“CORRELATION OF CARDIAC AUTONOMIC DYSFUNCTION WITH CD4 COUNT IN HIV PATIENTS”

By

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Dissertation submitted to BLDE University, Bijapur

In partial fulfillment of the requirements for the degree of

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IN

GENERAL MEDICINE

UNDER THE GUIDANCE

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BIJAPUR.

2014

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DR. DEEPAK KADELI

LIST OF ABBREVIATIONS USED

AIDS	-	Acquired Immune Deficiency Syndrome
HIV	-	Human Immunodeficiency Virus
CNS	-	Central Nervous System
PNS	-	Peripheral Nervous System
ANS	-	Autonomic Nervous System
cART	-	combined AntiRetroviral Therapy
RNA	-	Ribonucleic Acid
DNA	-	Deoxy Ribonucleic Acid
RT	-	Reverse Transcriptase
ELISA	-	Enzyme Linked Immunosorbent Assay
CDC	-	Center for Disease Control
PCR	-	Polymerase Chain Reaction
GI	-	Gastro Intestinal tract
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
ECG	-	Electro Cardiogram
HRV	-	Heart Rate Variability
HR	-	Heart Rate
GP	-	Glyco Protein
NACO	-	National Aids Control Association
WHO	-	World Health Organisation
ICTC	-	Integrated Counseling and Testing Center
ANC	-	Antenatal Care

SIV	-	Simian Immune deficiency Virus
CD	-	Cluster of Differentiation
HTLV	-	Human T cell Lymphotrophic Virus
TB	-	Tuberculosis
IL	-	Interleukin
Hep	-	Hepatitis
GBS	-	Guillane Barre Syndrome
TNF	-	Tumor Necrosis Factor
CMV	-	CytoMegalovirus

ABSTRACT

Background and Objectives

Cardiac Autonomic dysfunction has an important implication in health care of human immunodeficiency virus (HIV) seropositive patients. Evaluation of cardiac autonomic dysfunction on HIV positive/AIDS patients and to correlate the degree of dysfunction with CD4 count.

Materials and methods

Fifty one HIV seropositive patients with 20 HIV seropositive patients without AIDS and 31 with AIDS and 51 controls were studied for cardiac autonomic dysfunction at Shri B.M. Patil Medical College Hospital and Research Centre Bijapur Karnataka, India. Cardiac autonomic function was assessed by batteries of autonomic function tests which included systolic blood pressure response to standing, diastolic blood pressure response to persistent handgrip, heart rate variability to standing, Valsalva maneuver and to deep breathing. CD4 count was correlated with number of abnormal test results.

Results

Among the patients with HIV, abnormal cardiac autonomic functions were seen in 5.6% of patients without AIDS and 37.5% of patients with AIDS. There were significant differences between HIV seropositive patients and controls for systolic blood pressure response to standing (<0.001), diastolic blood pressure response to persistent handgrip (<.0.001), heart rate variability to standing (<0.001),Valsalva maneuver (<0.001) and to deep breathing heart rate variability to deep breathing, (p=0.001).

Abnormalities in cardiac autonomic function occurred at all levels of CD4 counts. Our study showed an increase in incidence of cardiac autonomic dysfunction as the CD4 count decreased.

Conclusion

Autonomic dysfunction in HIV infection could have far reaching consequences in the Indian setting. because HIV affects various organ systems, invasive procedures are often needed for diagnostic and therapeutic purposes.When HIV patients present with symptoms like dizziness and headache which can be present in many conditions, cardiac autonomic dysfunction should be first ruled out by performing simple autonomic dysfunction tests and resource consuming expensive and invasive tests must be performed later only if needed.

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is one of the greatest challenge faced by the medical fraternity in the 21st century, it is caused by a retrovirus known as human immunodeficiency virus (HIV) .The virus affects the immune system making the victim vulnerable to a host of opportunistic infections. AIDS was first reported in the United States of America in 1981 among homosexual men. Since then it has spread rapidly affecting almost every country on the planet.

HIV is known to affect almost all organ systems in the body. In addition to involving central nervous system it also affects the autonomic nervous system (ANS). Autonomic Nervous dysfunction has been known to severely affect the quality of life in HIV positive patients. It is known to have caused fatal consequences in late stage of the disease who go in for invasive diagnostic or therapeutic procedures.

Screening for cardiac autonomic dysfunction can help identify HIV patients at risk of syncope or cardiovascular collapse and as such extra precautions may be taken in these individuals before any invasive procedures are done.It may also help avoid unnecessary expensive investigations for symptoms such as syncope which maybe expected once the ANS is involved.

It may identify HIV infected patients with particular risk beyond their immunological deterioration and there by contribute to risk stratification. ANS involvement in HIV disease is one of the less researched topics especially when it comes to Indian patients. Hence this study is being taken up to help address this issue.

AIMS and OBJECTIVES

1. Evaluation of cardiac autonomic dysfunction on HIV/AIDS patients

2. To correlate the degree of dysfunction with CD4 count.

REVIEW OF LITERATURE

3.1 EPIDEMIOLOGY

World Scenario

According to WHO there are 35.3 million people living with HIV at the end of 2012.The highest density being in the sub-Saharan African countries which constitutes around 70%.Since the start of this epidemic around 75 million have become affected with nearly 25 million deaths. New HIV infections have fallen by 33% since 2001.AIDS related deaths have fallen by 30% since its peak in 2005.The UNAIDS in its Global Report 2013 publication on AIDS epidemic has noted a historic decline in AIDS-related deaths and new HIV infections.[1]

Indian Scenario

According to the data released by National Aids Control Association (NACO) Annual Report 2012-2013, the revised estimate of people with HIV as of 2011 is 2.089 million (equivalent to 0.27 percent of the adult population) which is a steady decline from 0.41% in 2001 .The estimates highlight an overall reduction in adult HIV incidence (new infections) as well as AIDS related mortality in India which is similar to the global trend.[2]

Regional Scenario

The four high prevalence states of Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu account for 53% of all HIV infected population in the country. Nonetheless they have been showing declining trend of HIV prevalence.

Integrated Counseling and Testing Center (ICTC) data shows a declining trend in the adult HIV prevalence rate in Karnataka. According to sentinel surveillance in Ante Natal Care (ANC) population the prevalence has dropped from 0.84% in 2007 to 0.22% in 2012.[3] In this region where this study has been conducted, a unique practice

called the Devadasi tradition is followed which has a bearing on HIV. In several parts of Bijapur district, families follow the tradition of dedicating one of their daughters to Goddess Yellamma, or to the local temples, as a means of propitiating the gods for helping them through difficult times. Traditionally, devadasis had specific tasks within the temple such as lighting the lamp, cleaning the temple premises and serving the deity through dance. In addition, they were also expected to provide sexual gratification to the main priest (who was considered a part of the deity) and to live as concubines with men who would protect them financially and physically. Over the years, this system has become commercialised with Devadasi sex workers increasingly operating as female sex workers . Also, since the Devadasi tradition retains a social and religious sanction, an increasing number of non-Devadasi women are dedicating their daughters as a means of earning income for the family. The HIV prevalence according to ICTC data in ANC women is 0.29% in 2012 down from 2.32 % in 2007.[4]

3.2 ORIGIN

The HIV belongs to the family of human retroviruses and the subfamily of lentiviruses. There are 2 subtypes, HIV-1 and HIV-2, the most prevalent is HIV -1 which comprises several subtypes with different geographic distributions. HIV-2 has reduced pathogenicity compared to HIV 1 and is more prevalent in Guinea-Bissau,West Africa and Portugal.

The origin of the virus is of much debate. It is now generally agreed upon that the know strain of HIV -1 is most closely related to the simian immunodeficiency virus (SIV) endemic in chimpanzees and sooty mangabeys populations of west central African nations of Cameroon, Gabon, Republic of Congo and Central African

Republic. HIV 2 is less transmittable and is largely confined to west African nations of Senegal, Guinea- Bissau, Guinea, Sierra Leone, Liberia, Ivory Coast.[5,6]

Viral transmission is believed to occur from chimpanzees to humans through zoonosis during the early 20th century.[7,8] This was suggested by a study published in 2008 which used phylogenetic analysis of viral sequences recovered from a preserved biopsy specimen done in 1960 at Kinshasa, Democratic Republic of Congo. The technique used to determine this is called molecular clock analysis.[9]

Most preferred theory for transfer of virus from the apes to humans is from 'Bush Meat' theory (Chimpanzee or monkey meat is called Bush Meat).According to this theory the SIV was transmitted when a hunter or Bush meat handler was bitten or cut while hunting or handling the animal.[10]This transfer has been occurring since earlier times but the epidemic proportions were reached because of rapid urbanization and colonisation. During the early 20th century there was massive movement of people from their tribes and forests to the city centers such as Kinshasa.This led to prostitution in cities with exponential transmission between sex workers and their clients.[11]

Oral Polio Vaccine

It has been proposed that various forms of HIV-1 and HIV-2 had their origins in polio vaccine preparations from different laboratories.In one particular case the cause of HIV 1 group M pandemic has been suggested to be the polio vaccine developed by a team led by Dr Hilary Koprowski and administered to roughly one million people in Belgian Congo, Rwanda and Burundi in the late 1950s.This research group had access to a primate facility near Kinsangani, Congo where locally caught chimpanzees were used for polio vaccine safety testing and other research projects.

It is suggested that kidneys harvested from these apes was used for polio vaccine production in the United States.There is no direct evidence to support this scenario but circumstantial evidence has been sufficiently persuasive.[10]

Unsterile Injections

In 2001 Sharp et al. and Marx et al. published various papers in which a definite connection has been made between the rapid spread of SIV with the emergence of vaccination programs. There was intensive vaccination program for small pox in French Equatorial Africa where unsafe and unsterile injection techniques were employed. Mass injection campaigns were also conducted for yaws and sexually transmitted diseases with the discovery of penicillin.[12]

It is postulated that serial passage which was hastened by the above mentioned factors caused SIV to mutate down to HIV in its present form.Non Human SIVs contain a Nef gene that down regulates CD3, CD4 and Major histocompatiblity class I expression therefore these virus do not induce immunodeficiency; the HIV1 nef gene however has lost its ability to down regulate CD3 which results in immune activation and apoptosis that is characteristic of chronic HIV infection.[13]

Transfer of the Virus to West

It is usually mentioned that the first cases of HIV were detected in USA in 1981 among homosexuals but it is now clear that HIV existed well before that period. Robert Rayford an African American male died at St Louis Hospital from Kaposi sarcoma in 1969. In 1990 when his preserved samples were analysed, a virus similar to present HIV was detected. It was suspected the patient was a male prostitute though he did not discuss his sexual history with his doctors in detail.[14,15]

A Norwegian sailor's family died of symptoms resembling AIDS in 1976. It was eight years after the patient ArvidNoe returned after his trip to the West African coastline during which he was sexually active with the local population.

Tissue samples taken from two patients in Leopoldville Belgian Congo from the 1960s turned out to be having HIV when they were tested again in 1990.[16]

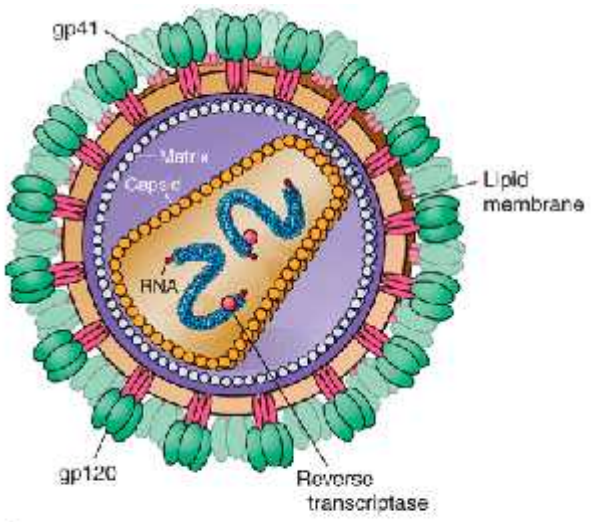
First cases in India

The first case of HIV in India was detected in Chennai among female commercial sex workers in 1986.[17] By the end of 1987, out of 52,907 who had been tested, around 135 people were found to be HIV positive and fourteen had AIDS.[18]

3.3 MORPHOLOGY AND LIFE CYCLE

Electron microscopy shows that the HIV virion is an icosahedral structure containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The virion buds from the surface of the infected cell and incorporates a variety of host proteins, including major histocompatibility complex class I and II antigens, into its lipid bilayer. In addition it contains RNA and reverse transcriptase enzyme.

Figure 1. Schematic representation of the structure of HIV



B

Source: Longo DL, Fauci AS, Kasper D, Hauser SL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 18th Edition: www.accessmedicine.com

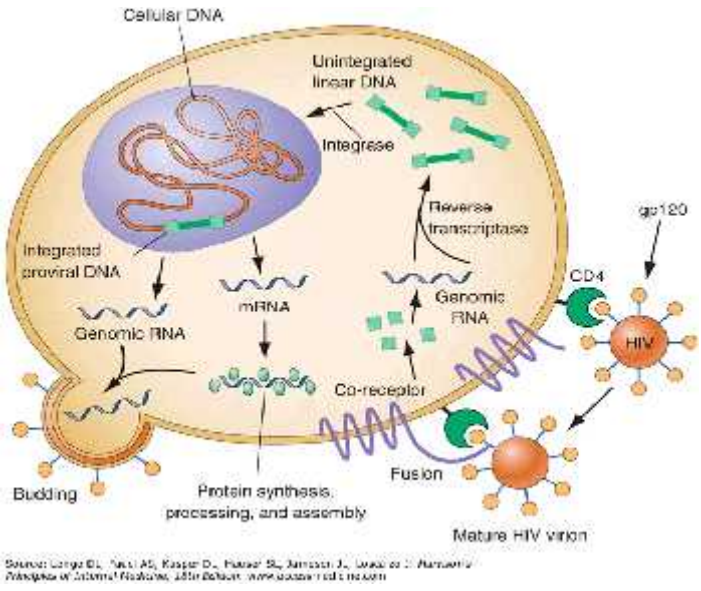
HIV is a RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase (RT). GlycoProtein 120 (gp120) binds with CD4+ molecule predominantly found on a subject of T-lymphocytes which are responsible for helper or inducer function in the immune system. After binding, fusion of membrane occurs with the host cell via gp 41 molecule. HIV genomic RNA is uncoated and internalized into the target cell. The RT catalysis conversion of RNA to double stranded DNA.

The DNA translocates to the nucleus where it is integrated randomly into the host cell chromosomes through virus encoded enzyme integrase. The activation of host cell is required for the initiation of transcription of integrated viral DNA into genomic RNA.

Following transcription, HIV mRNA is formed which is translated into proteins, enzymes and genomic RNA at the plasma membrane of the cells.

Budding of the progeny virion occurs through host cell membranes where the core acquires its external envelope.[19]

Figure 2. The replication of HIV



3.4 PATHOGENESIS

A. Overview of course of HIV Infection

The course of untreated HIV infection spans a decade. Stages include the primary infection, dissemination of virus to lymphoid organs, clinical latency, elevated HIV expression, clinical disease, and death.

Following primary infection, there is a 4 to 11 days period between mucosal infection and initial viremia. Virus is widely disseminated throughout the body during this time, and the lymphoid organs become seeded. An acute mononucleosis like syndrome develops in many patients, 3-6 weeks after primary infection. There is a significant drop in numbers of circulating CD4T cells at this early time. An immune response to HIV occurs one week to three months after infection, plasma viremia drops, and levels of CD4T cells rebound. However, the immune response is unable to clear the infection completely, and HIV infected cells persist in the lymph nodes.

This period of clinical latency may last for as long as 10 years, during this time, there is a high level of ongoing viral replication. It is estimated that 10 billion HIV particles are produced and destroyed each day. The half-life of the virus in plasma is about 30 to 60 minutes, and the virus life cycle averages two days.

Eventually, the patient will develop constitutional symptoms and clinically apparent disease, such as opportunistic infections or neoplasms. Higher levels of virus are readily detectable in the plasma during the advanced stages of infection. HIV found in patients with late-stage disease is usually much more virulent and cytopathic than the strains of virus found early in infection.

B. Lymphoid Organs

Lymphoid organs play a central role in HIV infection. It is in the lymphoid organs that specific immune responses are generated. The network of follicular dendritic cells in the germinal centers of lymph nodes traps antigens and stimulates an immune response. Throughout the course of untreated infection-even during the stage of clinical latency HIV is actively replicating in lymphoid tissues. The microenvironment of the lymph node is ideal for the establishment and spread of HIV infection.The trapped virion serve as source of immune activation causing cytokine release, and activating a large pool of CD4 T cells that are highly susceptible to HIV infection.

C. Neural Cells

Neurologic abnormalities are common in late stages of infection and are an AIDS defining condition. Central nervous system disease occurs in 40-90% of patients. These include HIV encephalopathy and peripheral neuropathies, both direct and indirect pathogenic mechanisms explain the neuropsychiatric manifestations.

The predominant cell types that are infected are monocytes and macrophages. Virus may enter the brain through infected monocytes and release cytokines that are toxic to neurons as well as chemotactic factors that lead to infiltration of the brain with inflammatory cells.

CLINICAL MANIFESTATIONS

The clinical features of HIV infection have been classified into the following categories:

A. Acute HIV Syndrome
B. Asymptomatic stage- Clinical Latency
C. Symptomatic Disease
D. AIDS

A. Acute HIV Syndrome

Around 50–70% of individuals with HIV infection experience an acute clinical syndrome 3–6 weeks after primary infection. The typical clinical findings in the acute HIV syndrome include fever, pharyngitis, lymphadenopathy, headache, arthalgia, anorexia, nausea, vomiting, and diarrhea. It has been reported that these symptoms occur less frequently in those infected by injection drug use compared with those infected by sexual contact. The syndrome is typical of an acute viral syndrome and has been likened to acute infectious mononucleosis. Symptoms usually persist for one to several weeks and gradually subside as an immune response to HIV develops and the levels of plasma viremia decrease. In most patients, primary infection with or without the acute syndrome is followed by a prolonged period of clinical latency or smoldering low disease activity. A small percentage of HIV-infected individuals treated with antiretroviral drugs during acute infection may revert to a negative enzyme linked immunosorbent assay (ELISA) test during the time they remain on therapy. They rapidly re-seroconvert with the discontinuation of treatment.

B. Asymptomatic stage- Clinical Latency

There is a lot of variation between the initial infection and onset of clinical disease, the median time is considered to be around 10 years. HIV disease with active virus replication is ongoing and progressive during this asymptomatic period. The rate of disease progression is directly correlated with HIV RNA levels. Some patients referred to as long-term nonprogressors show little if any decline in CD4 T cell counts over extended periods of time. These patients generally have extremely low levels of HIV RNA; a subset, referred to as elite nonprogressors, exhibits HIV RNA levels <50 copies per milliliter. Certain other patients remain entirely asymptomatic despite the fact that their CD4 T cell counts show a steady progressive decline to extremely low

levels. In these patients, the appearance of an opportunistic disease may be the first manifestation of HIV infection.

C. Symptomatic Disease

As mentioned above HIV is asymptomatic in its initial stages and symptoms start appearing with the decline in CD4 count. The more severe and life-threatening complications of HIV infection occur in patients with CD4 T cell counts < 200/μL.

The virus affects the immune system of the body rendering it susceptible to opportunistic infections. While the causative agents of the secondary infections are characteristically opportunistic organisms such as pneumocystis jiroveci, atypical mycobacteria, cytomegalovirus, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens. Following the widespread use of combined antiretroviral therapy (cART) and implementation of guidelines for the prevention of opportunistic infections, the incidence of these secondary infections has decreased dramatically.

Overall, the clinical spectrum of HIV disease is constantly changing as patients live longer and new and better approaches to treatment and prophylaxis are developed. In addition to the classic AIDS-defining illnesses, patients with HIV infection also have an increase in serious non-AIDS illnesses, including non-AIDS related cancers and, cardiovascular, renal and hepatic disease.

Non-AIDS events dominate the disease burden for patients with HIV infection receiving cART. Less than 50% of deaths among AIDS patients are as a direct result of an AIDS-defining illness. The physician providing care to a patient with HIV infection must be well versed in general internal medicine as well as HIV-related opportunistic diseases.

In general, it should be stressed that a key element of treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication through the use of cART and instituting primary and secondary prophylaxis for opportunistic infections as indicated.

D. AIDS

AIDS is the end-stage of HIV infection, the diagnosis is made in anyone with HIV infection with a CD4 T cell count <200/μL and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity. A number of opportunistic infections commonly occur at this stage and or cancers that occur in people with otherwise unexplained defects in immunity. Death is due to uncontrolled or untreatable infection. Tuberculosis and kaposi sarcoma are usually seen relatively early. Serious fungal infections such as candida esophagitis, cryptococcus meningitis and penicillosis, and parasitic infections such as pneumocystis jiroveci pneumonia or toxoplasma gondii encephalitis tend to occur, when T-helper cell count has dropped to around 100. People whose counts are below 50 have the late opportunistic infections such as CMV retinitis.

WHO case definition for HIV infection

Adults and children 18 months or older

HIV infection is diagnosed based on: positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics;

and/or positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination.

Children younger than 18 months:

HIV infection is diagnosed based on: positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth. Positive HIV antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age.[20]

Table 1: WHO immunological classification for established HIV infection

HIV-associated immunodeficiency	**Age-related CD4 values**			
	<11 months (% CD4)	12–35 months (% CD4)	36 –59 months (% CD4)	>5 years(absolute no. per µL or % CD4)
None or not significant	>35	>30	>25	> 500
Mild	30–35	25–30	20–25	350−499
Advanced	25–29	20–24	15−19	200−349
Severe	<25	<20	<15	<200 or <15%

Table 2 :WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection[20]

Clinical stage 1	Asymptomatic Persistent generalized lymphadenopathy
Clinical 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
Clinical stage 3	Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea 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 Pulmonary tuberculosis (current) Severe bacterial infections (such as pneumonia, empyema, pyomyositis bone or joint infection, meningitis or bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anemia (<8 g/dl), neutropenia (< 0.5×10^9 /L) or chronic thrombocytopenia (< 50×10^9/L)
Clinical 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)

	Esophageal 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 diarrhea) Chronic isosporiasis Disseminated mycosis (coccidiomycosis or histoplasmosis) Recurrent non-typhoidal Salmonella bacteremia Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

WHO case definition for AIDS surveillance

For the purposes of AIDS surveillance an adult or adolescent (> 12 years of age) is considered to have AIDS if at least two of the following major signs are present in combination with at least one of the minor signs listed below, and these signs are not known to be due to a condition unrelated to HIV infection[21].

Table 3 : Major and Minor signs of AIDS

Major signs • Weight loss ≥ 10% of body weight • Chronic diarrhea for-more than 1 month • Prolonged fever for more than 1 month (intermittent or constant) Minor signs • Persistent cough for more than 1 month. • Generalized pruritic dermatitis • History of herpes zoster. • Oropharyngeal candidiasis • Chronic progressive or disseminated herpes simplex infection. • Generalized lymphadenopathy.
The presence of either generalized kaposi Sarcoma or cryptococcal meningitis is sufficient for the diagnosis of AIDS for surveillance purposes.

LABORATORY INVESTIGATIONS

Screening tests: As antibodies to HIV are far easier to detect than the virus itself, their presence or absence in blood stream is the basis for the most widely used test of HIV infection. A person whose blood contains HIV antibodies is said to be HIV positive, or seropositive. There is now a wide range of screening tests based on detection of HIV antibodies.

Table 4 : Laboratory findings with HIV infection[21]

Test	Significance
HIV enzyme linked immunosorbent assay (ELISA)	Screening test for HIV infection. Sensitivity > 99.9% , to avoid false positive results, repeatedly reactive results must be confirmed with Western Blot.
Western Blot	Confirmatory test for HIV. Specificity when combined with ELISA >99.99%. Indeterminate results with early HIV infection, HIV-2 infection, autoimmune disease, pregnancy and recent tetanus toxoid administration.
Complete Blood Count	Anemia, neutropenia, and thrombocytopenia common with advanced HIV infection
Absolute CD4 lymphocyte count	Most widely used predictor of HIV progression. Risk of progression to an AIDS opportunistic infection or malignancy is high with CD4 <200 cel1s/µL.
CD4 lymphocyte percentage	Percentage may be more reliable than the CD4 count. Risk of progression to an AIDS, opportunistic infection or malignancy is high with percentage < 20%.
HIV viral load tests	These tests measure the amount of actively replicating HIV virus. Correlates with disease progression and response to antiretroviral drugs.
β microglobulin	Cell surface protein indicative of macrophage. Monocyte stimulation Levels>3.5 mg/dl associated with rapid progression of disease.
p24 antigen	Indicates active HIV replication. Tends to be positive prior to seroconversion and with advanced disease.

Table 5 :Characteristics of tests for direct detection of HIV[19]

Test	Technique	Sensitivity
Immunecomplex-dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients; detects down to 15 pg/ml of p24 protein
HIV RNA by PCR	PCR amplification of cDNA generated from viral RNA (target amplification)	Reliable to 40 copies/ml of HIV RNA
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Reliable to 50 copies/ml of HIV RNA
HIV RNA by NucliSens	Isothermic nucleic acid amplification with internal controls	Reliable to 80 copies/ml of HIV RNA

3.5 HIV AFFECTING DIFFERENT SYSTEMS

Neurological Disorders

Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of HIV positive patients.The neurologic problems may be either primary to the pathogenic process or secondary to opportunistic infections or neoplasms.

Table 6 :Neurological diseases in HIV infection are classified as follows[22]

Opportunistic infections
Toxoplasmosis
Cryptococcosis
Progressive multifocal leukoencephalopathy
Cytomegalovirus
Syphilis
Mycobacterium tuberculosis
HTLV-I infection
Amebiasis
Neoplasms
Primary CNS lymphoma
Kaposi's sarcoma
Result of HIV-1 infection
Aseptic meningitis
HIV-associated neurocognitive disorders, including
HIV encephalopathy/AIDS dementia complex
Myelopathy
Vacuolar myelopathy
Pure sensory ataxia
Paresthesia/dysesthesia
Peripheral neuropathy
Acute inflammatory demyelinating polyneuropathy (GBS)
Chronic inflammatory demyelinating polyneuropathy
Mononeuritis multiplex
Distal symmetric polyneuropathy
Myopathy

Diseases of the Respiratory System

Pulmonary diseases are the most frequent complications of HIV infection. Acute bronchitis and sinusitis are prevalent during all stages of HIV infection.The most common manifestation is pneumonia.

Three of the 10 most common AIDS defining illnesses are recurrent bacterial pneumonia,tuberculosis and pneumonia due to pneumocystis jiroveci.

In HIV patients bacterial pneumonia is mainly due to encapsulated organisms like hemophiles influenzae and streptococcus pneumonia. Mycobacterium tuberculosis has experienced a resurgence in developed countries where it was previously on its way to extinction.Worldwide one third of the AIDS related deaths are associated with TB. Patients with HIV infection are more likely to have TB by a factor of 100 when compared with an HIV negative population. Atypical Mycobacteria infections are seen with increased frequency in this group of patients.
Other infections include those caused by rhodococcusequi, coccidioides immitis, asperigillus, histoplasma, lymphoid interstitial pneumonia, non specific interstitial pneumonia.

Diseases of the Cardiovascular System

The most common form of heart disease in HIV patients is coronary heart disease which may be a direct consequence of HIV infection or a complication of cART along with classic risk factors.

Another form of disease associated with HIV infection is dilated cardiomyopathy with congestive heart failure referred to as HIV associated cardiomyopathy. Pericardial effusions are common and may be associated with pericarditis.

Diseases of the Oropharynx and Gastrointestinal System

Oropharynx and GI diseases are most frequently due to secondary infections. Oral lesions include thrush, hairy leukoplakia, aphthous ulcers. Esophagitis may be due to candida, CMV or herpes simplex virus.

Chronic diarrhea is the most common manifestation of gastrointestinal system involvement.Enteric infections are due to shigella, salmonella campylobacter and fungi like histoplasmosis, coccidiodomycosis, penicilliosis. Opportunistic protozoa like cryptosporidia, microspordia and isospora belli are also common causes of diarrhea. AIDS enteropathy is postulated to be caused by direct result of HIV on the mucosal surface of small bowel. It causes malabsorption and weight loss along with chronic diarrhea. Anorectal lesions are also common in HIV patients.

Hepatobiliary Diseases

Approximately one third of deaths in HIV patients are in some way related to liver disorders. The prevalence of coinfection with Hepatitis B virus can be upto 90%. Hep C infection and coinfection of Hep B, Hep C, Hep D and E is common in HIV patients.

Granulomatous hepatitis maybe seen as a consequence of mycobacterial or fungal infections particularly Mycobacterium avium complex infection. Hepatic masses maybe seen in the context of TB.

Biliary tract disease in the form of papillary stenosis or sclerosing cholangitis maybe seen secondary to cryptosporidiosis or CMV infections.Many of the HIV drugs are metabolized by the liver and can cause liver injury. Nevirapine has been associated with fatal fulminant hepatitis. Other major systems involved are the kidney and urinary tract, endocrine system, musculoskeletal, hematopoietic and skin among others.

3.5 HIV AND AUTONOMIC NEUROPATHY

Autonomic dysfunction occurs more frequently and with greater severity in patients with AIDS however it may be present in the early stages of HIV infection and appears to progress during the illness.[23]

Early clinical signs of autonomic dysfunction in HIV infected patients include syncope, presyncope, diminished sweating, diarrhea, bladder dysfunction, impotence. Although subclinical autonomic neuropathy has been found in upto 50% of HIV infected patients.

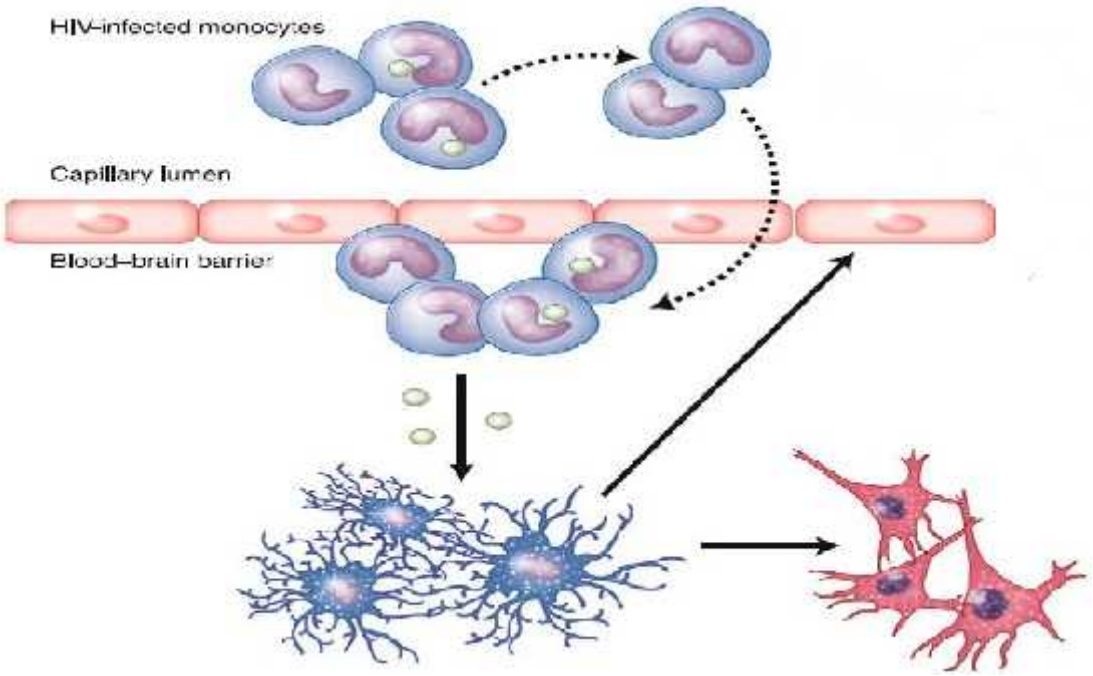
Various studies have reported prevalence of autonomic nervous system dysfunction from 5% to 77%.[24]

Autonomic dysfunction

Pathogenesis of the Autonomic Nervous System Dysfunction of HIV infections

HIV quickly enters the brain after initial exposure, probably through infected monocytes and lymphocytes that cross the blood brain barrier.[25]

Figure 3.Potential HIV specific mechanisms of central nervous system injury.



Crossing the Blood Brain barrier

The HIV surface glycoprotein gp160, which comprises two components, gp120 and gp41, allows the virus to attach to host cell receptors (the CD4 receptor and CXCR4 or CCR5 co-receptor) and to become internalized. CCR5 is the main co-receptor for macrophage- tropic HIV-1 strains, which comprise the vast majority of transmitted HIV and include the predominant strain found in the CNS. Following infection with HIV, CCR5-bearing macrophages expressing activation markers such as CD16 carry HIV into the brain through a 'Trojan horse' mechanism. Microglia, the brain's specialized, native immune cells, can also become infected through contact with these trafficking macrophages.[26]

Mechanism of Neuronal Injury

Although neurons are not infected by HIV, they can be injured via indirect mechanisms

1. Neurotoxins from infected microglial cells (arachidonic acid metabolites and platelet activating factor)
2. gpl20- mediated neuronal growth factor blockade or killing
3. neurotoxicity by HIV tat or other viral regulatory components.

All or any of these mechanisms may result in cytotoxic effects in neurons and/or oligodendrocytes . Secretory products from HIV-infected cells may alter neuronal viability, damage myelin, or stimulate neurotransmitters resulting in neuronal dysfunction[27,28].

Neuroinflammation is characterized by several pro-inflammatory events including the release of pro-inflammatory cytokines such as IL-1β, -6, TNF-α, and chemokines that drive this process . IL-1β leads to NF-kB dependent transcription of pro-inflammatory cytokines including TNF-α, IL-6 and interferon .Tat stimulates

cytokine/chemokine networks in monocytes and macrophages. HIV-1-encoded viral protein R (Vpr) has been shown to modulate several chemokines at the transcriptional level by regulating NF-kB-mediated transcription. [29-32]

Surface glycoprotein gpl20 may antagonize normal vasoactive intestinal peptide (VIP-ergic) function in brain or be directly toxic to neurons. Studies show that gpl20 can induce neuronotoxicity by activation of the N-methyl D-aspartate receptor with consequent influx into the cell of calcium and secondary synthesis of nitric oxide in those neurons containing nitric oxide synthetase.[33]

The tissue damaged by the cytokines then becomes secondarily infected. Moreover, as HIV-1 disease advances and there is a reduction in CD4 + cells there is a selection towards these infected microglial cells that further infect the brain.

Pathological outcomes of HIV-1 infection in brain tissue include neuronal loss, reactive astrogliosis, and myelin damage. Neuronal loss is strongly associated with axonal and dendritic damage in the cortex and subcortex of affected individuals.[34]

Peripheral nerves are also affected by the cytokines that are released by macrophage lineage cells in an attempt to control infection.[35]

Autonomic nervous system (ANS)

The "Autonomic" nervous system part of nervous system that is responsible for homeostasis. Except for skeletal muscle which gets its innervations from the somatomotar nervous system, innervations to all other organs is supplied by ANS.Autonomic nervous system may be defined as the part regulating all those bodily processes which are not under voluntary or volitional control.[36,37,38]

The autonomic nervous system includes parts of the central and peripheral nervous system. The latter being concerned with innervation of viscera, glands, blood vessels and non-striated muscles. It is intimately responsive to changes in the somatic

activities of body, and while its connections with somatic elements are not always clear in anatomical terms, the physiological evidence of visceral reflex activities stimulated by somatic events are abundant.[39,40]

Probably the most remarkable feature of the autonomic nervous system is the location of major part of it being outside the cerebrospinal axis, in proximity to the structures that it innervates. In distinction to somatic neuromuscular system, where a single motor neuron bridges the gap between central nervous system and the effector organ in the autonomic nervous system there are always two motor neurons,preganglionic and post ganglionic fibres. The autonomic out flow is regulated by centers in brain stem. Hypothalamus is the most important cell station which finally controls visceral and other autonomic activity. Hypothalamus is influenced by different parts of brain like hippocampus, amygdala, and prefrontal cortex and cingulate gyri and also from periphery through baro-receptors and chemoreceptors, receptors in skin, muscle and viscera.[41]

The ANS has two major and anatomically distinct divisions: the sympathetic and para-sympathetic nervous systems. These two systems are antagonistic of each other in their effects on the effector organs.

The preganglionic efferent fibers of parasympathetic nervous systems emerge through certain cranial and sacral spinal nerves and constitute the craniosacral out flow. On the other hand pre-ganglionic efferent fibers of the sympathetic nervous system emerge through thoracic and upper lumbar spinal nerves and constitute the thoracolumbar outflow.

The cell bodies of the preganglionic neurons area located in the intermediolateral column of spinal cord and in motor nuclei of some cranial nerves. Their axons traverse corresponding to cranial and spinal nerves to enter ganglia,

where they synapse with dendrite or somata of secondary neurons. One pre-ganglionic neuron will synapses with eight or nine post-ganglionic neurons, a circumstance which is associated with wide distribution of many autonomic effects. This disproportion of preganglionic to post ganglionic is greater in sympathetic than in parasympathetic nervous system.[42]

The cell bodies of post ganglionic neurons in the parasympathetic system are situated peripherally, either as discrete collection forming ganglia nearer to structures innervated than to the central nervous system or sometimes disperse in the walls of viscera themselves. The cell bodies of post ganglionic neurons in sympathetic trunk are in ganglia in more peripheral plexuses, almost always nearer to spinal cord that the organ innervated. The fibers which convey the message to ganglia (white rami communicants) are finely medullated but fibers ganglia to effector organ are non medullated; grey rami communicans.

The ANS is responsible for regulating and coordinating many physiological functions that include blood flow, blood pressure , heart rate, airflow through the bronchial tree, gastrointestinal motility, urinary bladder contraction, glandular secretions, pupillary diameter, body temperature and sexual physiology. Physiologically, parasympathetic reactions are generally localized, whereas sympathetic reactions are mass responses.

Passage of nervous impulses along all preganglionic fibers, parasympathetic, postganglionic fibers are associated with liberation of acetylcholine in the region of terminals. In case of post ganglionic sympathetic fibers substance released as adrenaline or noradrenaline. To this reason the above types of nerves are called cholinergic and adrenergic respectively. As an exception sweat glands are supplied by postganglionic sympathetic nerves but are cholinergic.[43]

Table 7 :Autonomic effects on various organs of the body[44]

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
EYE		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
GLANDS		
Lacrimal Parotid SubmandibularGastric Pancreatic	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for Nasal enzyme-secreting glands)
SWEAT GLANDS	Copioussweating (cholinergic)	Sweating on palms of hands
APOCRINE GLANDS	Thick, odoriferous secretion	None
BLOOD VESSELS	Most often constricted	Most often little or no effect
HEART		
Muscle	Increased rate and increased force of contraction	Slowed rateDecreased force of contraction (especially of atria)
Coronaries	Dilated (beta2); constricted (alpha)	Dilated
BLADDER		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed
GUT		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone	Relaxed
LUNGS		
Bronchi	Dilated	Constricted
BLOOD VESSELS	Mildly constricted	Dilated

Table 8 :Causes of Autonomic dysfunction[45]

Etiological Category	Selected Etiologies
Structural Disorders Developmental structural disorders	Arnold-Chiari malformation Syringomyelia Normal pressure hydrocephalus
Hereditary and Degenerative Disorders Movement disorders Degenerative motor, sensory and autonomic disorders Inherited muscle, neuromuscular and neuronal disorders	Multiple system atrophy Riley-Day syndrome Pure autonomic failure Amyloidosis
Acquired Metabolic and Nutritional disorders Endogenous metabolic disorders Nutritional deficiencies and syndromes associated with alcoholism	Diabetes mellitus Wernicke's encephalopathy
Infectious Disorders Viral infections Transmissible spongiform encephalopathy HIV and AIDS	Poliomyelitis Fatal familial insomnia HIV associated neuropathy HIV related Guillane Barre Syndrome
Neurovascular Disorders	Vertebrobasilar ischemia
Neoplastic Disorders Primary Neurological tumors	Brain stem glioma
Demyelinating Disorders Demyelinating disorders of CNS Demyelinating disorders of peripheral nervous system	Multiple sclerosis with bladder dysfunction Guillane Barre Syndrome
Autoimmune and inflammatory disorders	Lambert Eaton myasthenia syndrome
Traumatic Disorders	Spinal cord :blunt or penetrating trauma
Epilepsy	Temporal/Limbic seizures
Headache and facial pain	Cluster headaches
Drug induced and iatrogenic neurological disorders	Drugs:chemotherapeutic agents(vincristine)

Dysautonomia symptoms in HIV infected subjects[23]

Cardiovascular symptoms	Postural hypotension, vertigo, recent syncope, palpitation
Upper GI symptoms	Dysphagia, nausea/emesis, early satiety, gastric fullness or bloating, diarrhea or constipation
Lower GI symptoms	Involuntary loss of stool, feeling of incomplete fecal evacuation
Urogenital symptoms	Dysuria, involuntary loss of urine, prolonged dribbling, feeling of incomplete urinary evacuation, impotence
Others	Increased sensitivity to light, anhypo-or hyperhidrosis, or gustatory sweating.

Management of autonomic neuropathy

The most troublesome effect of the autonomic dysfunction is orthostatic hypotension. Management includes patient education to avoid factors that precipitate a fall in blood pressure. Patients should be made aware of hypotensive effects of certain drugs, large meals, environmental temperature increases and physical activities.[46,47]

Physical measures

- These patients are advised not to suddenly arise from beds; instead, they should first exercise the legs by crossing them and lowering the head in a stooped position,bending forward and placing a foot on a chair or squatting. They should avoid straining during micturition and defecation. A snug elastic abdomen binder and elastic stocking(Jobst or Barton-Carey Leotard) are often helpful.

- To avoid postprandial hypotension, patients should eat smaller,low carbohydrate meals more frequently.
- Elevation of head end of bed 15 to 30 cm at night is also advocated, which avoids supine hypertension and decreases nocturnal natriuresis and volume depletion.[48]

Drugs

- If patients are on diuretics they should be advised to stop if there are no contraindications.
- Fludrocortisone : It increases the blood volume and it has effect on noradrenaline release from sympathetic terminals and sensitizing the vascular receptors to vasopressor amines. It is recommended at dosage of 0.1mg PO qd this is increased slowly in 0.1 mg increments at 1 to 2 week intervalstill blood pressure is controlled.
- Vasoconstricting sympathomimetic agents-Ephedrine, methylphenidate, phenylpropanol, amineorphenylephrine, midodrine may be used.
- Other drugs used are Metoclopramide - which is a dopamine antagonist which blocks the vasodilator effect of dopamine and caffeine which prevents post prandial hypotension. Somatostatin also prevents the postprandial hypotension. Recombinant erythropoietin alpha corrects anemia which is usually present and increases blood pressure and orthostatic tolerance.[49,50]

Bladder Disturbances

In bladder obstruction due to increased tone, adrenergic blockers are advocated. Other methods are bladder neck resection, sphincterostomy, urethral

catheterization, and suprapubic cystostomy, atonic bladder by carbachol, bethanechol, and urinary tract infections are to be treated.[51]

Gastrointestinal disturbances

Gastric atony and reflux esophagitis may be helped by metoclopramide; diarrhea by bowel binding agents, loperamide, codeine, diphenoxylate can be tried. For constipation increased roughage in diet is advised.

Sweating abnormalities

- For hyperhidrosis -- Propanthelene
- For anhidrosis -- Petroleum jelly

Impotence: Treatment includes

1) Local papaverine with or without phentolamine.

2) Surgical implants.

Diagnosis of cardiac autonomic neuropathy

Many tests for testing autonomic functions have been described. However the following are standardized and well accepted.

1. Heart rate variation to deep breathing.
2. Valsalva ratio
3. Heart rate response to standing
4. Systolic fall in blood pressure to standing
5. Diastolic rise in blood pressure to sustained hand grip.

Heart rate variation deep breathing

During deep inspiration and expiration the heart rate varies which is called sinus arrhythmia. Sinus arrhythmia is a result of several circulatory reflexes. First, when blood pressure rises and falls during each cycle of respiration, the baro-receptors are alternatively stimulated and depressed, causing reflex slowing and speeding of heart. Second, during each respiratory cycle, the negative intra-pleural pressure increases and decreases effective pressure in veins of chest. This elicits a

waxing and waning Bainbridge reflex which alters heart rate. Third, when respiratory cycle, some impulses spill over from respiratory center into vasomotor center causing increase of heart rate.

Procedure : The patient is asked to breath normally and long lead two on electrocardiography (ECG) is recorded. The patient is then asked to take deep breaths at the rate of about six breaths per minute, after about one minute again a long lead two recording is repeated on ECG with the patient continuing deep breathing.

Interpretation : All these reflexes are blunted in autonomic neuropathy. Normal subjects have differences in heart rate of greater than 15 beats per minute, and a difference of less than 10 beats per minute if abnormal, between 11 to 15 in borderline.

Heart-rate response to Valsalva maneuver

The Valsalva maneuver was described in 1704 by Antanio M.Valsalva an Italian anatomist, When a person performs Valsalva maneuver a sharp reduction in venous return and cardiac output occurs as a result of which blood pressure falls; this causes baroreceptors to produce less impulses and reflex tachycardia and peripheral vasoconstriction occurs with releases of intrathoracic pressure, the venous return, stroke volume and blood pressure return to higher than normal, levels and stimulate baro-receptors resulting in bradycardia.

Procedure : A lead II recording is done on ECG. The patient is then asked to breathe through into a mouth piece connected to a modified sphygmomanometer and holding it at a pressure of 40 mm Hg for 15 seconds while a continuous lead II ECG is recorded.

Interpretation : In parasympathetic dysfunction during release phase, bradycardia does not occur. This is utilized in calculating Valsalva ratio, the longest R-R interval after maneuver is divided by shortest R-R interval during maneuver. A ratio greater than 1.21 is normal 1.11 to 1.20 is borderline and less than 1.10 abnormal.

Heart rate response to standing

Upon standing systemic pooling of blood in venous system occurs. This leads to reduction in cardiac output, decreased baro-receptor discharge and consequently vasomotor center is stimulated causing tachycardia.

Procedure : The patient is asked to lie supine and a lead two recording is done on ECG. The patient is asked to stand up and the recording continued.

Interpretation : Heart rate increases until it reaches a maximum at about fifteenth beat, the normal increase being in range of 11 to 29 beats per minute then its lows to a relatively stable rate at about thirtieth beat. The ratio of R-R intervals corresponding to thirtieth and fifteenth heart beat is known as 30:15 ratio. The ratio of one or less is considered abnormal

Systolic fall in blood pressure on standing

Normally as one stands the pull of gravity pools blood in distensible veins below heart, diminished venous return reduces cardiac output and in turn fall in arterial pressure. This triggers a series of physiologic adjustments designed to maintain adequate perfusion. Stimulated baro-receptors provoke autonomic nervous activity, which results in an increase in peripheral arterial and venous constriction, heart rate and myocardial contraction. Failure of these adjustments either the baro-receptors, its afferent fibers, vasomotor center and its central connections of sympathetic out flow may cause postural fall in blood pressure.

Procedure : The patient’s blood pressure is measured when the patient is in supine position and again when he is standing up.

Interpretation : A systolic pressure fall of 30mm of Hg. at end of three minutes indicates abnormal response of sympathetic system.

Diastolic rise of blood pressure in response to sustained hand grip (isometric contraction)

During sustained isometric contraction of a group of muscles an increase in heart rate, arterial blood pressure and cardiac output occurs. The cardiovascular responses are mediated partly by central contracting muscles that activate small fibers in afferent limb arc. This results in increased sympatho-adrenal discharge.

Procedure : The patient is asked to maintain sustained voluntary hand grip for as long as possible.Blood pressure is recorded before and during the procedure.

Interpretation : An increase in diastolic pressure of more than 16 mmHg in normal and less than 10mm of Hg is abnormal. This is also a test for sympathetic system. 11 mmHg to l6mmHg is border line.

Table 9 : TABLE FOR SCORING

Test	**Normal**	**Abnormal**	
		Borderline	**Definite**
Systolic fall of blood pressure on standing	Less than 10mm of Hg.	11-29 mm of Hg.	More than 30 mm of Hg
Expiratory inspiratory Ratio	More than 15 beats per mm.	11-15 beats per mm.	Less than 10 beats per mm.
Valsalva ratio	More than 1.21	1.11-1.20	Less than1.10
Heart rate response on Standing	More than 1.04	1.01-1.03	Less than1.00
Blood pressure to sustained hand grip	More than 16m of Hg	11-15mm of Hg	Less than 10mm of Hg.

Literature on cardiac autonomic dysfunction in HIV/AIDS patients

In one of the earliest studies done in 1999 Rogstadt et al**.** examined autonomic function in HIV positive patients at various stages of infection and in controls. Twenty five patients with seven asymptomatic HIV, eight AIDS related complex ,10 AIDS patients and 25 controls were studied. Autonomic function was assessed, CD4 count was correlated with number of abnormal test results. Twenty one patients had at least one abnormal test of autonomic function compared with one control ($p<0.0001$). There were significant differences between AIDS patients and controls for supine heart rate ($p<0.001$), Valsalva ratio ($p=0.05$), and cold face test ($p=0.05$), and almost significant results for mental stress ($p=0.051$), abnormalities in autonomic function occurred at all CD4 counts and all patients with four abnormal tests of heart rate variations had a CD4 count less than $300x10^6/\mu L$. They found evidence of substantial autonomic dysfunction in AIDS patients compared with controls and mild abnormalities in the majority of HIV infected patients studied irrespective of CD4 count.[56]

Heart rate variability in HIV positive individuals was investigated by Mittal C et al. in 2004.They conducted the study to find out if HRV is depressed in HIVpositive individuals without AIDS. They studied prospectively HRV by spectral analysis of short-term ECG monitoring in 21 HIV positive (33±11 years) and in 18 healthy volunteers (31±9years). All these individuals did not have any evidence of AIDS. Mean CD4 lymphocyte count was 426±166/µL. The ejection fraction (EF) of HIV patients was 62.4±6.4%. They found the total power of HRV was reduced significantly in HIV-positive individuals ($p<0.00001$) in early stages of infection as well without any clinical evidence of autonomic dysfunction.[57]

In one of the first studies in Africa in 2002 , Nzubontane D et al. investigated the effects of HIV on cardiac autonomic function. They performed standard heart-rate and blood pressure tests on 75 consecutive consenting patients referred for an HIV. Fifty four patients proved to be HIV-infected with 30 having progressed to AIDS. Cardiovascular autonomic dysfunction was present in eight (28%) patients with AIDS and in one (4%) HIV-positive patient without AIDS; no HIV-negative individuals had abnormal results. If borderline results are included, over 80% of HIV-positive patients had cardiovascular autonomic dysfunction.[58]

In 1997 Becker K et al**.** examined the degree, pattern, and natural history of cardiac autonomic nervous dysfunction in patients infected with HIV. They studied thirty-five consecutive HIV-infected patients who had either not yet developed AIDS (15 pre-AIDS patients) or who were at the Center for disease Control(CDC) AIDS stage (n = 20), and 29 healthy age- and sex-matched HIV-negative controls. They found pre-AIDS patients as a group did not exhibit any HRV parameters to be significantly different from healthy controls ($P > 0.017$), whereas AIDS patients demonstrated reduced HRV in 14 parameters (93.3%) compared with healthy subjects ($P < 0.017$). Median proportion of abnormal HRV parameters (< 10th percentile of controls) per individual was 9.1% in pre-AIDS patients and 61.3% in AIDS patients ($P= 0.0347$).They concluded that the cardiac autonomic nervous dysfunction is severe in AIDS patients, although not significant in pre-AIDS patients. Cardiac autonomic nervous dysfunction proceeds with HIV disease progression, although its individual course is slow.[24]

In a controlled trial in 1991 Ruttimann S. et al. conducted tests to determine frequency and severity of autonomic neuropathy in patients infected with the HIV. They studied 25 HIV-seropositive patients and 10 seronegative controls in HIV risk

groups by means of five cardiovascular tests, and autonomic neuropathy was graded with a scoring system. The overall autonomic test score differed between patients and controls and was higher in patients with advanced (CDC class IV) disease than in those with earlier (class II or III) HIV disease. Of the patients, 60% had findings of autonomic dysfunction. Their data demonstrate a high prevalence of autonomic neuropathy in HIV-infected patients. Advanced HIV disease is associated with more severe involvement than earlier disease states.[59]

The team of Freeman MD et al. in 1990 studied autonomic function in 26 patients infected by the HIV(18 AIDS and 8 ARC) to 22 controls. A significant decline in autonomic function was present across groups. Autonomic dysfunction correlated strongly with signs of HIV-associated nervous system disease. They observed significant differences across groups in tests of heart rate variation (expiratory-inspiratory ratio, maximum minus minimum heart rate difference, and mean square successive difference), the mean arterial blood pressure fall to tilting, and the blood pressure response to isometric exercise. A trend of declining autonomic function from controls to AIDS was present in the 30:15 ratio, the Valsalva ratio, the systolic blood pressure fall to standing and tilt, and the cold pressor test. They found the autonomic dysfunction occurs more frequently and with greater severity in patients with AIDS; however, it may be present in the early stages of HIV infection and appears to progress during the illness.[60]

Orthostatic hypotension as a result of generalized autonomic nervous system dysfunction was investigated by Cohen JA et al. in HIV positive patients in 1991. They used an ANS testing battery to determine if generalized ANS dysfunction was present in five HIV positive patients presenting with severe orthostatic hypotension . All five patients had abnormal ANS testing, which demonstrated both sympathetic

and parasympathetic defects, i.e., generalized ANS dysfunction. Treatment with fludrocortisone effectively reversed the orthostatic hypotension in four of the five patients. The orthostatic hypotension was transient in these four patients. They state that it is important to recognize that orthostatic hypotension may be the result of generalized ANS dysfunction in HIV-positive patients and that it can be effectively treated.[61]

MATERIALS AND METHODS

1. SOURCE OF DATA:

The information for the study was collected from HIV positive patients admitted to BLDEU'S Shri B.M. Patil Medical college Hospital and Research Centre, Bijapur between October 2012 to March 2014.The controls were patients admitted for other diseases who were not HIV seropositive but fit the exclusion criteria.

2. METHOD OF COLLECTION OF DATA:

Information was collected through prepared proforma from each patient. All patients were interviewed as per the prepared proforma and then a complete clinical examination was done.

Inclusion Criteria:

• HIV infection diagnosed as per NACO guidelines

Exclusion Criteria:

- History of cardiovascular diseases like acute coronary syndrome, congenital heart diseases before testing. Echocardiography is done to rule out structural heart diseases.
- Very ill patients who are unable to perform the autonomic function tests.
- Patients with history of diabetes mellitus.
- Known alcoholics.

The following tests were performed to assess the cardiac autonomic functions in the above patients:-

1. Heart rate variation to Valsalva maneuver
2. Heart rate response to deep breathing
3. Heart rate response to standing from supine position

4. Blood pressure response to standing up
5. Blood pressure response to sustained handgrip

Grading was given for each autonomic function test. Results were classified into normal, borderline, and abnormal (scored 0, 1 and 2 respectively).

An overall score of ≤3 was considered as normal, >3 and <8 was considered as Borderline and score of ≥8 was considered as abnormal. CD4 count was correlated with number of abnormal test results.

3. TYPE OF STUDY

Longitudinal study

4. SAMPLE SIZE:

With a 0.3% prevalence of HIV in India[5] and a 77% prevalence rate of cardiac autonomic dysfunction in HIV positive patients[6] at 95 % Confidence Interval and 15% allowable error the calculated sample size is 50.9 rounded off to 51.

$n = (1.96)^2 \` p \` q / l^2$

n – Sample size

p –prevalence rate

q – 100 - p

l – expected variation

Statistical analysis

The data was entered in MS Excel Sheet. Appropriate statistical test like Chi square and "z" test were used.

RESULTS

Out of 224 HIV positive patients admitted during the period of October 2012 to March 2014 the study on cardiac autonomic dysfunction was carried out in 51 patients.Fifty one controls who were matched for age sex were also included in the study for comparison. After compiling the data the following observations were made.

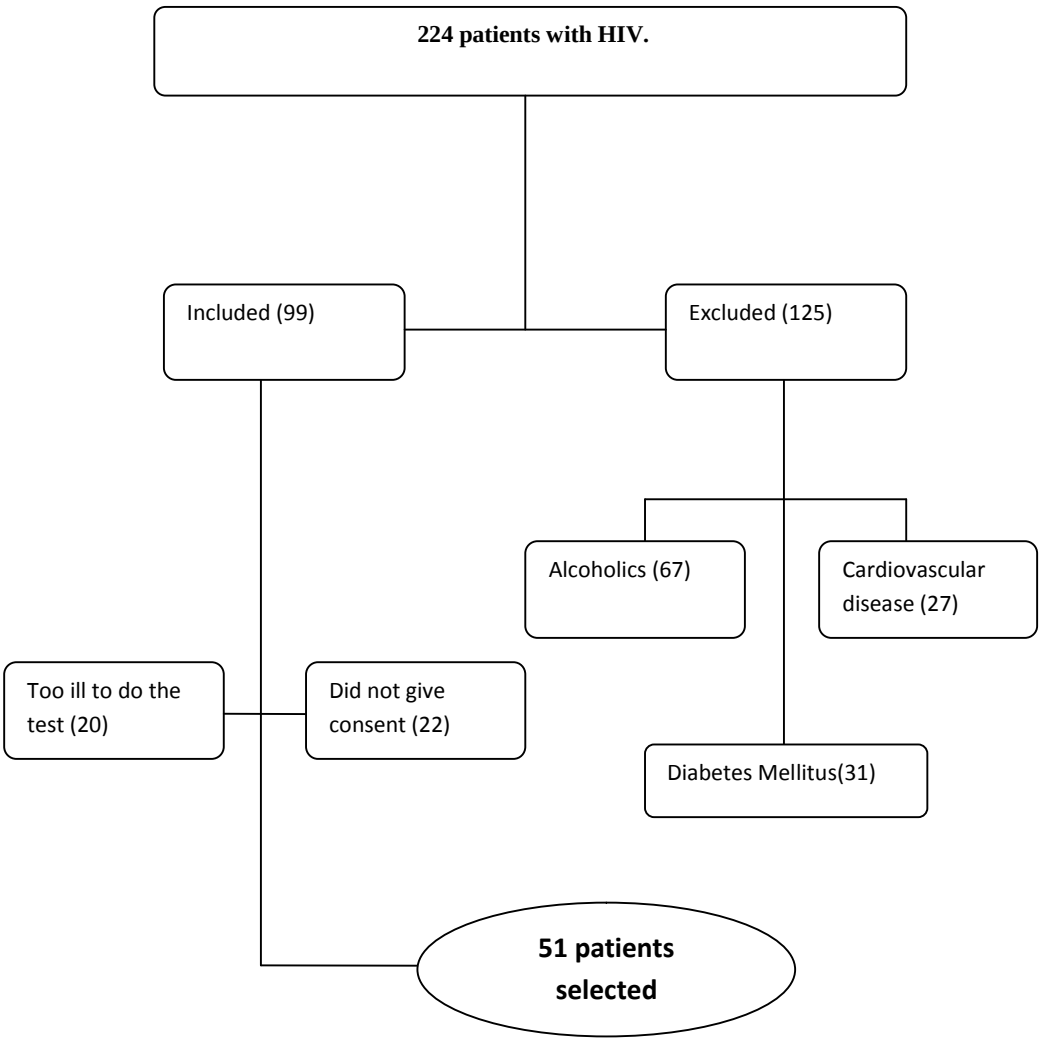
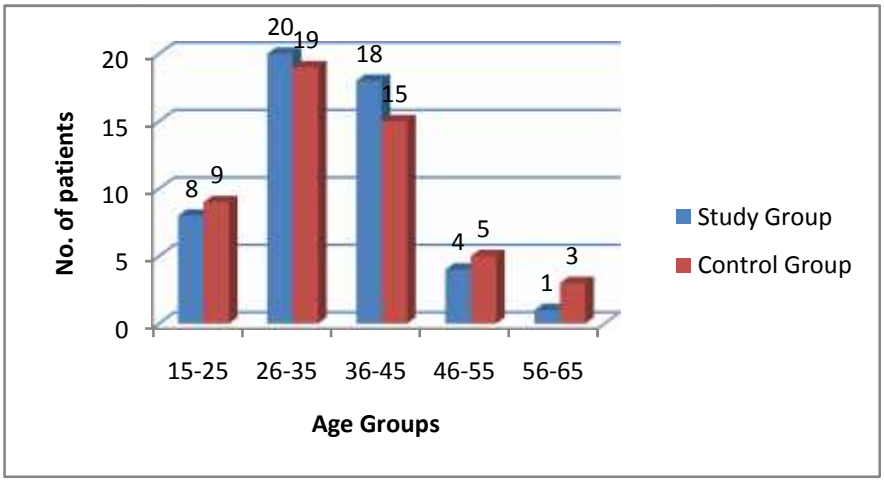


Table 10: Age distribution of patients among study and control groups

Age(yrs)	Study Group	Control Group	Total
15-25	8 (15.6%)	9(17.64%)	17(16.6%)
26-35	20(39.21%)	19(37.25%)	39(38.23%)
36-45	18(35.29%)	15(29.41%)	33(32.35%)
46-55	4(7.84%)	5(9.80%)	9(8.82%)
56-65	1(1.96%)	3(5.88%)	4(3.92%)
Total	51(100%)	51(100%)	102(100%)

Graph 1: Age distribution of study and control group

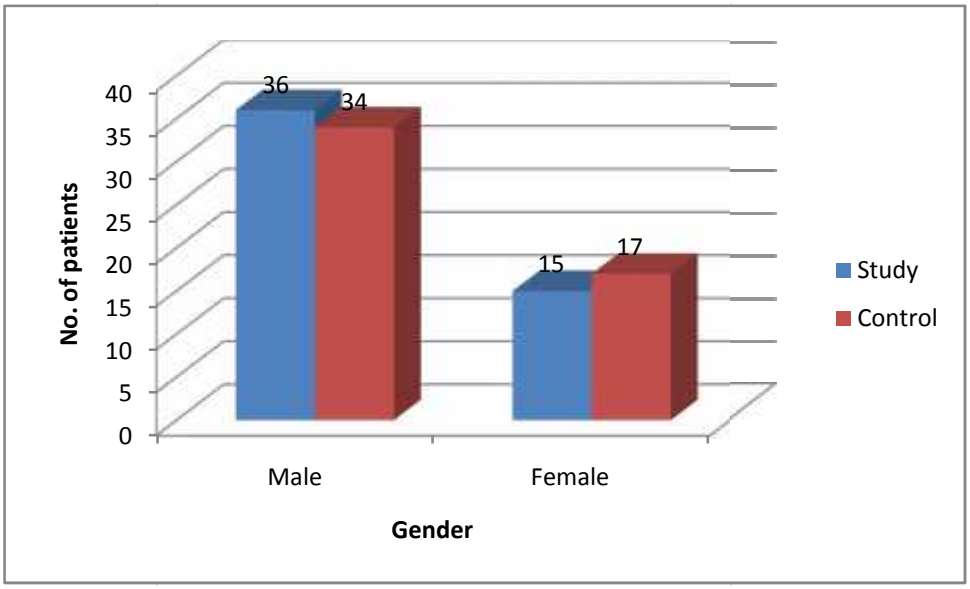


Age group ranged from 17-60 years with mean age of 36.6 years in the study group and 35.3 years in the control group. Majority of patients were in the age group of 26 to 35 years which was the most sexually active and economically productive group.

Table 11 : Gender distribution of study and control groups

Gender	Study	Control
Male	36(70.58%)	34(66.66%)
Female	15(29.42%)	17(33.44%)

Graph 2 : Showing Gender Distribution of study and control groups

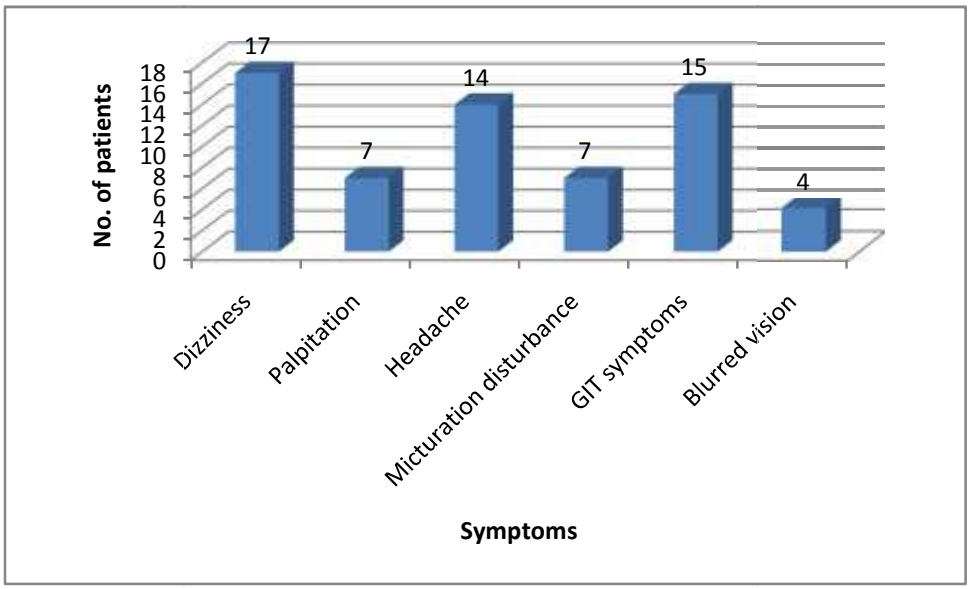


Male female ratio was 12:5.Male sex was predominantly affected, the difference was not statistically significant.(p=0.6)

Table 12 : Shows common mode of presentation and symptoms of the patients

Symptoms	No of patients	%
Dizziness	17	33.33
Palpitation	7	13.72
Headache	14	27.45
Micturation disturbance	7	13.72
GIT symptoms	15	29.41
Blurred vision	4	7.84

Graph 3 : Distribution of symptoms among patients

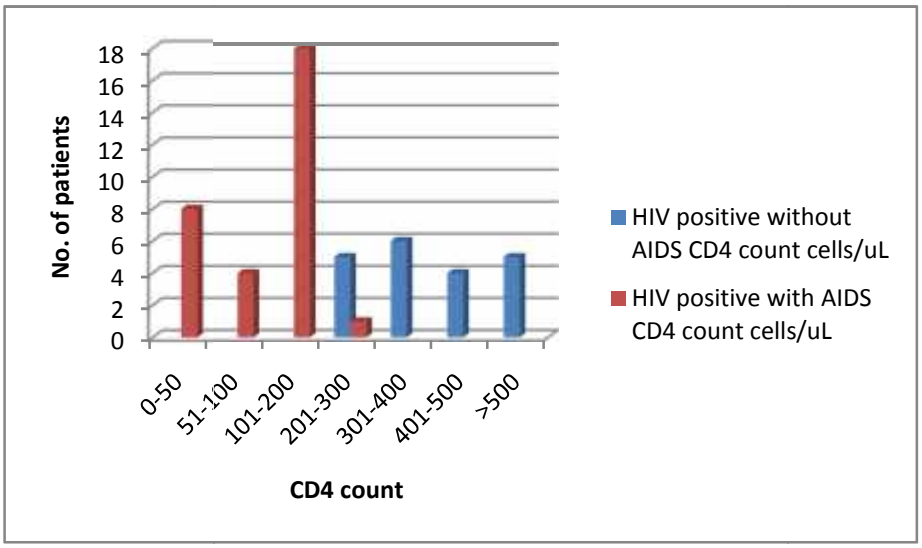


The most common symptoms associated with autonomic dysfunction were dizziness and headache. The least common presentation was blurred vision.

Table 13 : Distribution of patients by CD4 count

	HIV positive without AIDS CD4 count cells/uL	HIV positive with AIDS CD4 count cells/uL	%
0-50	-	8	15.68
51-100	-	4	7.84
101-200	-	19	35.29
201-300	5	-	9.80
301-400	6	-	11.76
401-500	4	-	7.84
>500	5	-	9.80
Total	20	31	100

Graph 4 : Graph depicting CD4 count distribution among patients

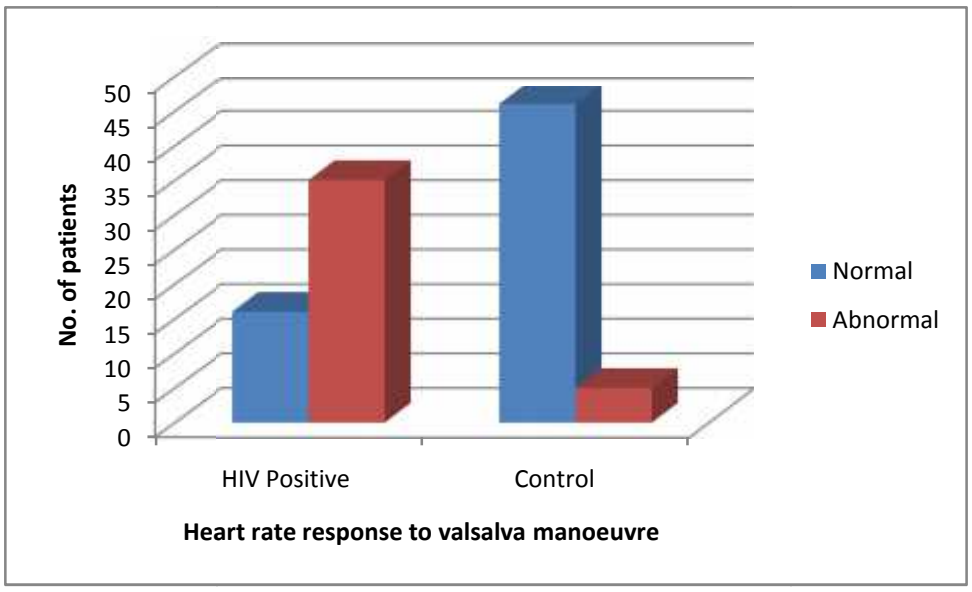


The mean CD4 count was 231 cells/µL. Thirty one patients had CD4 count below 200 cells/µL and were thus classified as AIDS.

Table 14 : Showing analysis of Valsalva ratio in HIV positive/AIDS group and control group

Valsalva Ratio	HIV without AIDS(20)	HIV with AIDS(31)	Total HIV with and without AIDS(51)	Control (51)
Normal	11 (55%)	5(16.12%)	16(31.38%)	46(90.16%)
Abnormal	9(45%)	26(83.88%)	35(68.62%)	5(9.8%)
Total	20(100%)	31(100%)	51(100%)	51(100%)

Graph 5 : Analysis of Valsalva ratio in HIV positive/AIDS group and control group

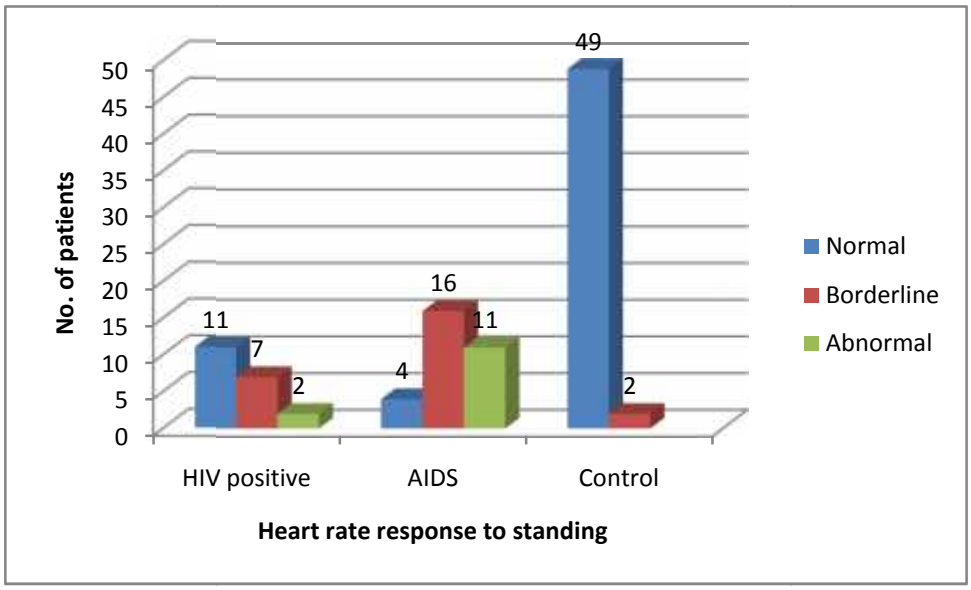


When the results of Valsava ratio was analyzed it was found that there was significant difference between HIV with or without AIDS group and control group (p = .001). There was statistically significant difference between HIV positive without AIDS and HIV positive with AIDS group.(p=0.003)

Table 15 : Showing the analysis of heart rate response to standing between HIVpositive group, AIDS group and control group

HR response to standing	HIV without AIDS(20)	HIV with AIDS(31)	Total HIV with and without AIDS(51)	Control (51)
Normal	11(55%)	4(12.90%)	15(29.40%)	49(96.07%)
Borderline	7(35%)	16(51.61%)	23(45.10%)	2(3.93%)
Abnormal	2(10%)	11(35.4%)	13(25.50%)	-
Total	20(100%)	31(100%)	51(100%)	51(100%)

Graph 6 : Showing the analysis of heart rate response to standing between HIV positive group, AIDS group and control group

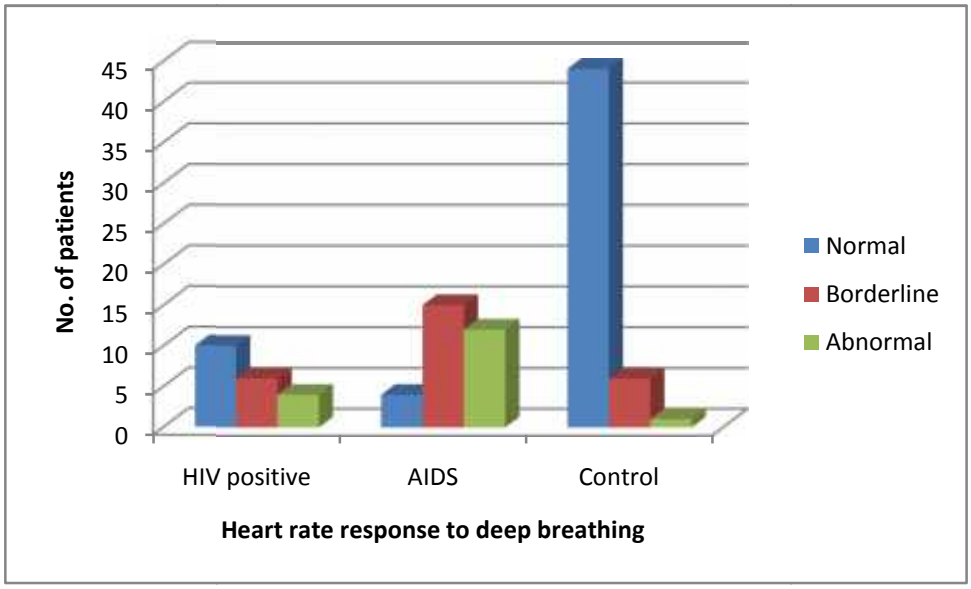


When the result of heart rate variation to standing was analyzed. It was found that there was significant differences between HIV positive with or without AIDS group and control group ($p < 0.001$). There was statistically significant difference between HIV positive without AIDS and HIV positive with AIDS group.($p=0.004$)

Table 16 : Showing analysis of heart rate response to deep breathing between HIV positive/AIDS and control group

Heart rate response to deep breathing	HIV without AIDS(20)	HIV with AIDS(31)	Total HIV with and without AIDS(51)	Control (51)
Normal	10(50%)	4(12.90%)	14(27.45%)	44(86.27%)
Borderline	6(30%)	15(48.38%)	21(41.17%)	6(11.76%)
Abnormal	4(20%)	12(38.70%)	16(31.37%)	1(1.96%)
Total	20(100%)	31(100%)	51(100%)	51(100%)

Graph 7 : Showing the analysis of heart rate response to deep breathing between HIV positive/AIDS in control group

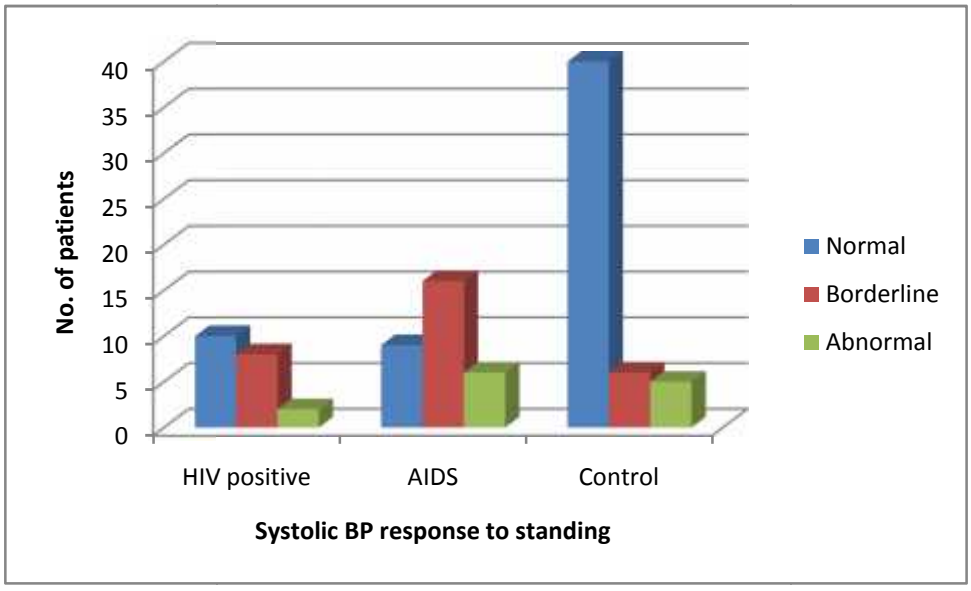


When the result of heart rate variation to deep breathing was analyzed. It was found that there was significant differences between HIV positive with or without AIDS and control group ($p< 0.001$). There was no statistically significant difference between HIV positive without AIDS and HIV positive with AIDS group.($p=0.015$)

Table 17 : Showing the analysis of systolic BP response to standing between HIV positive/AIDS and control group

Systolic BP response to standing	HIV without AIDS(20)	HIV with AIDS(31)	Total HIV with and without AIDS(51)	Control (51)
Normal	10(50%)	9(29.03%)	19(37.25%)	40(78.44%)
Borderline	8(40%)	16(51.61%)	24(47.1%)	6(11.76%)
Abnormal	2(10%)	6(19.35%)	8(15.65%)	5(9.80%)
Total	20(100%)	31(100%)	51(100%)	51(100%)

Graph 8 : Showing the analysis of systolic BP response to standing between HIV positive/AIDS and control group

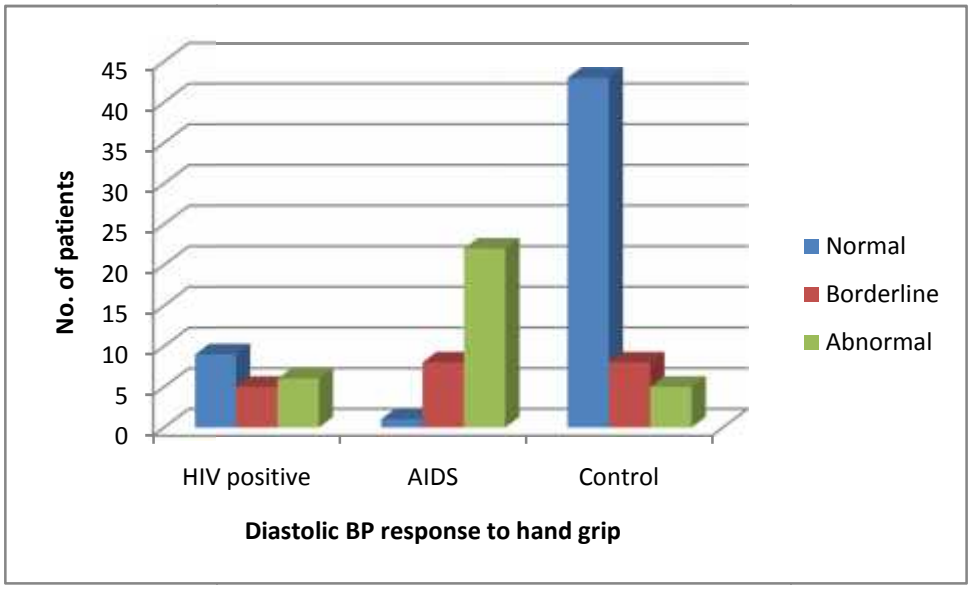


When the results of systolic BP response to standing was analyzed. It was found that there was significant differences between HIV with or without AIDS group and control group ($p < 0.001$). There was no statistically significant difference between HIV positive without AIDS and HIV positive with AIDS group.($p=0.292$)

Table 18 : Showing the analysis of diastolic BP response to sustained hand grip between HIV/AIDS and control group

Diastolic BP response to sustained hand grip	HIV without AIDS(20)	HIV with AIDS(31)	Total HIV with and without AIDS(51)	Control (51)
Normal	9(55%)	1(3.22%)	10(19.60%)	43(84.31%)
Borderline	5(25%)	8(25.80%)	13(25.49%)	8(15.6%)
Abnormal	6(30%)	22(70.96%)	28(54.90%)	-
Total	20(100%)	31(100%)	51(100%)	51(100%)

Graph 9 : Showing the analysis of diastolic BP response to sustained hand grip between HIV/AIDS and control group



When the results of diastolic BP response to sustained handgrip was analyzed. It was found that there was significant differences between HIV with or without AIDS group and control group ($p<0.0001$). There was no statistically significant difference between HIV positive without AIDS and HIV positive with AIDS group.($p=0.001$).

Table 19 : Comparative study of abnormal autonomic function between HIV positive group and control group

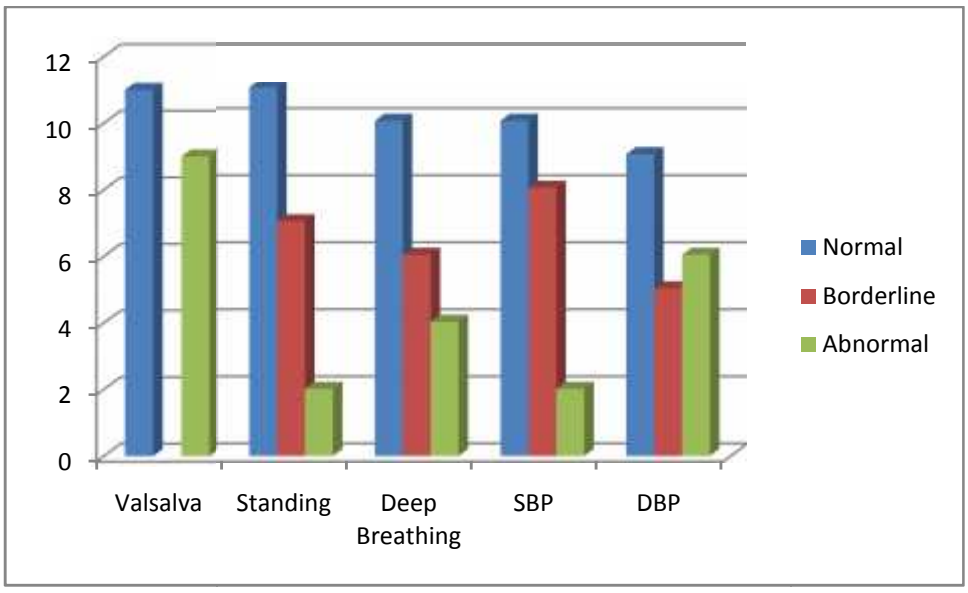
Cardiac Autonomic function test	HIV patients Group			Control group			p value
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal	
Valsalva	16 (31.38%)		35 (68.62%)	46 (90.16%)		5 (9.8%)	0.001
HR response to standing	15 (29.40%)	23 (45.10%)	13 (25.50%)	49 (96.07%)	2 (3.93%)	- -	<0.001
HR response to deep breathing	14 (27.45%)	21 (41.17%)	16 (31.37%)	44 (86.27%)	6 (11.76%)	1 (1.96%)	<0.001
SBP fall on standing	19 (37.35%)	24 (47.1%)	8 (15.65%)	40 (78.44%)	6 (11.76%)	5 (9.80%)	<0.001
DBP rise on hand grip	10 (19.60%)	13 (25.49%)	28 (54.90%)	43 (84.31%)	8 (15.6%)	- -	<0.001

The HIV positive group had statistically significant cardiac autonomic dysfunction compared to the control group. In all autonomic function tests, HIV positive patients had abnormal results compared to the control group.

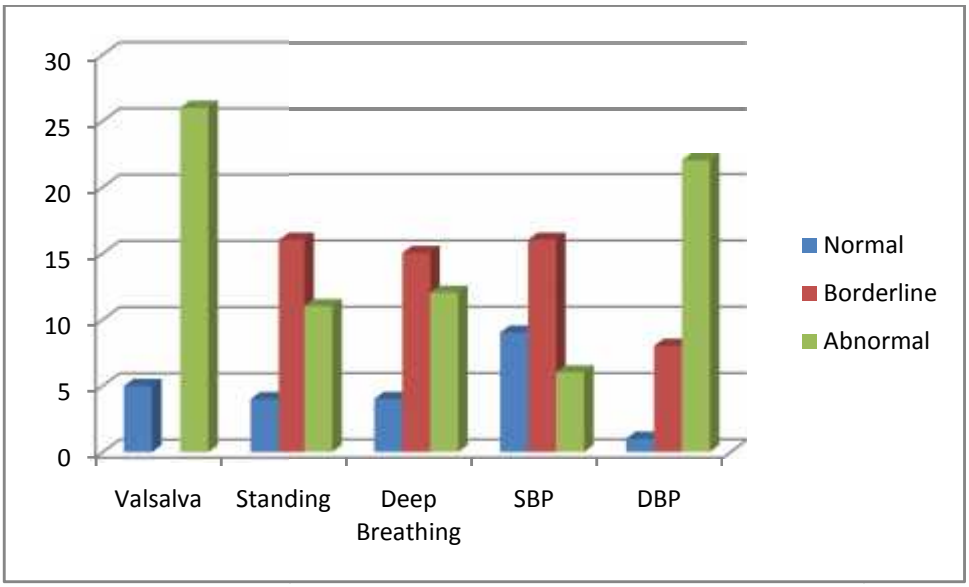
Table 20 : Comparative study of abnormal autonomic function between AIDS group and HIV positive group

Autonomic function test	HIV without AIDS			HIV with AIDS			P value
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal	
Valsalva	11 (55%)		9 (45%)	5 (16%)		26 (84%)	0.003
HR response to standing	11 (55%)	7 (35%)	2 (10%)	4 (12.9%)	16 (51.61%)	11 (35.4%)	0.004
HR response to deep breathing	10 (50%)	6 (30%)	4 (20%)	4 (12.9%)	15 (48.38%)	12 (38.70%)	0.015
SBP fall on standing	10 (50%)	8 (40%)	2 (10%)	9 (29.03%)	16 (51.61%)	6 (19.35%)	0.292
DBP rise on hand grip	9 (55%)	5 (25%)	6 (30%)	1 (3.22%)	8 (25.80%)	22 (7.96%)	0.001

Graph 10 : Showing study of abnormal autonomic function in HIV without AIDS group



Graph 11 : Showing study of abnormal autonomic function in HIV with AIDS group

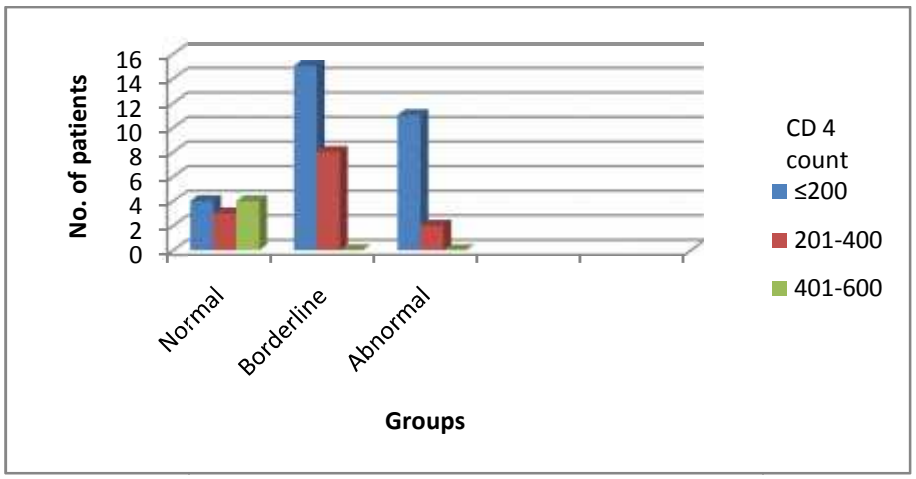


Only systolic BP response to standing and heart rate response to deep breathing was not statistically significant in AIDS group than the HIV positive without AIDS group.Rest of the parameters showed AIDS group having statistically significant results compared to HIV without AIDS group.

Table 21 : Showing frequency distribution of normal borderline, abnormal autonomic function between HIV positive, AIDS and control group

Result	CD4 cell count/µL				Total
	≤200	201-400	401-600	>600	
Normal	4(13.3%)	3(23.07%)	4(100%)	3(100%)	14(27.4%)
Borderline	15(50%)	8(61.5%)	0	0	23(45.09%)
Abnormal	11(36.6%)	2(15.38%)	0	0	13(25.49%)
Total	30(100%)	13(100%)	4(100%)	3(100%)	51(100%)

Graph 12 : Showing frequency distribution of normal borderline, abnormal autonomic function between HIV positive, AIDS and control group



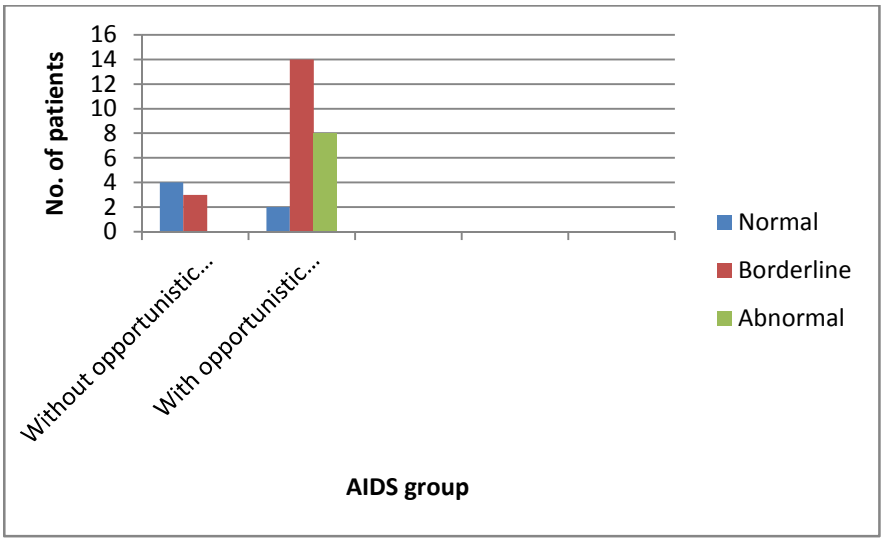
When the results of autonomic function tests was analyzed in HIV positive, AIDS and control group. It was found that autonomic function tests was abnormal in eight (32%), AIDS patients, but in only three (12%) HIV positive patients without AIDS.None of the HIV negative patients had abnormal function. Only two (8%), of 25 AIDS patients had completely normal autonomic function. More than 55% of HIV infected patients had borderline results. The results were statistically significant

($p < 0.001$).

Table 22 : Effect of opportunistic infections with autonomic dysfunction in AIDS patients

Results	AIDS		Total
	AIDS without Opportunistic infections	AIDS with Opportunistic infections	
Normal	4(57.14%)	2(8.34%)	6(19.35%)
Borderline	3(42.85%)	14(58.34%)	17(54.85%)
Abnormal	0	8(33.34%)	8(25.80%)
Total	7(100%)	24(100%)	31(100%)

Graph 13: Effect of opportunistic infections with autonomic dysfunction in AIDS patients



When the results of autonomic functions was analyzed in AIDS and AIDS with opportunistic infections. It was found that 25.80% of AIDS with opportunistic infections had abnormal results where as none of the AIDS patients without opportunistic infections had abnormal results. There was statistically significant correlation of effect of opportunistic infection on autonomic function. ($p<0.001$)

DISCUSSION

In this study conducted in Shri B.M. Patil Medical College Hospital and Research Centre Bijapur, fifty one HIV positive patients with or without AIDS were studied to evaluate the presence and extent of cardiac autonomic dysfunction and to correlate with levels of CD4 count. This study adds to the accumulating evidence that HIV affects autonomic nerves. It was observed in this study that there was evidence of substantial autonomic dysfunction in HIV patients compared with controls.

When the HIV patient group were further divided into HIV positive without AIDS and those with AIDS it was found that the latter group was having greater incidence of cardiac autonomic dysfunction. Incidence of cardiac autonomic nervous dysfunction increased with HIV disease progression.

When compared with similar studies, our findings corroborated with Nzuobontane et al. who reported a greater than 80%, and Becker et al. who found a 61.3% incidence of autonomic dysfunction compared to our finding of 50.98%. Rogsatadt et al. reported an incidence of 20%.

Table 23 : Occurrence of autonomic dysfunction

Study	Occurrence of Autonomic Dysfunction	
	HIV without AIDS	HIV with AIDS
Nzuobontane et al.(2002)	4%	80%
Rogsatadt et al.(1999)	14%	20%
Becker et al.(1997)	9.1%	61.3%
Present Study	43.14%	50.98%

Abnormal tests of cardiac autonomic dysfunction occurred at all levels of CD4 count but more number of abnormal results were found at a CD4 count of <200 cells/µL which was also the case with Rogsatadt et al. and Becker et al. All studies showed an increase in incidence of cardiac autonomic dysfunction as the CD4 count decreased.

Table 24 : Showing comparative study of correlation of CD4 level with autonomic dysfunction

Study	Mean CD4 count (cells /µL)	Maximum patients in CD4 range
Rogsatadt et al.	145.5	<300
Becker et al.	300	<100
Present Study	231	<200

All the studies had mean age of their participants ranging between 30 to 40 years.Most of those affected were in the age bracket of 26 to 35 years which is considered to the most economically productive group.In our study age group ranged from 17-60 years with mean age of 36.6 years.

Table 25 : Showing mean age with comparison to other studies

Study	Mean Age in years	
	Study group	Control group
Nzuobontane et al.(2002)	34	30
Rogsatadt et al.(1999)	38(26-58)	38.12 (26-60)
Mittal et al.(2004)	33±11	31±9
Present Study	36.60	35.35

As in most of the studies, our study showed a male preponderance with a male to female ratio of 12:5.Nzuobontane et al. had 7:4 ratio with Mittal et al. having 16:5. The higher incidence in male population can be attributed to increased travel and contact with multiple sexual partners compared to females of the region.

This study was based on the model of Nzuobontane et al. who studied autonomic dysfunction in HIV patients using cardiovascular autonomic function assessed by standard blood pressure and heart-rate tests. This study also found significant cardiac dysfunction in three of the five cardiac autonomic function tests. Nzuobontane et al. did not find statistically significant difference in cardiac dysfunction in heart response to deep breathing and standing tests whereas in our study systolic blood pressure response to standing and heart rate response to standing tests did not have statistically significant results when comparing HIV group without AIDS to the one with AIDS.

Table 26 : Showing the comparative studies (in percentage) of abnormal autonomic function test

	Nzuobontane et al. (2002)			Present Study		
	HIV without AIDS	HIV with AIDS	p value	HIV without AIDS	HIV with AIDS	p value
Valsalva ratio	23%	22%	< 0.01	45%	84%	0.003
HR response to deep breathing	22%	30%	NS	10%	35.4%	0.004
HR response to standing	23%	22%	NS	20%	38.70%	0.015
SBP response to standing	40%	31%	< 0.01	10%	19.35%	0.292
DBP response to handgrip	33%	27%	< 0.01	3%	7.96%	0.001

Table 27 : Showing comparative studies of frequency distribution of normal borderline and abnormal autonomic function.

Result	Present study		Nzuobontane et al.(2002)		Rogstadt et al.(1999)	
	HIV without AIDS	HIV with AIDS	HIV without AIDS	HIV with AIDS	HIV without AIDS	HIV with AIDS
Normal	10(52.63%)	4(12.5%)	1 (3.5%)	4(16.7%)	3 (30%)	1(7%)
Borderline	8(42.10%)	16(50%)	20(60%)	19(79.2%)	5 (50%)	12 (84%)
Abnormal	1(5.26%)	12(37.5%)	8 (27.6%)	1 (4.2%)	2 (20%)	2(14.1%)

37.5 % of AIDS group showed abnormal autonomic function compared to 4.2% and 14.1% of Nzuobontane et al. and Rogstadt et al. studies.

Maximum number of patients in the HIV without AIDS and AIDS group had borderline dysfunction in all studies.

In the present study unlike other studies we have included AIDS patients with opportunistic infections and those who are on ART to ascertain if the presence of opportunistic infection of ART had any effect on autonomic function patients with opportunistic infection like tuberculosis were known to have autonomic dysfunction owing to adrenalities and some of antiretroviral drugs are capable of causing autonomic neuropathy like stavudine, didanosine, zalcitabine.

Presence of opportunistic infection and therapy with ART has not shown significant effect on autonomic function.In HIV infected patients simple tests such as blood pressure responses to standing or handgrip can warn of cardiovascular autonomic dysfunction thus signaling the need for added precautions when invasive procedure are proposed.

CONCLUSION

This study found a significant cardiac autonomic dysfunction in HIV positive patients compared to general population. The severity of dysfunction increases with decrease in CD4 count. When HIV patients present with symptoms like dizziness and headache which can be present in many conditions, cardiac autonomic dysfunction should be first ruled out by performing simple cardiac autonomic dysfunction tests and resource consuming expensive tests must be performed later only if needed. In cases where invasive diagnostic or therapeutic tests are needed extra caution is needed. Anti retroviral therapy does not have any effect on cardiac autonomic dysfunction.

SUMMARY

- The study of cardiac autonomic dysfunction was carried out in 51 cases of HIV infection and 51 controls during the period of October 2012 and March 2014
- There were 20 HIV positive patients without AIDS and 31 HIV positive patients with AIDS and 51 controls.
- Age group ranged from 17-60 years with mean age of 36.6 years in the study group and 35.3 years in the control group. Majority of patients were in the age group of 26 to 35 years
- Male female ratio was 12:5
- The most common symptoms associated with autonomic dysfunction were dizziness and headache.The least presentation was blurred vision.
- The mean CD4 count was 231 cells/µL. Thirty one patients had CD4 count below 200 cells/µL.
- In HIV without AIDS group 45% patients had abnormal Valsalva response and 10% had abnormal heart rate response to deep breathing with 20% patients having abnormal heart rate response to standing. Ten percent had abnormal systolic blood pressure fall on standing and 3% had abnormal DBP response to sustained hand grip.
- In AIDS group 84% patients had abnormal Valsalva response and 35% had abnormal heart rate response to deep breathing with 38% patients having abnormal heart rate response to standing.Nineteen percent had abnormal systolic blood pressure fall on standing and 8% had abnormal DBP response to sustained hand grip.

- 37.5 % of AIDS group showed abnormal autonomic function compared to 5.6% of HIV positive patients without AIDS.
- Around 50% patients showed borderline autonomic dysfunction.
- Presence of opportunistic infection and therapy with ART has not shown significant effect on autonomic function.

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ANNEXURE I

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 18-10-2012 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Correlation of cardiac autonomic dysfunction with CD4 count in HIV patients"

Name of P.G. student Dr. Deepak Kadeli
Medicine

Name of Guide/Co-investigator Dr Sharanabasawappa Badiger
Prof of Medicine

DR.TEJASWINI VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE II

INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR- 586103

TITLE OF THE PROJECT: "CORRELATION OF CARDIAC AUTONOMIC DYSFUNCTION WITH CD4 COUNT IN HIV PATIENTS"

PRINCIPAL INVESTIGATOR - DR. DEEPAK KADELI
7406167025

P.G.GUIDE NAME - DR. BADIGER SHARANABASWAPPA
PROFESSOR OF MEDICINE
08352-262770, Ext-2148,2283

CHAIRMAN ETHICAL COMMITTEE DR A.A. NAIKWADI
PROFESSOR OF PHARMACOLOGY
9342355742

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to patients survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or

videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime. DR. DEEPAK KADELI is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr DEEPAK KADELI may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

DR. DEEPAK KADELI Date

(Investigator)

II) **STUDY SUBJECT CONSENT STATEMENT:**

I confirm that DR. DEEPAK KADELI has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE –III

BLDE'S SHRI B.M.PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE, BIJAPUR

"CORRELATION OF CARDIAC AUTONOMIC DYSFUNCTION WITH CD4 COUNT IN HIV PATIENTS"

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Residence:

Presenting complaints with duration:

History of present complaints:

Past History:

History of hypertension

History of diabetes mellitus

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits :

Smoking/Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes/beedis pack year smoked

Amount of tobacco chewed/snuff inhaled

Alcohol

Duration

Quantity/Frequency

Type

Sexual History

History of multiple sexual partners

Family History:

History of suggestive of Ischemic Heart Disease/hypertension diabetes mellitus

Treatment History :

General Physical Examination

Height : Weight :

Body Mass Index :

Vitals

PR:

BP:

RR:

Temp:

Hair :

Eyes :

Nose :

Ears :

Oral Cavity :

Neck :

Upper Limbs :

Chest :

Abdomen :

Genetilia :

Lower Limbs :

Skin

SYSTEMIC EXAMINATION.

- Respiratory System
- Cardiovascular System
- Central Nervous System
- Per abdomen

INVESTIGATIONS

Haematology –

Hemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

BIOCHEMISTRY–

Random blood sugar	
Blood Urea	
Serum creatinine	

URINE EXAMINATION -

Albumin	
Sugar	
Microscopy	

ECG in all leads

HIV spot test

ECHOCARDIOGRAPHIC FINDINGS :

CARDIAC AUTONOMIC FUNCTION TESTS

Sl no.	PARAMETERS		SCORE	PATIENTS SCORE
1	BP in Supine. BP Response to standing.	NORMAL ≤10 mm of Hg BORDERLINE 11-29 ABNORMAL ≥30	0 1 2	
2	BP at Rest. BP Response to handgrip.	NORMAL ≥16 mm of Hg BORDERLINE 11-15 ABNORMAL ≤10	0 1 2	
3	HR at Rest. Variation to deep breathing.	NORMAL ≥15 beats/min BORDERLINE 11-14 ABNORMAL ≤10	0 1 2	
4	HR Variation during standing (ratio)	NORMAL ≥1.04 BORDERLINE 1.01-1.03 ABNORMAL ≤1.00	0 1 2	
5	HR Variation to Valsalva (ratio)	NORMAL >1.21 ABNORMAL ≤1.21	0 2	

FINAL DIAGONOSIS

ANNEXURE IV

MASTER CHART

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	Sadashiv	30424	45	M	P	Y	N	Y	Y	Y	N	N	N	N	N	N	182	Y	141	60	110/70	70 /1.14/N	1.3 N	82	98 B	82 B	Y	Y	N
2	Bhimashankar	567	34	M	P	Y	N	Y	Y	Y	N	N	N	N	Y	N	398	N	162	86	100/70	90/1.04/N	1.16 B	92	96 N	74 A	N	Y	B
3	Kareppa	2089	37	M	P	Y	Y	Y	Y	Y	N	N	N	N	N	N	76	Y	60	90	110/70	92/1.02/B	1.07 A	100	90 N	84 A	Y	Y	A
4	Mahadevi	2119	32	F	P	Y	N	N	Y	Y	N	N	N	N	N	N	35	Y	89	84	114/86	84/1.00/A	1.09 A	90	86 A	88 A	Y	Y	A
5	Tarabai	2467	38	F	P	Y	N	N	N	Y	N	N	N	N	Y	N	62	Y	116	92	116/84	94/1.02/B	1.08 A	98	82 A	86 A	Y	Y	A
6	Siddu	3286	40	M	P	Y	N	N	Y	Y	N	N	N	N	Y	N	13	Y	161	86	118/70	88/1.02/B	1.09 A	98	92 B	82 B	Y	Y	A
7	Siddu	4070	52	M	P	Y	Y	N	N	Y	N	N	N	N	N	N	165	Y	232	86	90/70	88/1.02/B	1.11 B	98	86 N	72 A	Y	Y	B
8	Chandrashekar	4798	38	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	96	Y	126	86	116/72	88/1.02/B	1.02 A	92	68 A	80 B	Y	Y	A
9	Narsingh	12224	37	M	P	Y	N	Y	N	Y	N	N	N	N	N	N	356	N	166	80	100/70	84/1.05/N	1.12 B	92	96 N	88 N	N	Y	B
10	Shantabai	16205	40	F	P	Y	N	Y	Y	Y	N	N	N	N	N	N	187	N	80	92	116/84	92/1.00/A	1.08 A	98	112 N	86 A	Y	Y	A
11	Suresh	16102	24	M	P	Y	N	Y	Y	Y	N	N	N	N	N	N	14	Y	135	80	120/80	80/1.00/A	1.09 A	84	78 A	86 A	Y	Y	A
12	Sharada	16149	35	M	P	Y	N	Y	N	Y	N	N	N	N	N	N	353	N	80	84	114/80	90/1.12/N	1.15 B	90	110 N	100 N	N	Y	B
13	Sangappa	16319	41	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	40	Y	108	78	120/80	80/1.02/B	1.10 B	86	76 A	84 A	N	Y	B
14	Ranjana	17138	32	F	P	Y	N	N	Y	Y	N	N	N	N	Y	N	25	Y	85	72	90/60	80/1.11/N	1.08 A	78	70 B	72 B	Y	Y	A
15	Mahesh	17147	38	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	373	N	151	76	110/70	84/1.10/N	1.21 N	84	102 N	78 A	N	Y	N
16	Suresh	17777	34	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	18	Y	96	82	118/70	80/0.97/A	1.04 A	90	98 B	62 B	Y	Y	A
17	Chandrashekar	18054	40	M	P	Y	Y	N	Y	Y	N	N	N	N	N	N	198	Y	85	84	124/84	98/1.16/N	1.23 N	98	114 N	96 B	N	Y	N
18	Sunil	18282	42	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	180	Y	152	82	116/72	92/1.12/N	1.27 N	98	108 N	80 N	N	Y	N

19	Ahamad	18512	25	M	P	Y	Y	N	N	N	N	N	N	N	N	N	217	N	91	86	132/86	88/1.02/B	1.16 B	92	126 N	94 A	N	Y	B
20	Imran	18681	29	M	P	Y	Y	N	N	N	N	N	N	N	N	N	163	Y	173	88	126/88	90/1.02/B	1.16 B	98	104 B	94 A	N	Y	B
21	Basappa	18878	50	M	P	Y	N	Y	Y	N	N	N	N	N	N	N	128	Y	106	68	100/80	72/1.05/N	1.26 B	84	84 B	90 A	N	Y	B
22	Prakash	18652	32	M	P	Y	N	N	N	Y	Y	N	N	N	N	N	330	N	176	88	118/86	86/0.97/A	1.06 A	96	88 A	92 A	N	Y	A
23	Gouspak	19674	30	M	P	Y	N	Y	N	N	N	N	N	N	N	N	440	N	116	70	100/70	86/1.22/N	1.28 N	88	80 B	82 B	N	Y	N
24	Ramakka	20034	35	F	P	Y	N	N	Y	N	N	N	N	N	Y	N	490	N	102	82	110/80	96/1.17/N	1.26 N	98	102 N	98 N	N	Y	N
25	Parvati	20240	40	F	P	Y	N	N	N	Y	N	N	N	N	N	N	298	N	64	86	108/82	86/1.00/A	1.02 A	90	60 A	86 B	N	Y	A
26	Mallanagouda	19742	41	M	P	Y	N	Y	Y	Y	N	N	N	N	N	N	101	Y	183	84	120/84	82/1.02/B	1.13 B	90	106 B	96 B	Y	Y	B
27	Sahebgouda	20531	30	M	P	Y	N	N	Y	N	N	N	N	N	N	N	707	N	134	84	118/86	102/1.21/N	1.28 N	100	106 B	90 A	N	Y	N
28	Ramappa	20897	20	M	P	Y	N	N	N	Y	N	N	N	N	N	N	142	Y	142	88	122/80	90/1.02/B	1.14 B	98	100 B	86 A	Y	Y	B
29	Kashibai	20781	55	F	P	Y	N	N	N	N	N	N	N	N	N	N	100	Y	200	86	126/84	88/1.02/B	1.11 B	90	120 N	90 A	Y	Y	B
30	Jayashri	24150	25	F	P	Y	N	N	N	N	Y	N	N	N	Y	N	124	Y	196	74	128/86	72/0.97/A	1.16 B	80	116 B	90 A	Y	Y	B
31	Chandrashekar	24150	25	M	P	Y	N	N	N	N	N	N	N	N	Y	N	167	Y	256	80	130/80	82/1.02/B	1.18 B	84	120 N	86 A	Y	Y	B
32	Sukanya	24219	30	F	P	Y	N	N	N	N	N	N	N	N	N	N	155	Y	98	80	116/82	82/1.02/B	1.10 B	84	84 A	86 A	Y	Y	B
33	Shantappa	21913	33	M	P	Y	N	N	N	N	N	N	N	N	N	N	198	Y	88	82	138/86	96/1.20/N	1.24 N	100	118 B	92 A	Y	Y	N
34	Durgappa	21914	25	M	P	Y	Y	N	Y	N	N	N	N	N	N	N	133	Y	214	80	128/84	82/1.02/B	1.17 B	92	116 B	90 A	Y	Y	B
35	Shivappa	22000	45	M	P	Y	N	N	Y	N	N	N	N	N	N	N	151	Y	208	80	132/84	82/1.02/B	1.17 B	96	120 B	88 A	Y	Y	B
36	Parvatayya	22059	46	F	P	Y	N	N	N	N	N	Y	N	N	N	N	163	Y	124	70	100/70	72/1.01/B	1.20 B	82	90 N	80 A	Y	Y	B
37	Sangappa	25687	33	F	P	Y	Y	Y	N	N	N	N	N	N	N	N	25	Y	236	84	126/82	82/0.97/A	1.09 A	86	100 B	90 A	Y	Y	A
38	Laxmibai	26143	33	F	P	Y	N	N	N	N	N	N	N	N	Y	N	654	N	160	70	100/70	84/1.20/N	1.22 N	86	90 N	86 N	N	Y	N
39	Hanamawwa	21290	30	F	P	Y	N	N	N	N	N	N	N	Y	Y	Y	437	N	154	80	120/80	92/1.15/N	1.30 N	96	110 N	96 N	N	Y	N
40	Sanganna	27061	35	M	P	Y	N	N	Y	N	N	N	N	N	Y	N	382	N	80	84	126/72	88/1.05/N	1.22 N	96	114 A	90 N	N	Y	N
41	Ankush	27033	28	M	P	Y	N	N	N	N	N	N	N	N	Y	N	718	N	110	84	122/76	90/1.07/N	1.25 N	100	112 N	90 B	N	Y	N

42	Mallikarjun	26352	38	M	P	Y	N	N	Y	N	N	N	N	N	N	N	218	N	108	82	122/84	82/1.00/A	1.17 B	94	100 B	96 B	N	Y	B
43	Ramesh	27039	28	M	P	Y	N	Y	Y	N	N	N	N	N	N	N	775	N	178	84	126/80	98/1.16/N	1.21 N	100	116 N	96 N	N	Y	N
44	Basavaraj	27667	45	M	P	Y	N	Y	Y	N	N	N	N	N	N	N	290	N	105	62	110/70	68/1.09/N	1.15 B	76	98 B	82 B	N	Y	B
45	Anjali	27325	17	F	P	Y	N	N	N	N	N	N	N	N	N	N	36	Y	207	86	116/82	86/1.00/A	1.06 A	94	84 A	84 A	Y	Y	A
46	Sattewwa	27796	30	F	P	Y	N	Y	Y	N	N	N	N	N	N	N	243	N	98	78	122/84	80/1.02/B	1.15 B	88	110 B	90 A	N	Y	B
47	Channu	28490	40	M	P	Y	Y	N	N	N	N	N	N	N	N	N	276	N	294	84	126/82	90/1.7/B	1.11 B	98	114 B	90 A	N	Y	B
48	Ashok	27961	45	M	P	Y	N	N	Y	N	N	N	N	N	N	N	449	N	84	90	126/82	104/1.15/N	1.29 N	106	120 N	98 N	N	Y	N
49	Eranna	28181	28	M	P	Y	Y	N	N	N	N	N	N	N	N	N	26	Y	87	82	126/82	82/1.00/A	1.05 A	90	90 A	90 A	Y	Y	A
50	Shivappa	28692	60	M	P	Y	N	N	Y	Y	N	N	N	N	N	N	140	Y	118	92	126/82	104/1.13/N	1.10 B	106	108 B	94 B	Y	Y	B
51	Bapugouda	25279	25	M	P	Y	N	Y	Y	Y	N	N	N	N	N	N	140	Y	96	86	126/80	86/1.0/A	1.11 B	98	114 B	90 A	Y	Y	B

KEY TO MASTER CHART

1. Sl. No

2. Name

3. IP No./OP No.

4. Age

5. SexM- Male, F-Female

6. HIV status P positive, N Negative

7. Weight lost ≥10% of body weight

8. Chronic diarrhea for more than 1 month

9. Chronic cough for more than 1 month

10. Prolonged fever for more than 1 month

11. Weakness/tiredness – Y/N

12. Dizziness on standing – Y/N

13. GIT symptoms – Y/N

14. Palpation – Y/N

15. Blurred vision – Y/N

16. Headache – Y/N

17. Micturition disturbances – Y/N

18. CD4 count

19. AIDS positive- Y/N

20. Random blood sugar

21. Resting heart rate

22. Blood pressure

23. Heart rate response to standing

24. Valsalva ratio

25. Heart rate response to deep breathing

26. Systolic BP response to standing

27. Diastolic BP response to persistent hand grip

28. AIDS – patients with opportunistic infection

29. AIDS with ART

30. Results SC –Score: N- Normal, B-Borderline, A – Abnormal