardiac enlargement or pulmonary oedema.[97]

Echocardiography offers a practical, non-invasive means of assessing cardiac size and function. The Echo features of myocarditis are non-specific and often identical to those associated with cardiomyopathy. Indeed, differentiation between the two conditions can only be made histologically. Some workers have demonstrated dyskinesia of the left ventricle with or without dilatation or generalized four chamber enlargement.[98]

2.Dilated cardiomyopathy (DCM*)*

HIV-associated cardiomyopathy has been shown to be associated with more advanced immunosuppression and lower CD4 lymphocyte counts and is independently associated with death. Clinical left ventricular dysfunction is rapidly fatal in the later stages of AIDS.[99] Both LV systolic and diastolic function deteriorate as the CD4 lymphocyte count decreases in HIV infection.[100]

Cardiac failure due to DCM was first described in 1986 in three patients with AIDS. HIV/AIDS has subsequently become an important aetiologic factor, responsible for up to 10% of cases in the general population.[101]

In the developed world, postmortem and echocardiography studies suggest that the prevalence of HIV-associated cardiomyopathy in the pre-HAART era was 30% to 40%. DCM emerged as the most clinically significant cardiac complication of HIV infection in the western world in the pre-HAART era.[102-104]

In Africa, the home to the majority of the world's HIV infected population, cross-sectional echocardiographic studies of outpatient and inpatient HIV-infected patients suggest a prevalence of cardiomyopathy of 9% to 57%.[105] Although DCM is associated with a significantly reduced CD4 cell count[106], no association has been found between progression of left ventricular dysfunction and the rate of cell count decline.[107]

3.Isolated right ventricular dysfunction

Right ventricular hypertrophy (RVH) has been described as the second most frequent cardiac finding at autopsy of AIDS patient after pericardial effusion.[108]

By use of echocardiography, dilatation and dysfunction of the right ventricle have been noted in 4% of HIV positive patients.[106] This may be part of a global myopathic process that leads to biventricular dysfunction and four-chamber dilatation, although it can also occur in isolation.

RVH may also result from HIV related pulmonary hypertension (HRPH). Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature involving endothelial and vascular smooth muscle cell (VSMC) proliferation, vasoconstriction, right ventricular hypertrophy, and eventually, right heart failure and death.

PAH occurs 1000-fold more frequently in HIV patients than in the general population.[107] Although conventional HIV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) leads to regression of PAH, HAART; two NRTI plus a protease inhibitor increases the incidence of HIV- associated PAH as much as twofold.

Although there are relatively few models for PAH, previous reports indicate that the disease can be initiated by endothelial injury and release of the mitogen endothelin-1 (ET-1). ET-1, in turn, stimulates VSMC proliferation.[108]

Tricuspid valve damage from endocarditis is potentially capable of causing right ventricular dilatation as a result of excessive volume load. Right ventricular hypertrophy (RVH) may be evident on the ECG, but echocardiography remains the most useful method for assessing right ventricular function.

DIAGNOSIS OF HIV RELATED MYOCARDIAL DISEASE

Clinical presentation of HIV associated cardiomyopathy in symptomatic patients is generally similar to cardiac disease due to other causes. The absence of symptoms and signs of heart disease does not, however, exclude cardiac involvement, as an occurrence of sub-clinical cardiac abnormalities with possible fatal consequences in this population has been described.[109]

Diagnosis requires the possibility of cardiac involvement to be borne constantly in mind and suspected if symptoms and/or compatible physical findings emerge.

Electrocardiography (ECG) is a useful screening tool in patients with HIV infection, and ECG changes may precede echocardiographic abnormalities. Patients with abnormal ECG patterns should be further investigated. Echocardiography has been shown to be extremely useful for the diagnosis and monitoring of HIV associated myocardial disease.[109]

Asymptomatic HIV infected subjects may have an abnormal echocardiographic examination, usually with isolated diastolic dysfunction. As the disease progresses systolic dysfunction develops which is initially reversible.

In advanced HIV disease, echo findings could be similar to those of idiopathic DCM with dilatation of all heart chambers and evidence systolic dysfunction which is irreversible. Although an early diagnosis of cardiac dysfunction might be beneficial, the cost-effectiveness of routine echocardiographic examination in these patients has not been well established.[109]

However, the echocardiogram is well indicated for patients with clinical suspicion or when the CD4 count is below 200 cell/microliter.

METHODOLOGY

The observational study is a cross sectional study, which was carried out in the department of medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of 1 year. The patients admitted in general war, ICU and OPD basis with the diagnosis of HIV were included in the study. All the patients symptomatic or asymptomatic for cardiac diseases were included in the study. Patients found to have hypertension, diabetes mellitus, rheumatic heart disease, congenital heart disease or ischemic heart disease were excluded from the study.

A total of 100 cases of HIV/AIDS were included in the study irrespective of duration of illness, whether on treatment or the presence or absence of clinical symptoms of cardiac involvement after ethical clearance and obtaining a signature on a consent from the patient where he/she was explained about the study and the procedures involved. Detailed general and systemic examination was carried out of all the patients to look for any evidence of cardiovascular involvement or for cardiovascular complications. The patients underwent laboratory investigations for complete blood count, HIV test by ELISA and CD4/CD8 cell count. ECG and Echocardiography were also performed on these patients.

Haemoglobin estimation was done by automated method. Total and differential leucocyte count was carried out using flow cytometry by automated method.

All patients underwent a 12 lead ECG to look for cardiac involvement. They were then subjected to 2 Dimensional- Echocardiography.

Left Ventricular Hypertrophy was diagnosed on ECG when it showed the changes as per the criteria given by Romhilt-Estes point score system. Increased QRS

magnitude=3 points (Any limb lead R wave or S wave >= 2mV or S in V1 >= 3mV or R in V5 to V6 >= 3mV).

Two dimensional and M mode echocardiography were carried out in all the cases using a Philips 2D-echocardiography machine. Each two dimensional study consist of parasternal long axis and short axis, and apical two and four chamber views. Left ventricular volumes were measured and Ejection fraction was calculated. Left Ventricular diastolic dysfunction was said to be present on 2D echocardiography when it showed abnormal myocardial relaxation. The mitral E (Early diastolic mitral flow velocity) and A (late diastolic mitral flow velocity) was calculated. The patient was said to have pericardial effusion if the 2D echocardiography showed echo-free space between the visceral and parietal pericardium throughout the cardiac cycle. The diagnosis of restrictive cardiomyopathy was made when the 2D echocardiography showed limited ventricular filling resulting from an idiopathic non-hypertrophied myocardial abnormality and typical ventricular diastolic pressure tracing in the dip and plateau or square root configuration also the E/A ratio is increased markedly (>2).

Definitions:

Left ventricular ejection fraction

Normal, left ventricular ejection fraction 71% (mean value of controls minus two standard deviations); mildly depressed, left ventricular ejection fraction between 60% and 51%; moderately depressed, left ventricular ejection fraction between 50% and 31% and severely depressed, left ventricular ejection fraction 30%. Left ventricular diastolic diameter

Normal 53mm (mean value of controls plus two standard deviations); borderline, 54-55mm; dilated more than 55mm.

Abnormal transmitral flow velocity pattern was classified as pattern I (suggestive of delayed left ventricular relaxation with normal or slightly elevated left atrial pressure) if the patient was under 60 and resented with atleast one of the following: isovolumic relaxation time ~100ms, E 60cm/s, E-wave deceleration time 275ms, E/A ratio 1.0 or an atrial filing fraction 35%.

Abnormal transmitral flow velocity patterns were classified as pattern II (suggestive of decreased left ventricular compliance with elevated left atrial pressure). If the patients presented evidence of heart disease and atleast one of the following: isovolumic relaxation time 90 ms, E wave deceleration time 110 ms, E/A ratio 1.5, atrial filling fraction ~ 20% or an interval between the end of the A wave and R wave of the ECG 20 ms.

If the acoustic window permitted, when a normal transmitral flow velocity pattern was obtained, it was reclassified as a pseudonormal pattern (suggesting delayed left ventricular relaxation with moderately elevated left atrial pressure) if peak velocity of atrial reversal (AR wave) of pulmonary venous flow was 20 cm/sec.

Dilated cardiomyopathy was diagnosed in the presence of a LVEF of <50 % and a Left ventricular end diastolic diameter more than 3.2 cm /m^2.

Pericardial effusion was graded as mild (500ml), if it was localised posteriorly and not cranially obscure the atrio-ventricular sulcus; moderate (500-1000ml), if it was more uniformly distributed in the pericardial cavity; severe (1000ml), if it was diffusely detected (postero-medially, laterally and anteriorly), and around the apex.

Mitral valve prolapse was diagnosed on the basis of:

- Increased thickness (5mm) in the mid-portion of one or both valvular leaflets as assessed from the long axis view at diastole

- Extreme valvular leaflet redundancy i.e. a disproportionate increase in the leaflet circumferences with respect to left ventricular dimensions, as assessed at the level of free mitral margin from short axis parasternal view
- Left atrium systolic dislocation of one or both mitral leaflets from the mitral valve ring plane, as visualised from the long axis view.

Myocarditis was suspected on the basis of clinical data and later confirmed at necropsy, according to Dallas criteria. The echocardiographic findings were:

i. Diffused ventricular hypokinesia, as shown by a decreased left ventricular ejection fraction
ii. Normal or slightly increased left ventricular end-diastolic diameter and parietal thickness
iii. Reversible or irreversible increase of the left ventricular mass adjusted for body surface.

Endocarditis was diagnosed as either 'definite' or 'probable', according to Von Reyn et al. Identification of a vegetative lesion was based on evidence of anomalous echoes adherent to the endocardial surface and displayed motion independent of cardiac structure.

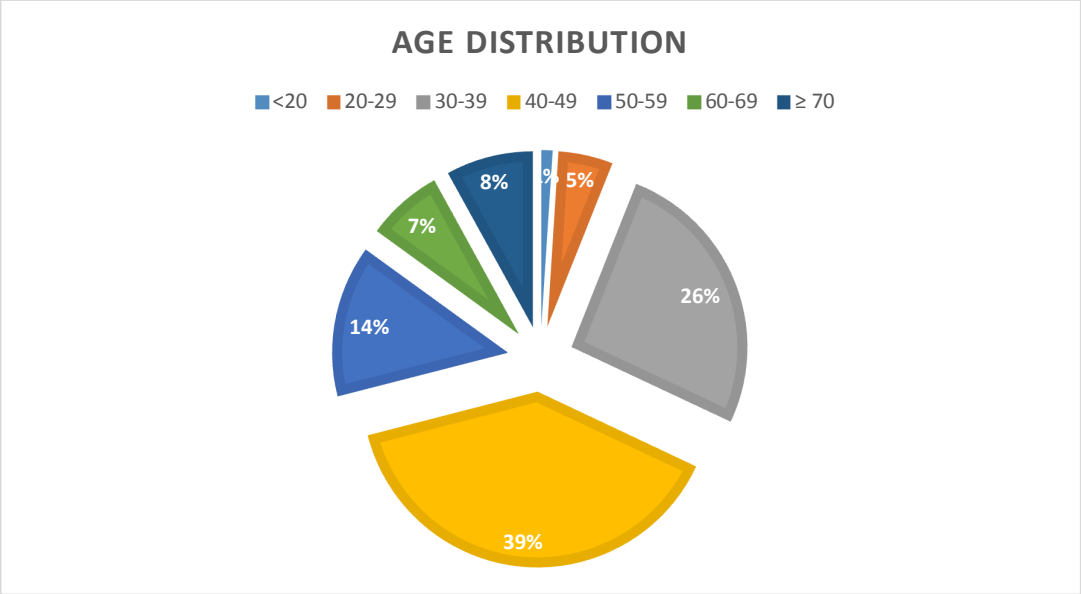
Abnormal wall motion was assessed by evaluating the shift and changes in thickness of the left ventricular walls by means of computer digitization of systolic and diastolic endocardial borders. The endocardial outlines were divided into 24 equivalent segments and the motion of the individual radians or areas were expressed as a bar graph.

RESULT

100 consecutive patients of HIV including both outpatient and the hospitalized inpatients in the department of medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied. The duration of the study was from January 2016 to December 2016. The findings/ observations and final results are tabulated as follows:

Table 1. Age Distribution

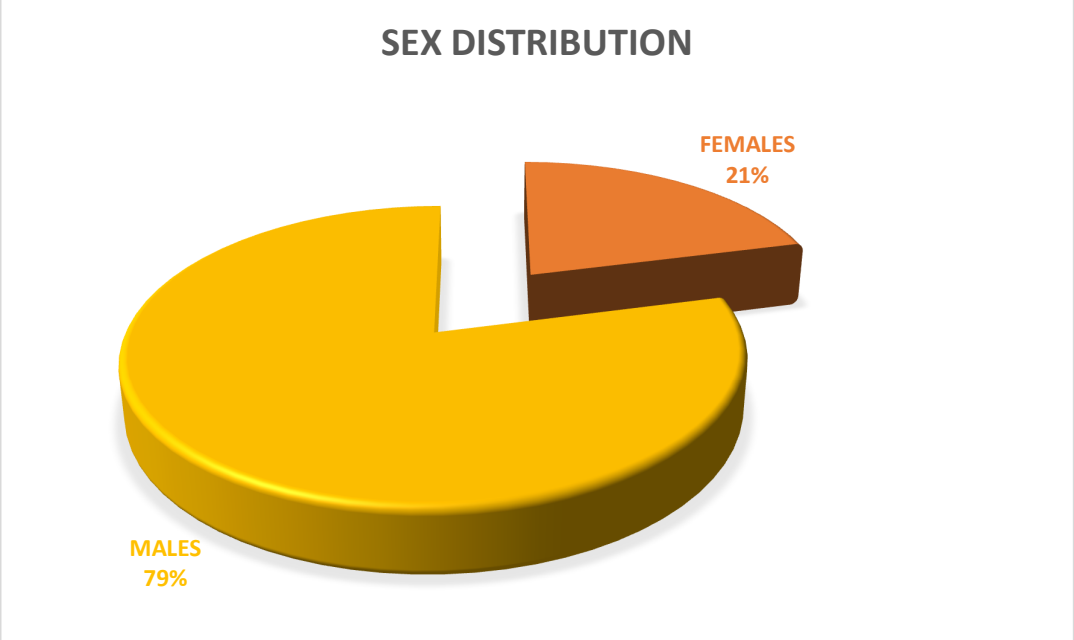
Age(Years)	Distribution (n=100)	
	Number	Percentage
<20	1	1
20-29	5	5
30-39	26	26
40-49	39	39
50-59	14	14
60-69	7	7
≥ 70	8	8
Total	100	100



The age of the patients ranged from 18 to 71 years, maximum number of cases were in the age group of 40 to 49 years that is 39 patients (39%).

Table 2. Sex Distribution

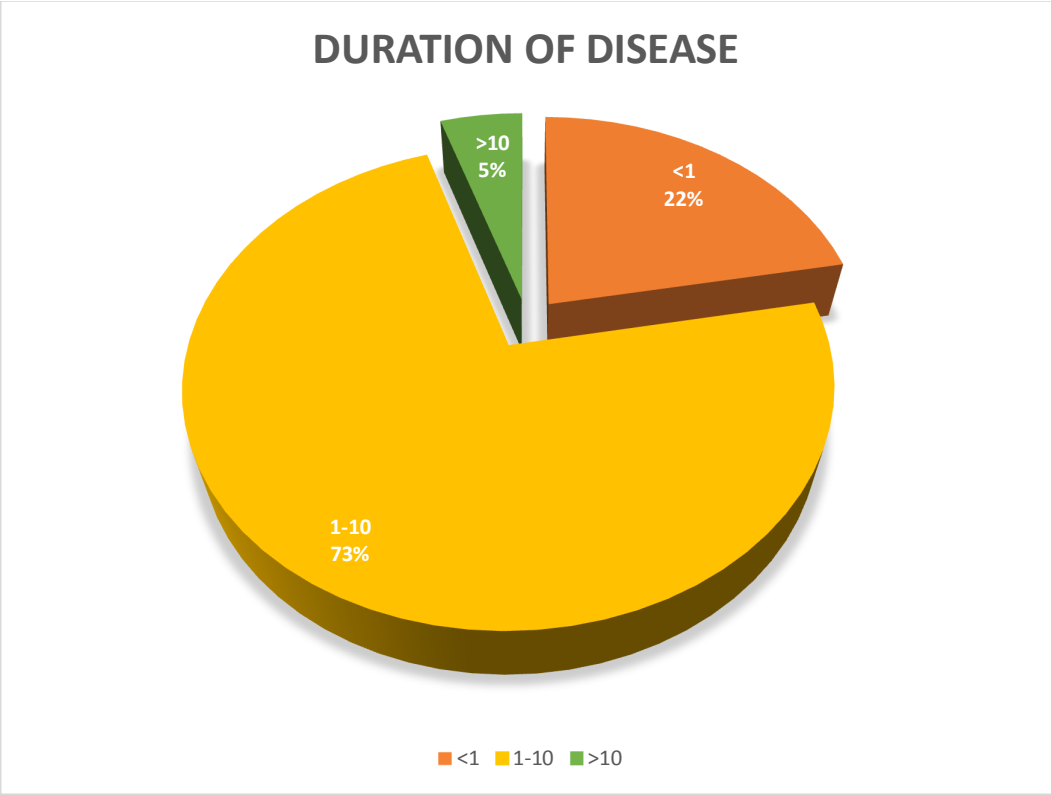
Sex	Distribution(n=100)	
	Number	Percentage
Male	76	76.00
Female	24	24.00
Total	100	100.00



Out of 100 patients 76 were male (76%) and 24 were females (24%) accounting to a ratio of male: female 3.16:1.

Table 3. Duration of HIV infection

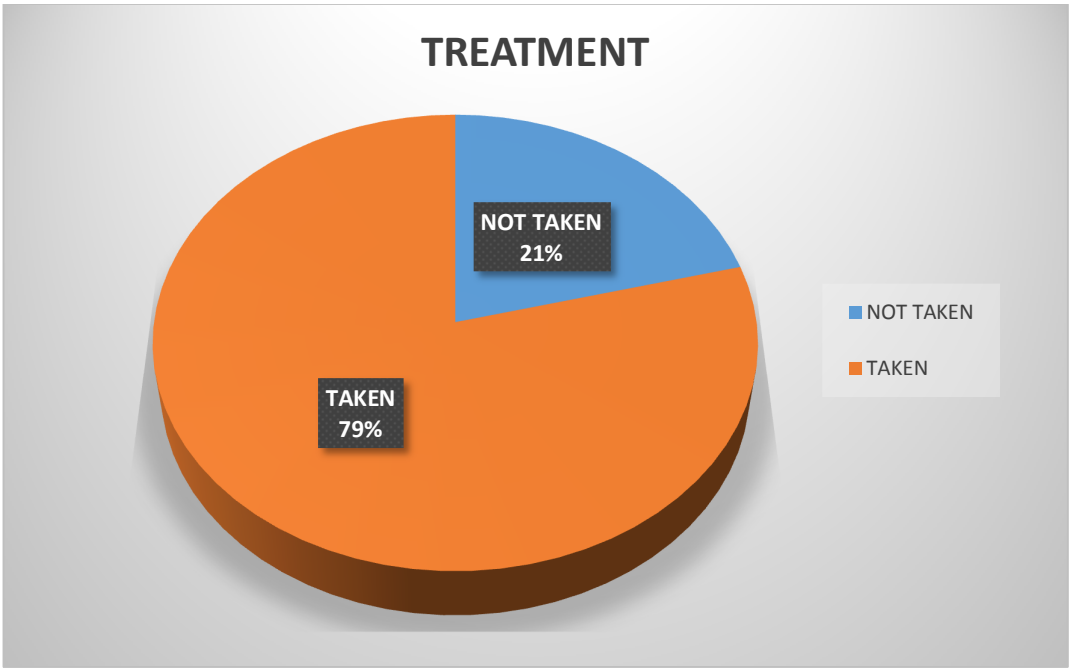
Duration of disease	Distribution (n=100)	
	Number	Percentage
<1	22	22
1-10	73	73
>10	5	5
Total	100	100



In the present study, we observed the duration of HIV infection varied from a few days to more than 10 years. In 73 patients (73%) duration was between 1 to 10 years. In 5 patients (5%) it was more than 10years.

Table 4. Treatment (ART)

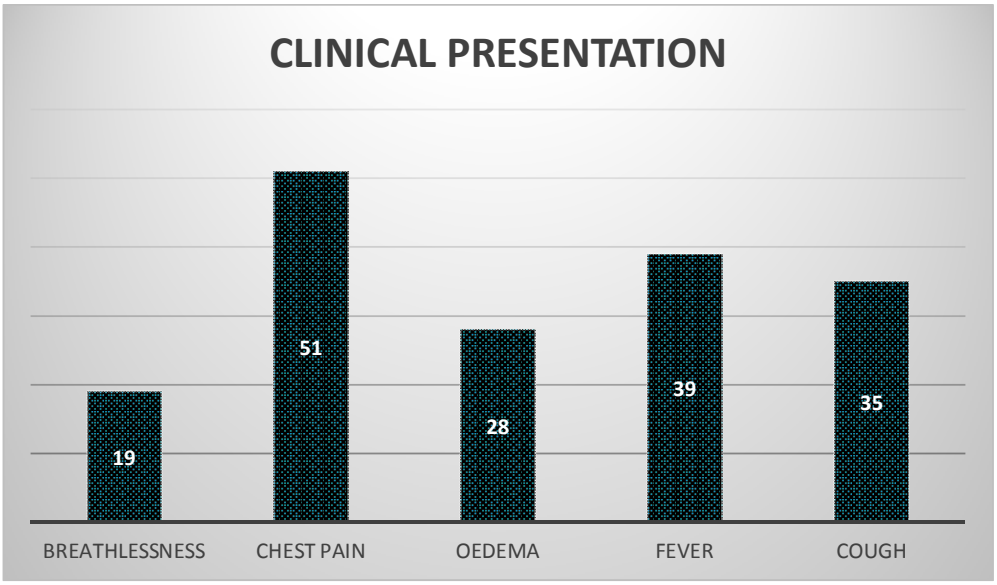
Treatment	DISTRIBUTION	
	Number	Percentage
On ART	79	79
Not on ART	21	21
Total	100	100



We observed 79 patients (79%) were on treatment with Anti-Retroviral drugs, remaining 21 patients (21%) were not on ART.

Table 5. Clinical Presentation

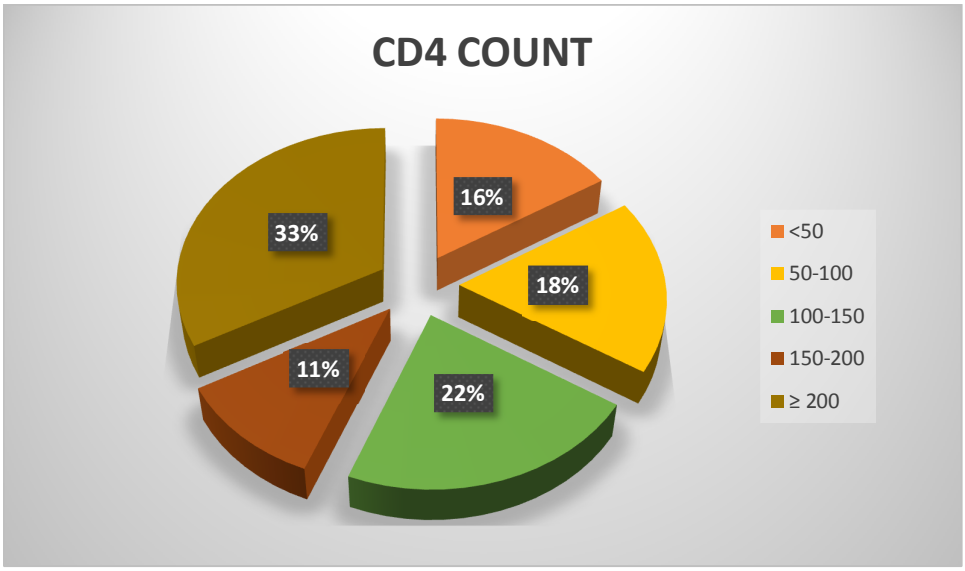
Symptom	DISTRIBUTIzON (n=100)	
	Number	Percentage
Breathlessness	19	19
Chest pain	51	51
Oedema	28	28
Fever	39	39
Cough	35	35



In our study, majority of the patients had chest pain accounting to 51%, followed by fever which was present in 39 patients (39%), followed by cough in 35 patients (35%), followed by oedema in 28 patients (28%) and breathlessness in 19 patients (19%).

Table 6. CD4 count

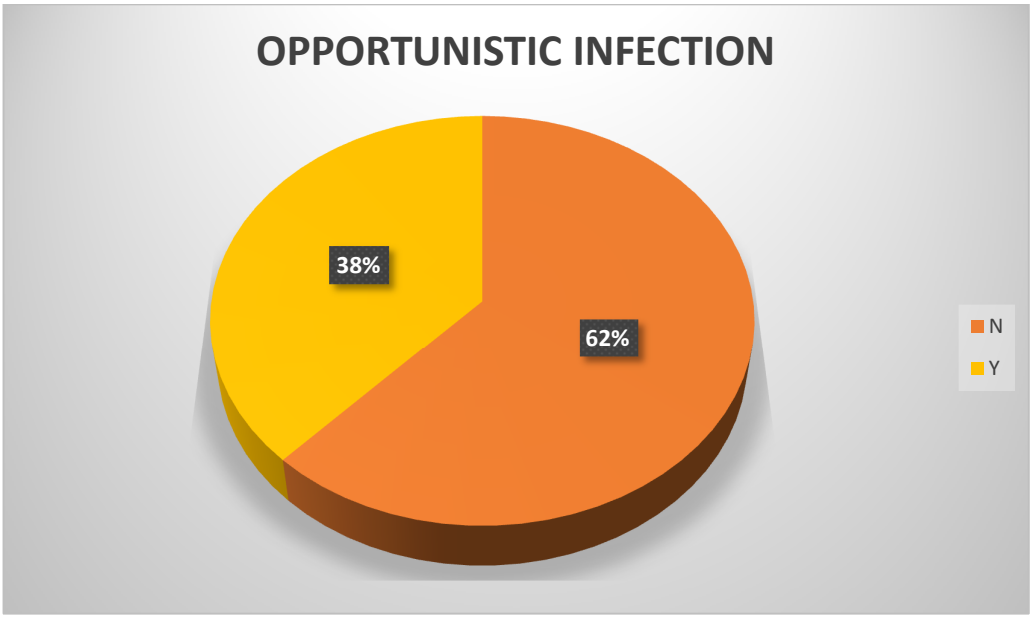
CD4 count	DISTRIBUTION (n=100)	
	Number	Percentage
<50	16	16
50-100	18	18
100-150	22	22
150-200	11	11
≥ 200	33	33
Total	100	100



33 patients (33%) had a CD4 count of more than 200, followed by 22 patients (22%) who had a CD4 count between 100-150, followed by 18 patients (18%) with a CD4 count between 50-100, followed by 16 patients (16%) with a CD4 count less than 50 and 11 patients (11%) with a count between 150-200.

Table 7. Opportunistic infection

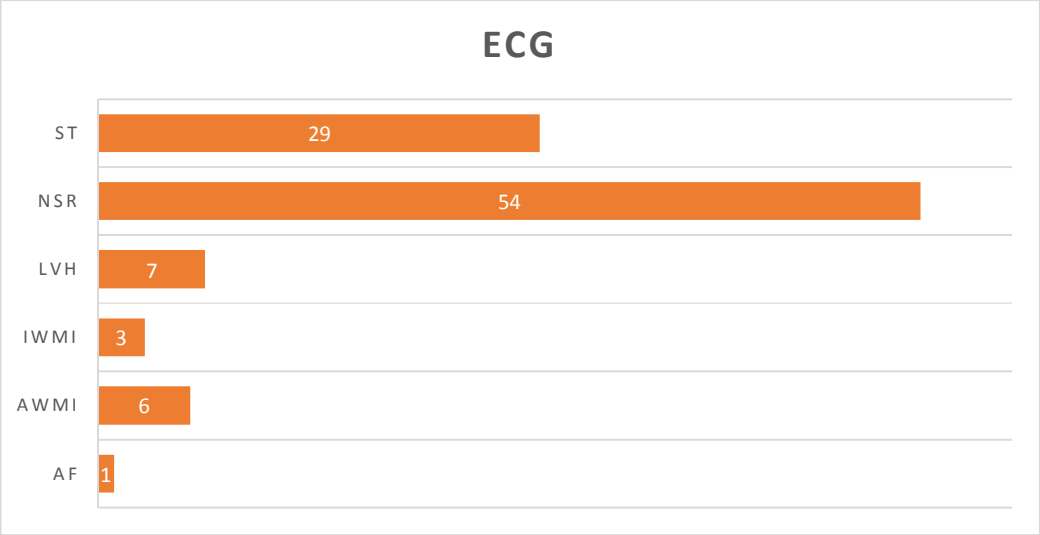
Opportunistic infection	Distribution (n=100)	
	Number	Percentage
Present	38	38
Absent	62	62
Total	100	100



Opportunistic infections were present in 38 patients (38%) and absent in 62 patients (62%).

Table 8. ECG findings

ECG	Distribution (n=100)	
	Number	Percentage
Atrial fibrillation	1	1
AWMI	6	6
IWMI	3	3
LVH	7	7
Sinus Tachycardia	29	29
Normal	54	54
Total	100	100

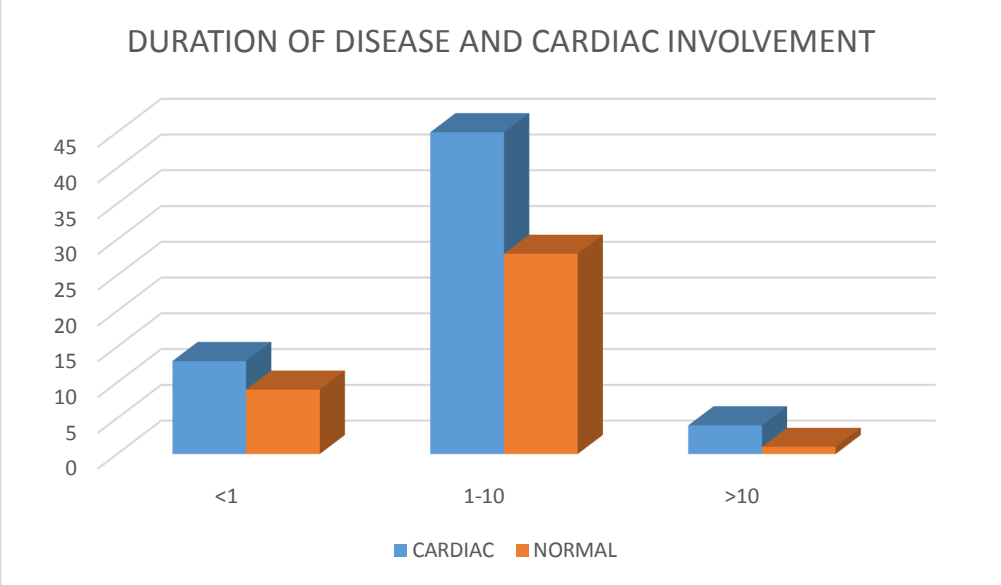


ECG was normal in majority of the patients, i.e., 54 patients (54%), sinus tachycardia was observed in 29 patients (29%), followed by LVH in 7 patients (7%), Anterior wall MI was seen in 6 patients (6%), inferior wall MI in 3 patients (3%). Atrial Fibrillation was observed to be in 1 patient (1%).

Table 9. Association of cardiac manifestations with duration of HIV infection

Duration (Years)	Cardiac Manifestations(n=62)		
	Present	Absent	Total
<1	13	9	22
1-10	45	28	73
>10	4	1	5
Total	62	38	100

p= 0.6803



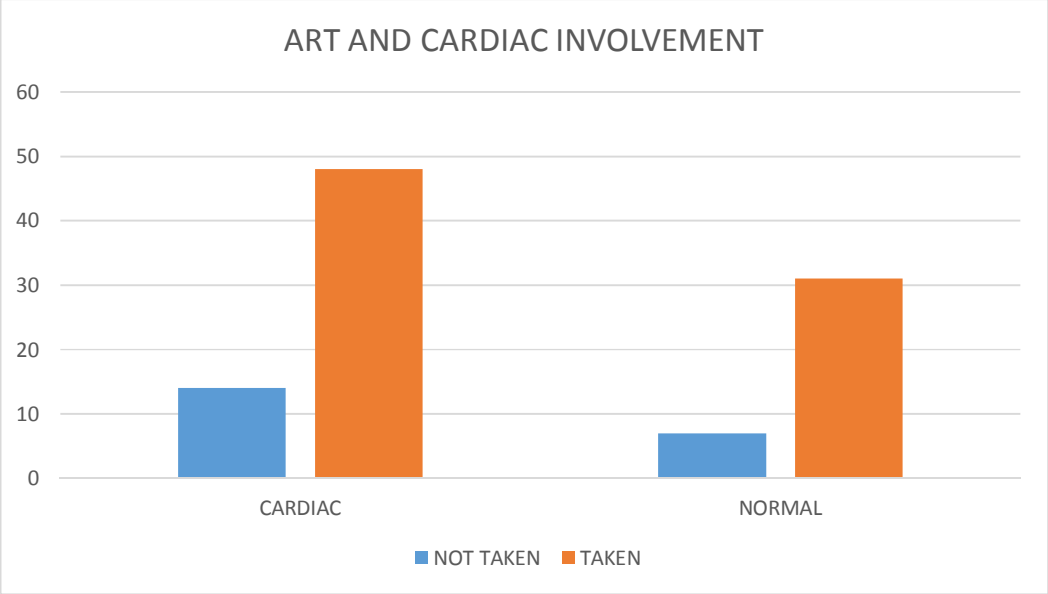
We observed that in this study, 45 out of the 73 patients were infected with HIV for the time period of 1 to 10 years, these patients were diagnosed with cardiac abnormalities. 4 among the 5 patients who had been diagnosed with HIV infection for more than a period of 10 years had cardiac abnormalities. Out of 22 patients who were infected with HIV for less than a year, 13 patients were diagnosed with cardiac abnormalities.

*(p value= 0.6803 being statistically insignificant).

Table 10. Association of cardiac disease with patients on ART/ not on ART

ART	Cardiac abnormalities(n=62)		
	Present	Absent	Total
NOT TAKEN	14	7	21
TAKEN	48	31	79
TOTAL	62	38	100

p=0.8082



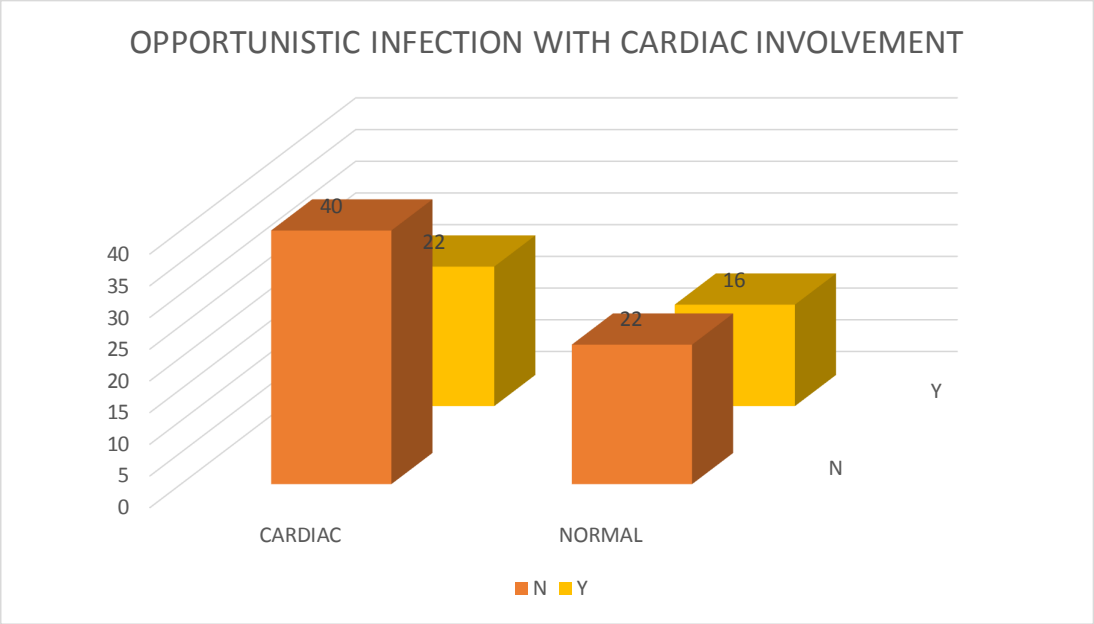
We observed that, among the 79 patients on treatment with ART 48 had cardiac abnormalities, and among 21 patients not on treatment, 14 had cardiac abnormalities.

*(p value=0.8082 which is statistically insignificant).

Table 11. Association of cardiac disease with presence or absence of Opportunistic infection

Opportunistic infection	Cardiac abnormalities (n=62)		
	Present	Absent	Total
Present	22	16	38
Absent	40	22	62
Total	62	38	100

p=0.6528



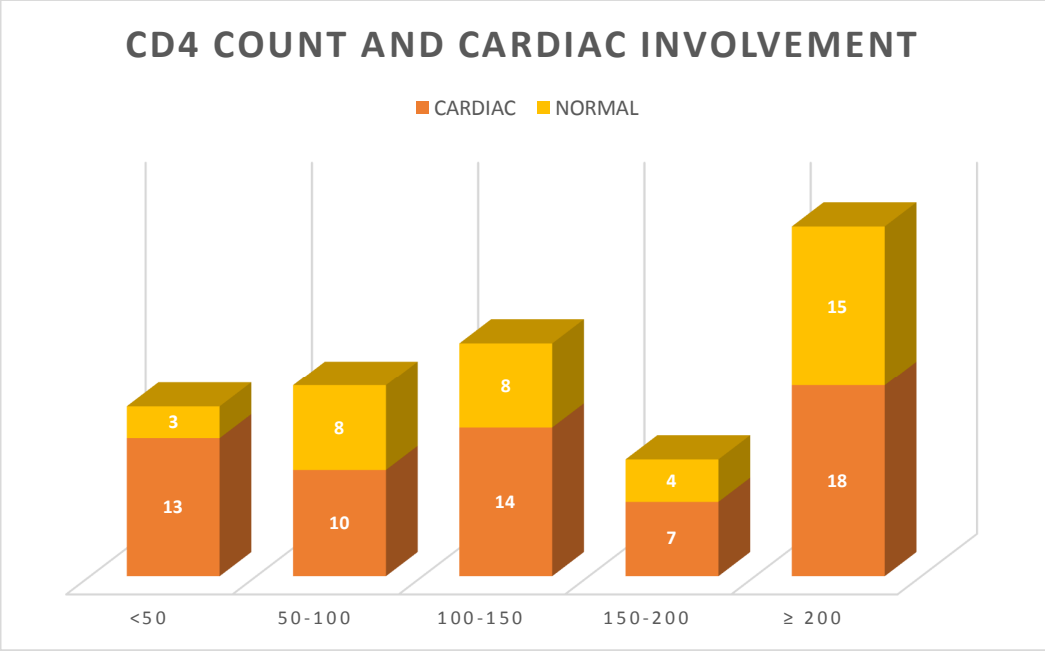
We observed that, among the 62 patients with cardiac abnormalities, opportunistic infection was present in 22 patients and among the 38 patients with no cardiac abnormality, opportunistic infection was present in 16 patients.

*(p value=0.6528 which is statistically insignificant).

Table 12. Association of cardiac disease with CD4 count

CD4 count	Cardiac abnormalities (n=62)		
	Present	Absent	Total
<50	13	3	16
50-100	10	8	18
100-150	14	8	22
150-200	7	4	11
≥ 200	18	15	33
Total	62	38	100

p=0.4555



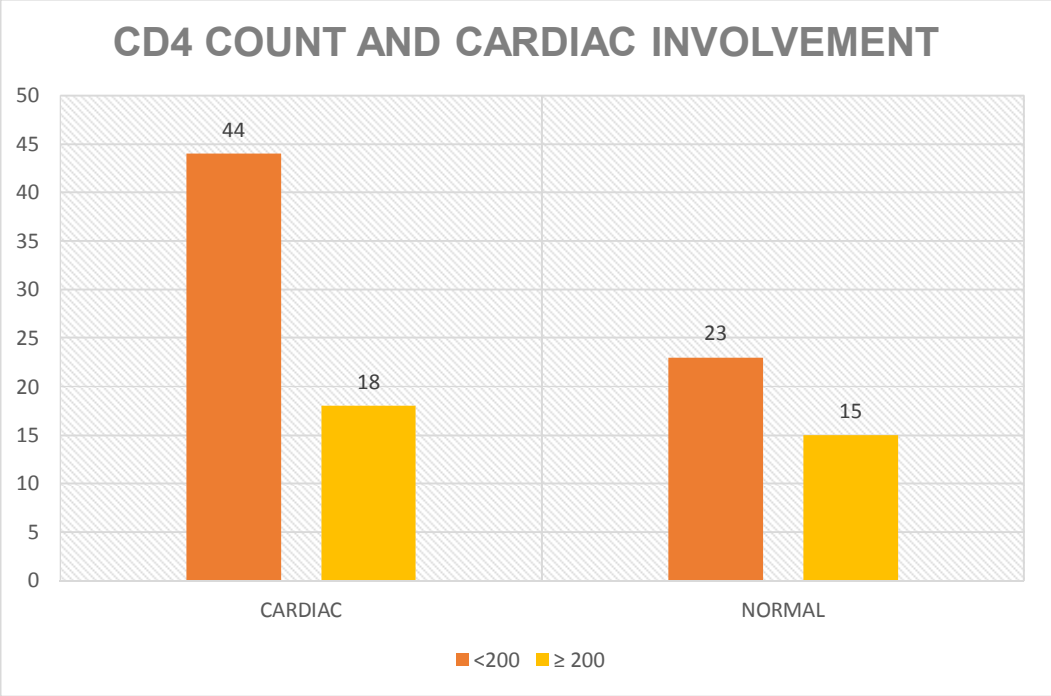
Among the 62 patients with cardiac involvement, 18 patients had a CD4 count more than 200 and 13 patients had a CD4 count less than 50.

*(p value=0.4555 being statistically insignificant).

Table 13. Association of cardiac disease with CD4 count

CD4 count	Cardiac abnormalities (n=62)		Total
	Present	Absent	
<200	44	23	67
>200	18	15	33
Total	62	38	100

p=0.3905



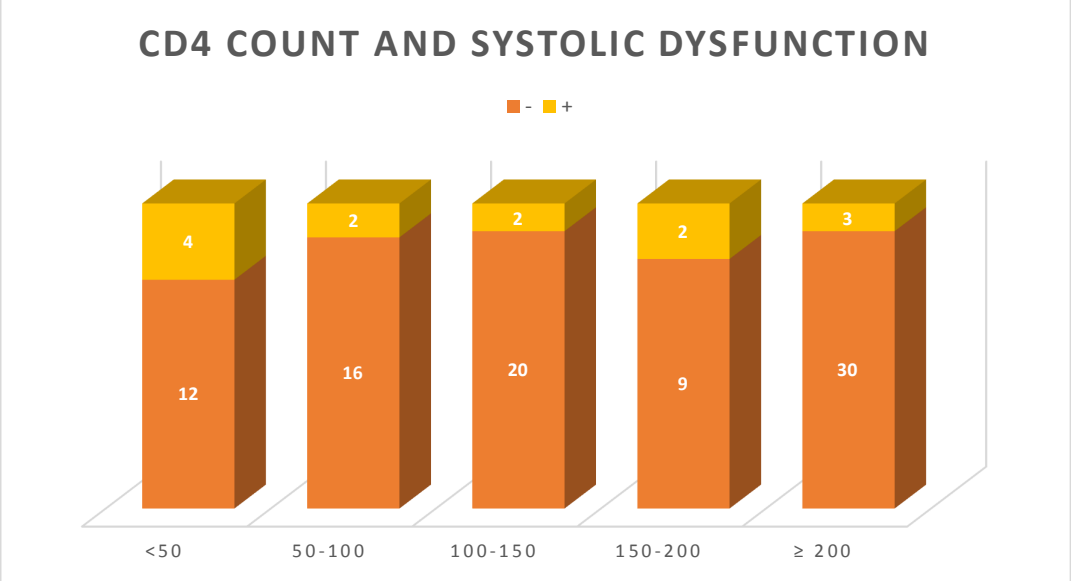
Among the 62 patients with cardiac involvement, 44 patients had a CD4 count was less than 200.

*(p value=0.3905)

Table 14. Association of CD4 count with Left Ventricular Systolic Dysfunction

Systolic Dysfunction	CD4 count					
	<50	50-100	100-150	150-200	≥ 200	Total
Absent	12	16	20	9	30	87
Present	4	2	2	2	3	13
Total	16	18	22	11	33	100

p=0.5415



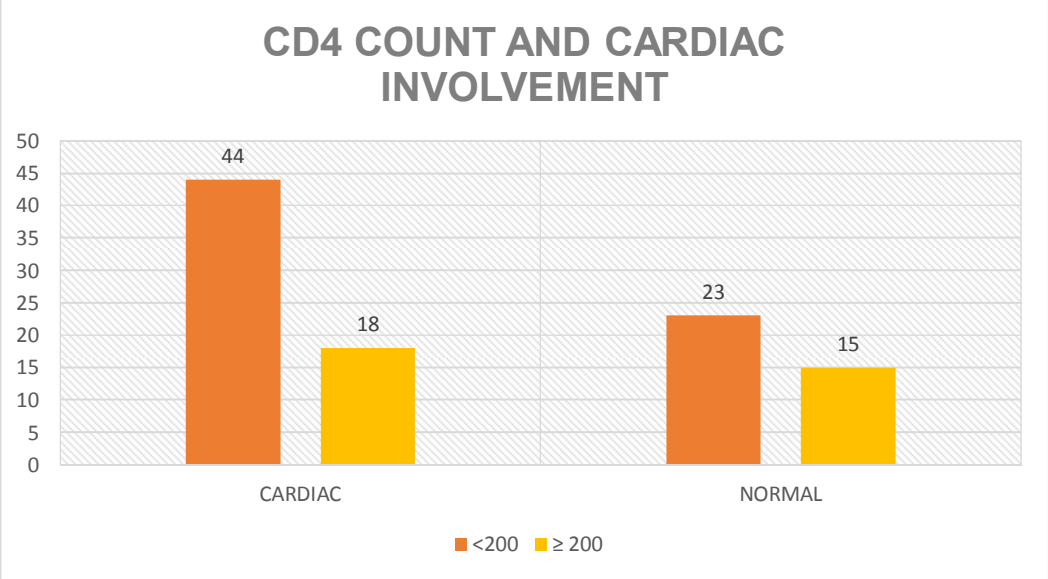
Among the 13 patients with systolic dysfunction, 4 patients had a CD4 count of less than 50, and 3 had a CD4 count of more than 200.

*(p value=0.5415 which is statistically insignificant).

Table 15. Association of CD4 count with Left Ventricular Systolic Dysfunction

Systolic dysfunction	CD4 count		
	<200	>200	Total
Present	10	3	13
Absent	57	30	87
Total	67	33	100

p=0.6174



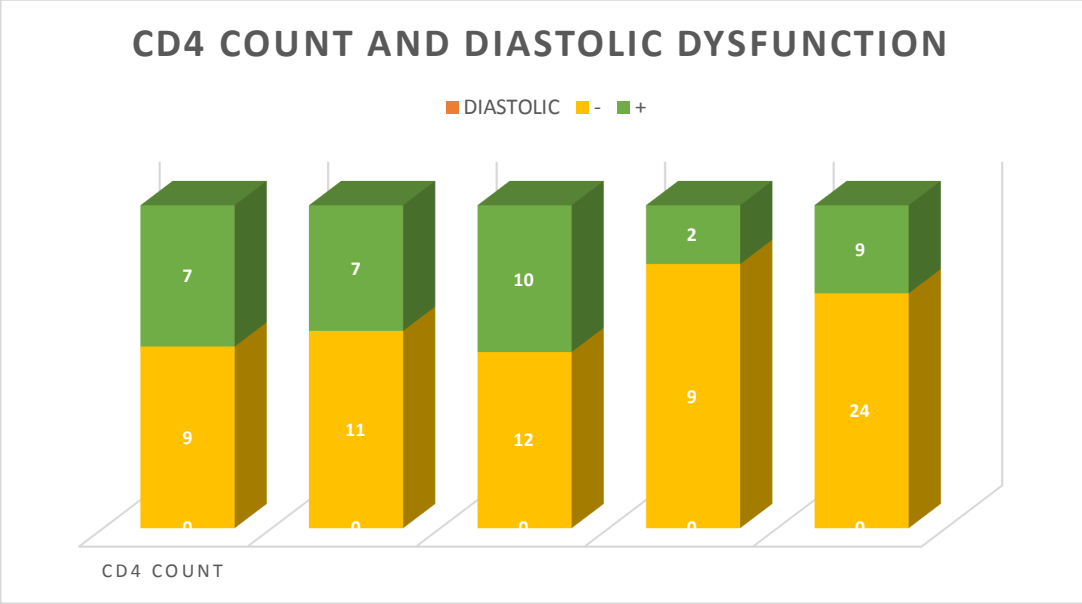
Among the 13 patients with systolic dysfunction, 3 patients had a CD4 count of more than 200 and 10 had a CD4 count of less than 200.

*(p value=0.6174 which is statistically insignificant)

Table 16. Association of CD4 count with Left Ventricular Diastolic Dysfunction

Diastolic Dysfunction	CD4 count					
	<50	50-100	100-150	150-200	≥ 200	Total
Absent	9	11	12	9	24	65
Present	7	7	10	2	9	35
Total	16	18	22	11	33	100

p=0.4130



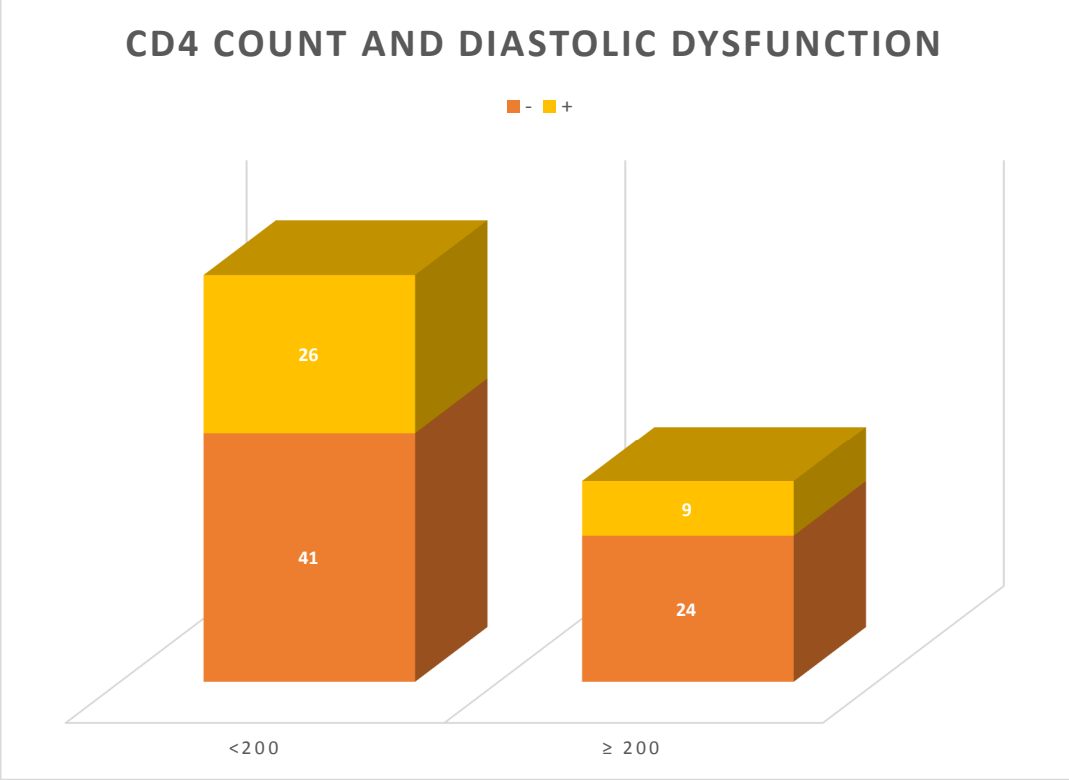
Among the 35 patients with diastolic dysfunction, 7 had a CD4 count of less than 50, 9 had a CD4 count of more than 200.

*(p value=0.4130 which is statistically insignificant).

Table 17. Association of CD4 count with Left Ventricular Diastolic Dysfunction

Diastolic dysfunction	CD4 count		
	<200	>200	Total
Present	26	9	35
Absent	41	24	65
Total	67	33	100

p=0.3607



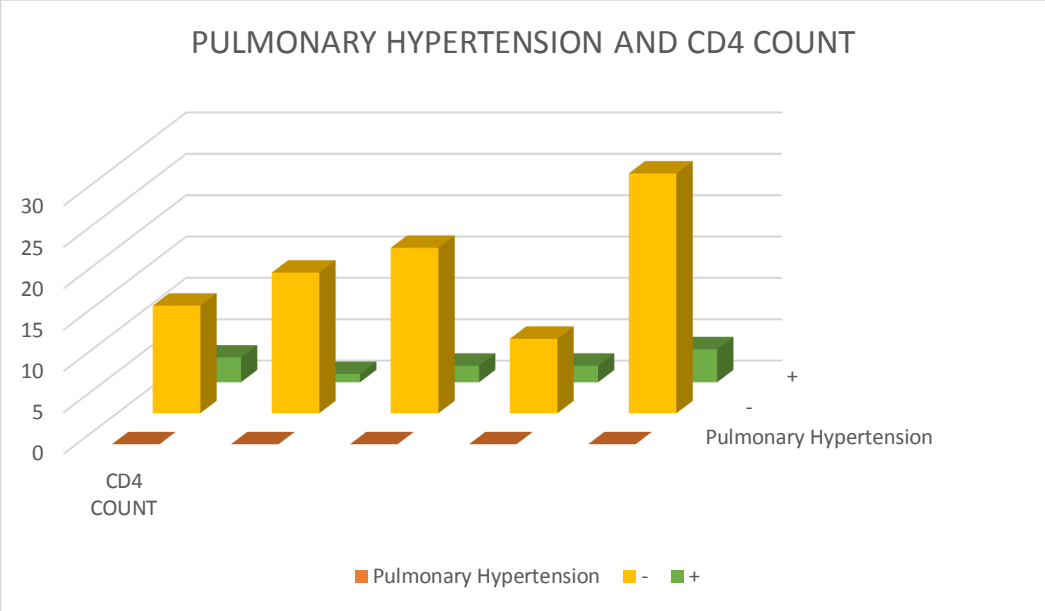
Among the 35 patients with diastolic dysfunction, 26 patients had a CD4 count <200.

*(p value=0.3607 which is statistically insignificant).

Table 18. Association of Pulmonary Hypertension with CD4 count

Pulmonary Hypertension	CD4 count					
	<50	50-100	100-150	150-200	≥ 200	Total
Absent	13	17	20	9	29	88
Present	3	1	2	2	4	12
Total	16	18	22	11	33	100

p=0.7404



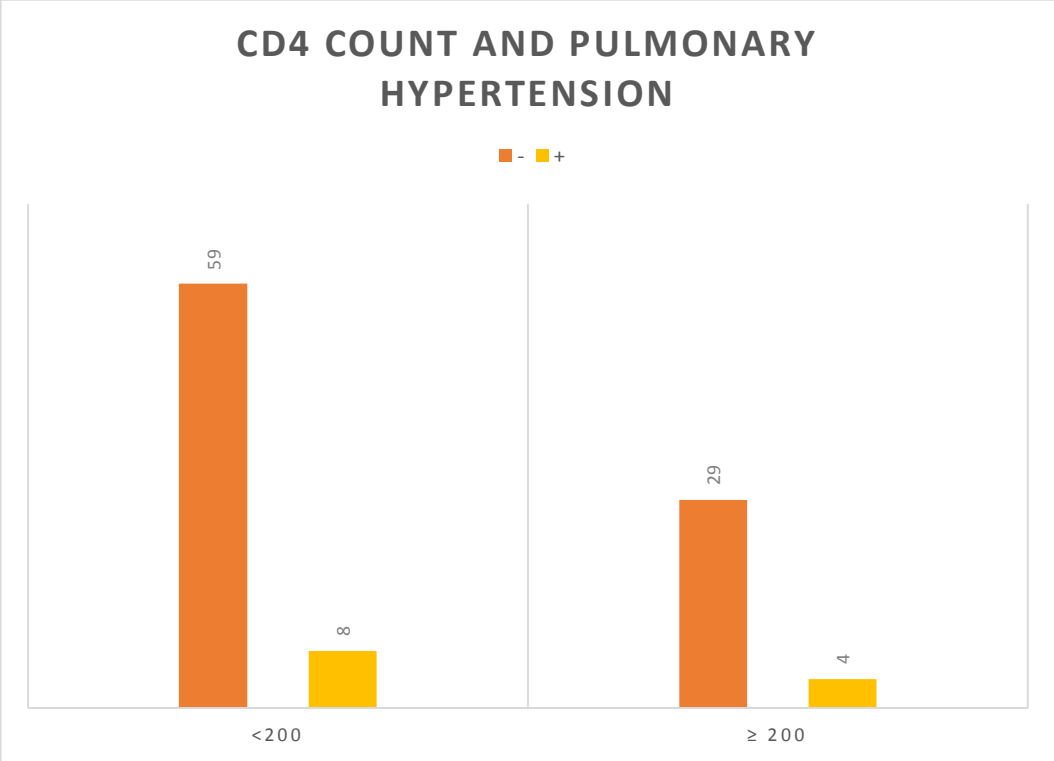
Among the 12 patients with Pulmonary Hypertension, 4 had a CD4 count of more than 200 and 3 had a CD4 count of less than 50.

*(p value=0.7404 which is statistically insignificant).

Table 19. Association of Pulmonary Hypertension with CD4 count

Pulmonary Hypertension	CD4 count		
	<200	>200	Total
Present	8	4	12
Absent	59	29	88
Total	67	33	100

p=0.9791



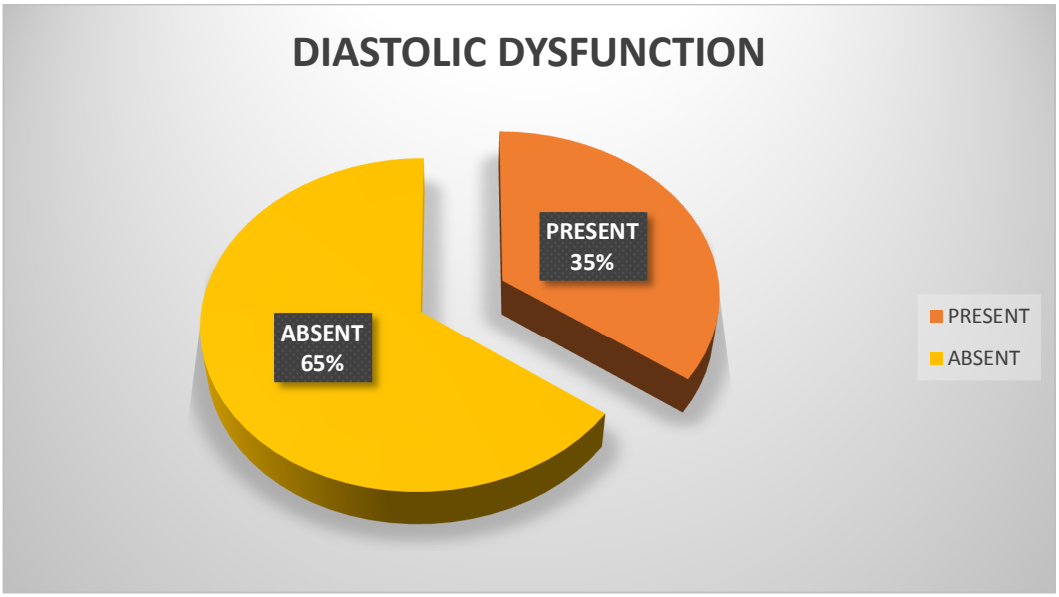
Among the 12 patients with pulmonary hypertension, 8 patients had a CD4 count less than 200.

*(p value=0.9791 which is statistically insignificant)

Table 20. Presence of Left Ventricular Diastolic Dysfunction in HIV patients

Diastolic Dysfunction	HIV patients(n=100)	
	Number	Percentage
Present	35	35
Absent	65	65
TOTAL	100	100

p=0.0119



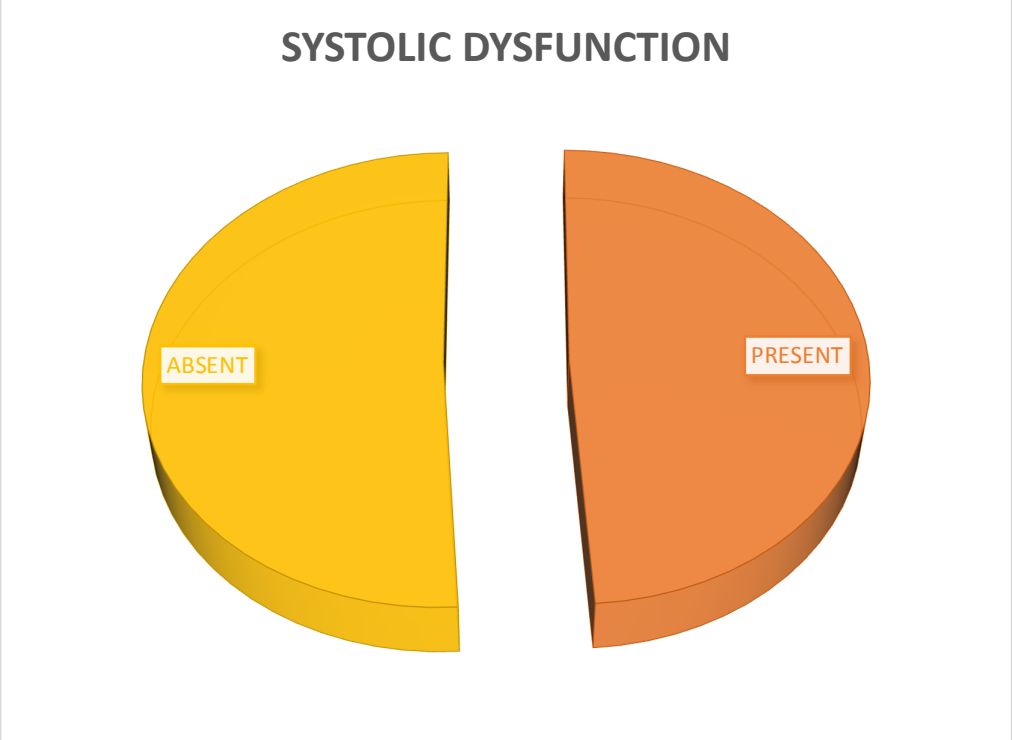
We observed that, among the 100 patients (100%) of HIV infection diastolic dysfunction was present in 35 patients (35%).

*(p value=0.0119 being statistically significant).

Table 21. Systolic Dysfunction among HIV patients

Systolic Dysfunction	HIV patients (n=100)	
	Number	Percentage
Present	49	49
Absent	51	51
Total	100	100

p<0.0001



Among the 100 patients with HIV infection, 49 patients have systolic LV dysfunction.

*(p value<0.0001 which is statistically significant).

DISCUSSION

HIV compromises the immunity of a person to such a level that the person becomes highly vulnerable to a variety of diseases both infectious and non-infectious. Cardiac complications of HIV infection tend to occur late in the disease or are associated with therapies. Hence, cardiac involvement in HIV infected patients is becoming more prevalent as therapy and longevity improve. Cardiovascular disease has become an increasingly important cause of morbidity and mortality among HIV infected patients.[111]

The most frequent cardiovascular disorders in HIV infected patients are pericarditis, pulmonary vascular disease and pulmonary hypertension, valvular heart disease, myocarditis, cardiomyopathy and an increased incidence of coronary artery disease. There is also an increased incidence of abnormalities found in the ECG described as QTc prolongation, ectopic beats, sinus tachycardia and ventricular tachycardia.[111]

One hundred consecutive outpatient and inpatient HIV infected patients in the department of medicine were included in the current study. The average age in our study was 45.04 years and a similar study by Guha et al also had an average age of 33.24 years. The male to female ratio was 3.16:1, a similar study by Shrinivas et al (2006) had a male to female ratio of 4:1. 76% of the patients were males and 24% patients were females. Also, a study carried out by Chengat et al on 284 patients, 63.1% were males and 36.9% were females. It was in concordance with NACO annual report which showed most PLHA in India were young adults.[112]

Clinical features such as fever (39%), cough (35%), breathlessness (19%), oedema (28%) and chest pain (51%) were observed in our study, which was similar to a study conducted by Basavraj et al (2001) in which the commonest symptoms were

fever (82.5%), cough (67.5%) and breathlessness (45%). In a study by Andrew et al fever was present in 81% of the patients whereas cough and weight loss were observed in 55% and 51% of the patients respectively.[112]

CD4 count was <50 cells/mm^3 in 16% of the patients and >200 cells/mm^3 in 33% of the patients which was similar to the study conducted by Shrinivas et al in which, 32% patients had a CD4 count >200 cells/mm^3 and 12% had a CD4 count <50 cells/mm^3.

Majority of the patients were diagnosed as having a seropositive status for a time period of 1 to 10 years i.e. 73%. Only 5% of the patients were diagnosed as seropositive status for a period of more than 10years.

In our study 79% of the patients were on antiretroviral therapy at the time of inclusion and 21% were not on any treatment.

In the present study, out of 100 cases studied, 54% had a normal ECG. The commonest abnormality was sinus tachycardia which is found in 29% of the patients, left ventricular hypertrophy in 7% of the patients, AWMI in 6% of the patients, IWMI in 3% of the patients and AF in 1%. A study undertaken by Hamide et al (2002) has noticed sinus tachycardia in 40% cases, low voltage complexes in 10% cases and left ventricular hypertrophy in 4% cases. The sinus tachycardia may be an early evidence of cardiac failure or left ventricular diastolic dysfunction.[112]

Echocardiographic abnormalities (LVEF<60%, LV Dysfunction, Pericardial effusion, Pulmonary arterial hypertension) were seen in 62% of the cases in the present study while it was seen in 42.3% of the cases in studies done by other workers in India. In a study conducted by Mirri et al, the prevalence of echocardiographic abnormalities was 17%. The commonest echocardiographic abnormality was Left ventricular dysfunction which is seen in 48% of the patients. In our study, Diastolic

dysfunction was observed to be more common with a prevalence of 35%. This was consistent with the findings of a study by Reinsch N et al where the prevalence of Diastolic dysfunction in HIV infected patients was 48%. Basavraj et al and Hamide et al noticed left ventricular diastolic dysfunction in 10% and 7% of the cases respectively. A very high prevalence of 64% was noted by Schuster et al in 2008. The left ventricular diastolic dysfunction is one of the earliest evidence of myocardial involvement and in early stages, it may be asymptomatic.

Reduction in EF was seen in 24% of the patients in the present study. According to a study done by Twagirumukiza et al, 17% of the cases had a low EF. Reduction in ejection fraction without global hypokinesia or chamber enlargement but without any symptom probably represented a mild form of cardiac disease, that would eventually progress to dilated cardiomyopathy. Dilated cardiomyopathy was seen in 9% of the patients. In studies by Moreno et al and Hakim et al, dilated cardiomyopathy was detected in 6% and 5% of the cases respectively.[112]

In our study, 17% of the patients were found to have valvular regurgitations. The incidence of valvular regurgitation was much higher than that found in the general population.

Pericardial effusion was seen in 6% of the cases studied which was lesser than the Indian studies done by Aggarwal et al (11.5%) and studies performed in the United States of America by Himelman et al. The pericardial effusion detected was often small in amount and didn't have any haemodynamic significance. Pericardial effusion in HIV patients may be a marker of end stage HIV infection because it is associated with a low CD4 count.[112]

In our study, even though it was observed that there was no statistical significance found between cardiac abnormalities and other factors like CD4 count

and the duration of the disease we noticed that the cardiac abnormalities were more prevalent among the patients who were infected with HIV for a duration of more than 1 year, and among those who had a CD4 count of less than 200 cells/mm3 although. It was also observed that a higher percentage of patients with a CD4 count of less than 200 cells/mm^3 had Left Ventricular Dysfunction (systolic as well as diastolic).

In the present study, Systolic and diastolic dysfunction were found to be statistically significant, wherein systolic dysfunction was found to be highly significant.

In summary, among the several causes proposed for left ventricular dysfunction in HIV infected patients, our study was consistent with an effect of HIV infection itself. However, since this was an echocardiographic study we could not investigate the mechanism by which HIV may be associated with cardiac abnormalities. Currently, there are three main hypothesis:[113]

I. It could involve a direct cytolytic effect due to HIV infection of the myocytes or coinfection with cytomegalovirus or other cardiotropic viruses.

II. Myocytes could be damaged by proteolytic enzymes and cytokines through "innocent bystander destruction" which are released by HIV replicating HIV in the myocardial interstitial dendritic cells, lymphocytes and macrophages.

III. Postviral cardiac autoimmunity may play an important role. According to Herskowitz et al, increased MHC class I antigen expression by cardiac myocytes and an associated CD8 cytotoxic lymphocyte response as well as high circulating levels of antimyosin and antimitochondrial autoantibodies in HIV infected patients with heart muscle disease.

CONCLUSION

HIV infection in India is mostly a consequence of heterosexual contact than other modes of transmission identified in the western population. The results of this study conclude that LV dysfunction in HIV infected patients are common and can occur even without any clinical manifestation.

In the present study of 100 patients with HIV infection, we observed various cardiac abnormalities and compared them to various factors.

In our study, cardiac abnormality was detected by 2D echocardiography in 62% of the patients. Left Ventricular Dysfunction was found to be statistically significant among HIV patients, Systolic dysfunction being more significant than Diastolic dysfunction.

In our study, even though it was observed that there was no statistical significance found between cardiac abnormalities and other factors like CD4 count and the duration of the disease we noticed that the cardiac abnormalities were more prevalent among the patients who were infected with HIV for a duration of more than 1 year, and among those who had a CD4 count of less than 200 cells/mm3 although.

It was also observed that a higher percentage of patients with a CD4 count of less than 200 cells/mm^3 had Left Ventricular Dysfunction (systolic as well as diastolic).

Thus our aim should be to start ART in these patients as soon as possible so as to improve the morbidity and the quality of life of these patients.

SUMMARY

The present study of 100 patients with HIV infection studied in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied between January 2016 and December 2016, to find out Left Ventricular Dysfunction among these patients.

In our study, even though it was observed that there was no statistical significance found between cardiac abnormalities and other factors like CD4 count and the duration of the disease we noticed that the cardiac abnormalities were more prevalent among the patients who were infected with HIV for a duration of more than 1 year, and among those who had a CD4 count of less than 200 cells/mm3 although.

It was also observed that a higher percentage of patients with a CD4 count of less than 200 cells/mm^3 had Left Ventricular Dysfunction (systolic as well as diastolic).

The result observed was that LV dysfunction was statistically significant in HIV patients, Systolic dysfunction being more statistically significant than diastolic dysfunction.

LIMITATIONS

The present study was a cross-sectional study hence has several limitations commonly associated with this study design. Especially since our primary outcomes likely reflect a life-time of exposure to various risk factors, and since many of these factors are difficult to quantify retrospectively, a longitudinal study in which all such factors are measured is currently needed.

HIV infection wasn't confirmed by western blot except for in a few patients in whom it couldn't be confirmed with ELISA.

HIV viral load of the patients were not available and could not be done due to the cost factor.

The sample size was small hence was difficult to assess the correlation between cardiac abnormalities and other factors like CD4 count, duration of the disease, and its correlation with ART treatment.

Diagnosis of diastolic dysfunction was based on E/A ratio and colour doppler was not used.

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ANNEXURE I

CONSENT FOR PARTICIPATION IN RESEARCH

Mr. /Mrs._____ we are requesting you to enroll yourself in study titled "A Study of Left Ventricular Dysfunction by Echocardiography in HIV Infected Patients – A One Year Cross Sectional Study In A Tertiary Care Hospital" -A Study conducted by_____, postgraduate student in MD GENERAL MEDICINE under the guidance of _____. at J.N.Medical College, Belagavi.

You have been requested to participate in research because your profile matches with the study group. All the patients admitted with Metabolic Syndrome can become participants of study. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge.

Your participation in the research is absolutely voluntary. Your decision to participate in the study or otherwise will not affect your relationship with J.N.M.C. If you decide not participate you are free to withdraw at any time.

The purpose of research is to study the Waist Height Ratio in the assessment to Metabolic Syndrome and compare it with the routinely used anthropometric parameter BMI.

Procedure involved

A detailed history taking, clinical examination, measurement of anthropometric parameters and blood investigations.

Risks and benefits

There are no risks involved and benefits are many. The study helps to screen high risk individuals from the general population who are more likely to get Metabolic Syndrome using a more sensitive parameter, Waist Height Ratio instead of the conventionally used anthropometric parameter Body Mass Index. The results deduced at the end of study will help all similar patients admitted in the hospital to assess their prognosis.

Alternatives

Even if you decline to participate, there will not be any change in the line of your management or the relationship with your doctor. You will be told about all the new information that may affect your decision to participate in the study.

Withdrawing/removal from study

You can withdraw any time from the study as you wish. You will not be penalized for such a decision.

Privacy and confidentiality

The only people to know that you are a research subject are the members of research team. No information about you or provided by you during the research will be disclosed to others without your written permission except:

In emergency to protect your rights and welfare.

If required by law.

Financial incentives for participation

You will not be paid any monetary benefits or free gifts for participation in the research. You will not be reimbursed for expenses.

Authorization to publish results

When the results of the research are published or discussed in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

CONSENT STATEMENT

I, the undersigned, have been explained in my own vernacular language about the study and my participation in the study is voluntary. If I want I can withdraw at any time. Also I have been given enough time to clear my doubts about the study and my rights as a study participant.

In case you have any questions related to the study you can contact Dr. _____.

In case you have any questions about your rights as a study participant you can contact Dr._____

Signature or the left thumb impression of the participant or legally authorized representative.

Participant's name: _____Signature: _____

Witness name: _____ Signature: _____

Experimenter's name: _____ Signature: _____

Guardian's name: _____ Signature: _____

Place: _____

Date: _____

ANNEXURE II – PROFORMA

Case No:

NAME:

AGE/SEX:

IP No.

ADDRESS:

OCCUPATION:

HISTORY OF HIV INFECTION YES/NO

IF YES WHEN DIAGNOSED

IF NO WAS IT DIAGNOSED ON ADMISSION YES/NO

CD4, CD8 COUNT

IF ON ANTIRETROVIRAL THERAPY YES/NO

IF YES THEN THE DRUGS

WHEN WAS ANTIRETROVIRAL THERAPY STARTED

IF ANY OPPORTUNISTIC INFECTION IS PRESENT YES/NO

IF YES WHAT KIND OF INFECTION

WHEN WAS IT DIAGNOSED

TREATMENT OFFERED

HISTORY SUGGESTIVE OF CARDIOVASCULAR INVOLVEMENT:

CHEST PAIN

BREATHLESSNESS

OEDEMA

FEVER

COUGH

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS:

Temperature:

Pulse:

Blood pressure:

Respiratory Rate:

SYSTEMIC EXAMINATION:

Cardiovascular System:

Respiratory System:

Per Abdomen:

Central Nervous System:

INVESTIGATIONS:

Hemoglobin

Total leucocyte count

Differential leukocyte count

- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Platelet count

RBC count

CD4/CD8 Count

ECG:

2D ECHO:

EJECTION FRACTION

DYSFUNCTION: SYSTOLIC

DIASTOLIC

PULMONARY HYPERTENSION

VALVULAR LESIONS

CALCIFICATION

CLOT

VEGETATION

DILATED CARDIOMYOPATHY

HYPOKINESIA/AKINESIA

ANNEXURE III – KEY TO MASTER CHART

+	-	Present
-	-	Absent
M	–	Male
F	–	Female
m	-	Months
y	-	Years
D	-	Days
Y	-	Yes
N	-	No
g/dl	–	gram per deciliter
CD4	–	Cluster of differentiation 4
ECG	–	Electrocardiography
LVH	–	Left Ventricular Hypertrophy
NSR	–	Normal Sinus Rhythm
ST	–	Sinus Tachycardia
IWMI	–	Inferior Wall Myocardial Infarction
AWMI	–	Anterior Wall Myocardial Infarction
AF	–	Atrial Fibrillation
MR	–	Mitral Regurgitation
AR	–	Aortic Regurgitation
AML Prolapse	–	Anterior Mitral Leaflet Prolapse
TR	–	Tricuspid Regurgitation
MS	–	Mitral Stenosis

MASTER CHART

Serial number	In/Out patient number	Age	Sex	Duration of disease	Treatment	Duration of treatment	Opportunistic infection	Chest pain	breathlessness	Oedema	Fever	Cough	CD4 count	Haemoglobin(g/dl)	ECG	ECHOCARDIOGRAPHY						
																EJECTION FRACTION	DYSFUNCTION		PULMONARY HYPERTENSION	VALVULAR LESION	DILATED CARDIOMYOPATHY	HYPOKINESIA / AKINESIA	PERICARDIAL EFFUSION
																	SYSTOLIC	DIASTOLIC					
1	766785	30	M	1y	+	1y	N	-	+	+	-	+	140	9.9	NSR	60%	-	+	-	-	-	-	-
2	765936	40	M	10y	+	10y	Y	-	-	+	+	-	150	10.5	ST	35%	-	-	+	-	+	-	-
3	757587	48	M	6y	+	6y	N	-	+	+	-	+	550	8.2	LVH	50%	-	-	-	MR	-	-	+
4	793915	38	F	7y	+	7y	N	-	+	+	-	+	247	12.1	LVH	55%	-	-	-	-	-	-	-
5	754491	45	M	5y	-	-	Y	-	+	-	+	+	420	13.1	ST	60%	-	-	-	-	-	-	-
6	753343	71	F	12y	+	12y	N	-	-	-	-	-	530	12.6	NSR	35%	+	+	-	AR	+	-	-
7	754227	46	M	5D	-	-	Y	-	+	-	+	+	100	10.5	ST	60%	-	+	-	-	-	-	-
8	735283	55	M	10y	+	10y	N	-	-	-	-	-	161	12.7	NSR	55%	-	-	-	-	-	-	-
9	731922	63	M	5m	-	-	N	-	-	-	-	-	630	8.6	NSR	40%	-	-	-	-	-	+	-
10	724536	40	M	1y	+	6m	N	-	+	--	-	+	50	9.8	ST	60%	-	-	-	-	-	-	-
11	721893	75	M	8y	+	8y	N	+	+	-	-	-	360	10.6	AWMI	40%	-	-	-	-	-	+	-
12	718900	74	M	6y	+	6y	Y	-	+	-	+	+	161	10.6	ST	25%	+	-	+	TR	+	+	-
13	714758	32	M	4y	+	4y	Y	-	-	-	+	-	300	14.2	ST	60%	-	-	-	-	-	-	-
14	813514	70	M	6y	+	6y	Y	-	+	-	+	+	120	10.2	ST	48%	-	-	+	-	-	-	-
15	803800	44	M	3y	-	-	Y	+	+	-	+	+	39	10.1	LVH	40%	-	-	+	MR	-	-	-
16	802326	59	M	15y	+	10y	N	-	+	+	+	+	320	9.5	NSR	55%	-	+	-	-	-	-	-
17	800553	42	M	8y	+	8y	N	-	-	-	-	-	160	11.6	NSR	60%	-	-	-	-	-	-	-
18	795031	40	M	2y	+	2y	N	+	+	-	-	-	138	11.4	AWMI	55%	-	-	-	-	-	+	-
19	784412	71	F	10D	-	-	Y	-	+	+	+	-	40	13.3	NSR	40%	+	+	-	MR, TR	-	+	-
20	785326	55	M	3y	+	3y	N	-	+	+	+	+	326	8.4	ST	58%	-	+	-	-	-	-	-
21	778796	48	M	1y	-	-	N	-	+	+	+	+	83	10.3	NSR	60%	-	-	-	-	-	-	-
22	721161	62	F	2y	+	2y	N	+	+	-	-	-	200	12.2	AWMI	45%	-	+	-	-	-	+	-
23	774443	37	M	6m	+	6m	Y	-	-	-	-	-	383	8.3	AF	35%	+	+	-	AR, MR	-	+	-
24	764616	38	M	2y	+	2y	N	-	+	-	-	-	146	13.7	NSR	60%	+	+	+	AML PROLAPSE, MR,TR	+	-	-
25	752390	45	M	4y	+	4y	N	+	+	-	-	+	126	14.5	NSR	55%	-	-	-	MR	-	+	-
26	9227	55	M	1y	+	1y	Y	-	-	-	-	-	48	8.5	NSR	60%	-	+	-	-	-	-	-
27	9350	51	M	3y	+	3y	Y	-	+	+	-	-	36	7	NSR	60%	-	+	-	-	-	-	-
28	758304	45	F	1y	+	1y	N	+	+	-	-	+	88	12.1	NSR	60%	-	-	-	MS, AR, TR	--	-	-
29	763192	32	F	6m	+	6m	N	-	-	-	-	-	294	9.4	LVH	60%	-	-	+	MR, TR	-	-	-
30	766030	26	F	3y	+	3y	Y	-	-	-	+	-	133	12.4	NSR	60%	-	-	-	-	-	-	-
31	764701	49	M	5y	+	5y	Y	-	-	+	+	-	56	9.7	ST	60%	+	+	-	-	-	-	+
32	767862	35	F	2y	+	2y	Y	-	-	-	-	-	27	8.2	ST	60%	-	+	-	-	-	-	-
33	782390	38	M	3m	+	3m	N	-	+	+	-	-	249	4	NSR	60%	-	-	-	-	-	-	-
34	787450	44	M	4y	+	4y	Y	-	-	-	+	-	114	10.3	ST	60%	-	-	-	-	-	-	-
35	715878	56	F	6m	+	6m	N	-	-	-	-	-	86	12.7	NSR	60%	-	-	-	-	-	-	-
36	777533	40	M	3y	+	3y	Y	-	+	+	+	+	300	6.9	ST	60%	-	+	-	-	-	-	-
37	717232	71	F	5y	+	5y	N	-	+	-	+	+	156	12.6	LVH	30%	-	+	-	MR	-	-	-
38	719765	37	M	2y	+	2y	Y	-	-	-	+	-	45	13.2	NSR	60%	-	-	-	-	-	-	-
39	777434	40	M	3y	+	3y	Y	+	-	+	+	+	134	9.8	NSR	60%	-	-	-	-	-	-	-
40	778796	55	M	6y	+	6y	N	-	-	-	-	-	14	10.3	ST	55%	-	+	-	-	-	-	-
41	721842	38	F	2y	+	2y	Y	+	-	+	+	+	38	7.7	ST	60%	-	-	-	-	-	-	-
42	728058	48	M	8y	+	8y	N	-	+	+	-	-	139	6.6	NSR	60%	-	+	-	-	-	-	-
43	730296	38	M	4y	+	4y	Y	-	-	+	+	+	300	11	ST	60%	-	-	-	-	-	-	-
44	745587	37	F	2y	+	2y	N	-	-	-	-	-	141	10.6	ST	60%	-	+	-	-	-	-	-
45	747690	45	M	5y	+	5y	Y	-	+	-	+	+	90	11.5	ST	60%	-	+	-	-	-	-	+
46	748243	38	M	3.5y	+	3y	N	-	-	-	-	-	32	17.7	NSR	55%	-	-	-	-	-	-	-
47	749419	35	F	1m	+	1m	N	-	-	-	-	-	645	11.5	NSR	35%	+	-	+	MR, TR	-	-	+
48	753061	80	M	4y	+	4y	N	+	+	-	-	-	81	13.4	IWMI	30%	+	+	-	-	-	+	-
49	753315	26	M	5m	+	5m	Y	-	+	-	+	+	144	12	NSR	60%	-	-	-	-	-	-	-
50	761315	40	F	3y	+	3y	N	-	-	-	-	-	512	14.6	NSR	60%	-	-	-	-	-	-	-
51	763845	39	M	2.5y	-	-	Y	-	+	-	+	+	34	10.9	ST	50%	-	+	-	-	-	-	-
52	715873	56	F	6m	+	6m	N	+	+	-	-	-	40	7.4	IWMI	45%	+	+	-	-	-	+	-

MASTER CHART

Serial number	In/Out patient number	Age	Sex	Duration of disease	Treatment	Duration of treatment	Opportunistic infection	Chest pain	breathlessness	Oedema	Fever	Cough	CD4 count	Haemoglobin(g/dl)	ECG	ECHOCARDIOGRAPHY						
																EJECTION FRACTION	DYSFUNCTION		PULMONARY HYPERTENSION	VALVULAR LESION	DILATED CARDIOMYOPATHY	HYPOKINESIA / AKINESIA	PERICARDIAL EFFUSION
																	SYSTOLIC	DIASTOLIC					
53	719765	37	M	2m	-	-	N	-	+	+	-	+	209	13.2	NSR	55%	-	-	+	MR	-	-	-
54	720999	58	M	7y	+	7y	N	-	+	-	-	+	43	9.1	NSR	35%	+	-	+	MR, TR	+	-	-
55	721842	38	F	6m	-	-	N	-	-	-	-	-	50	7.7	NSR	60%	-	-	-	-	-	-	-
56	728058	48	M	3y	-	-	N	-	+	+	-	+	125	6.6	NSR	40%	-	+	-	-	+	+	-
57	730296	38	M	2y	+	2y	N	-	+	-	-	-	206	11	NSR	55%	-	+	-	-	-	-	-
58	732491	36	M	4D	-	-	Y	-	+	+	+	+	60	6.7	NSR	58%	-	-	-	-	-	-	-
59	735838	34	M	1y	+	1y	N	-	+	+	-	-	37	10.8	NSR	30%	+	-	+	-	+	+	-
60	743636	55	M	8y	+	8y	N	-	-	-	-	-	115	15.2	ST	60%	-	-	-	-	-	-	-
61	764616	46	F	3y	-	-	N	-	+	-	-	-	89	13.7	NSR	60%	-	+	-	-	-	-	-
62	785326	55	M	1D	-	-	N	-	-	-	-	-	103	8.4	NSR	55%	-	-	+	MR	-	-	-
63	784412	71	M	10y	+	10y	N	-	+	+	-	-	57	13.3	ST	45%	-	+	+	-	+	-	-
64	795031	40	M	3.5y	+	3.5y	N	_	_	_	_	_	60	11.4	NSR	60%	-	+	-	-	-	-	-
65	800553	42	M	2y	-	-	Y	+	+	-	+	+	204	11.6	ST	55%	-	-	-	-	-	-	-
66	802326	59	M	6m	-	-	Y	-	-	-	+	-	167	9.7	NSR	60%	-	-	-	-	-	-	-
67	803800	44	M	1.5y	+	1.5y	N	-	-	-	-	-	200	10.1	NSR	60%	-	-	-	-	-	-	-
68	764701	49	M	7y	+	7y	N	-	+	-	-	-	356	9.7	ST	50%	-	+	-	-	-	-	-
69	766491	48	M	3D	+	1D	N	-	-	-	-	-	100	10.8	ST	60%	-	-	-	-	-	-	-
70	767200	38	M	5y	+	5y	N	-	-	-	-	-	150	9.3	NSR	60%	-	-	-	-	-	-	-
71	767862	35	F	2y	+	2y	Y	-	-	-	+	+	112	8.2	NSR	60%	-	-	-	-	-	-	-
72	769268	40	M	12D	-	-	Y	+	+	-	+	+	33	15	NSR	55%	-	-	-	-	-	-	-
73	770586	43	M	4y	+	4y	N	-	-	-	-	-	89	10.7	ST	60%	-	-	-	-	-	-	-
74	772290	48	M	1y	+	1y	N	-	-	-	-	-	456	10.6	ST	60%	-	-	-	-	-	-	-
75	777079	45	M	6y	+	2y	N	-	-	-	-	-	302	9.6	NSR	60%	-	-	-	-	-	-	-
76	779478	56	F	2y	-	-	Y	+	+	+	+	+	156	3.9	NSR	60%	+	-	-	-	-	-	+
77	782390	38	M	3y	+	3y	N	-	+	+	+	-	103	4	LVH	60%	-	-	-	-	-	-	-
78	786302	43	M	5y	+	5y	Y	-	-	-	+	-	230	7.4	NSR	60%	-	-	-	-	-	-	-
79	788165	44	M	3y	+	3y	N	-	-	-	-	-	48	11.6	NSR	60%	-	-	-	-	-	-	-
80	789217	42	M	8y	+	8y	N	+	-	-	-	-	180	12.3	ST	50%	-	+	-	MR	-	-	-
81	785326	55	M	1m	-	-	Y	-	-	-	+	-	102	8.4	NSR	60%	-	+	-	-	-	-	-
82	789148	45	M	15D	-	-	Y	-	-	-	+	-	76	13.4	NSR	60%	-	-	-	-	-	-	-
83	789215	41	M	2y	+	2y	N	-	-	-	-	-	90	14.4	NSR	60%	-	-	-	-	-	-	-
84	786743	48	F	5D	-	-	N	-	-	-	-	-	391	14.3	NSR	60%	-	-	-	-	-	-	-
85	791723	60	M	5y	+	4y	N	-	-	-	-	-	500	12.9	AWMI	60%	-	-	-	-	-	-	-
86	795031	40	M	17y	+	10y	y	-	-	-	+	-	300	11.4	NSR	60%	-	-	-	-	-	-	-
87	796736	43	M	10y	+	10y	N	-	+	+	-	+	227	15.6	ST	50%	-	-	+	MR	-	-	-
88	797747	47	M	13y	+	13y	N	-	+	+	-	+	130	11.4	LVH	40%	-	+	-	-	+	-	-
89	798726	18	M	8y	+	8y	N	-	-	-	-	-	294	11.7	NSR	60%	-	-	-	-	-	-	-
90	777533	45	M	6y	+	2y	N	+	+	+	-	-	105	6.9	AWMI	45%	-	+	-	-	-	+	-
91	769268	40	M	5y	+	5y	Y	+	+	-	+	+	45	15	NSR	48%	-	-	-	-	-	-	+
92	797979	60	M	3y	+	3y	Y	-	-	-	+	-	57	10.4	ST	60%	-	-	-	-	-	-	-
93	799606	64	M	1y	+	1y	N	-	+	-	-	-	226	8.5	NSR	60%	-	-	-	-	-	-	-
94	799373	26	F	6m	+	6m	Y	-	-	-	+	-	93	10.4	ST	55%	-	-	-	-	-	-	-
95	798595	29	M	1.5m	-	-	Y	+	+	+	+	+	900	6.8	NSR	60%	-	-	-	-	-	-	-
96	800553	42	M	16y	+	12y	N	+	+	-	-	-	100	11.6	IWMI	35%	+	+	-	MR	-	+	-
97	800775	27	M	3y	+	3y	N	-	-	-	-	-	185	16.4	NSR	60%	-	-	-	-	-	-	-
98	809002	38	M	3y	+	3y	Y	-	+	+	+	+	192	5.7	NSR	58%	-	-	-	-	-	-	-
99	804275	38	M	10y	+	8y	N	+	+	-	-	-	209	11.4	AWMI	50%	-	+	-	-	-	+	-
100	807267	61	M	6y	+	6y	N	-	-	-	-	-	54	16.1	NSR	55%	-	+	-	-	-	-	-