# STUDY OF CARDIAC ABNORMALITIES IN HIV PATIENTS AND THEIR CORRELATION WITH CD4 COUNT

**DISSERTATION SUBMITTED FOR**

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**DR.M.G.R. MEDICAL UNIVERSITY**

**CHENNAI**

## CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled**"STUDY OF CARDIAC ABNORMALITIES IN HIV PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"** is the bonafide work of **Dr G.CHINNA MARIAPPAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015.**

**Captain.Dr.B.SANTHAKUMAR ,**

**M.Sc(F.Sc), M.D(F.M)., PGDMLE., Dip.N.B (F.M) .,**

THE DEAN ,

Madurai Medical College and

Government Rajaji Hospital,

Madurai.

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**DR. S.VADIVEL MURUGAN,M.D.,**

Professor and HOD,

Department Of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai.

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**DR.G.BAGIALAKSHMI.M.D.,**

Professor of Medicine ,

Department Of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai.

## DECLARATION

I **Dr.CHINNA MARIAPPAN** declare that, I carried out this work on**"STUDY OF CARDIAC ABNORMALITIES IN HIV PATIENTS AND THEIR CORRELATION WITH CD4 COUNT"** at the Department of Medicine, Govt. Rajaji Hospital during the period APRIL 2014 to August 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine

**Place :** Madurai **Dr.G.CHINNA MARIAPPAN**

**Date:**

## ACKNOWLEDGEMENTS

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## ABBREVIATIONS

| | |
|---|---|
| HIV | Human Immunodeficiency Virus |
| AIDS | Acquired Immunodeficiency Syndrome |
| PLHA | People Living With HIV and AIDS |
| HAART | Highly Active Antiretroviral Therapy |
| PCP | Pneumocystis carrnii Pneumonia |
| OIs | Opportunistic Infections |
| DCM | Dilated cardiomyopathy |
| CDC | Centre for Disease Control |
| WHO | World Health Organisation |
| ELISA | Enzyme Linked Immunosorbent Assay |
| Cart | Combibation antiretroviral therapy |
| CD4 | Cluster of Differentiation 4 |
| RWMA | Regional wall motion abnormality |
| CRF | Circulating Recombinant Forms |
| HAD | HIV associated dementia |
| EBV | Epstein barr virus |
| CMV | Cytomegalovirus |
| PHT | Pulmonary hypertersion |
| HIVAN | HIV associated nephropathy |

## CONTENTS

ABSTRACT

INTRODUCTION

Human immunodeficiency virus is a retrovirus that affects all systems in the body.Among this cardiovascular disease is one of the leading causes of non HIV related death in HIV patients.

Although many cardiovascular complications have been described like pulmonary hypertension, systemic hypertension, infective endocarditis and accelerated atherosclerosis in HIV patients,the most common complications include diastolic dysfunction, left ventricular systolic dysfunction ,pericardial effusion, dilated cardiomyopathy and coronary artery disease.

As the disease progresses the CD4 count declines which increases the cardiovascular complications leading to death. So echocardiographic screening should be performed in all HIV patients with low CD4 count for early detection and management of the complications.

**AIMS AND OBJECTIVES**

1.To assess the cardiac abnormalities such as systlolic dysfunction, diastolic dysfunction, dilated cardiomyopathy, coronary artery disease, pulmonary

hypertension and infective endocarditis and their correlation with CD4 count.

2.To evaluate whether this parameter can be used as prognostic marker of disease progression in HIV patients

## MATERIALS AND METHODS

### STUDY POPULATION :

This study was conducted among 200 HIV positive patients coming to ART centre, Govt.Rajaji Hospital, Madurai.

### STUDY PROTOCOL

Cases were classified as HIV patients into four groups depending upon the CD4 cell count >500 ( stage1),CD4 cell count 200 – 500 (stage 2), and 50-200(stage 3) and <50 (stage 4). CD4 count, ECG and Echocardiogrram were done in all the participants of the study.

### RESULTS

In this study pericardial effusion was the most common finding and was present in 15% of the study population, followed by systolic dysfunction(13%),diastolic dysfunction (11.5%) and dilated cardiomyopathy (9%) and all were statistically significant.All cardiac abnormalities were present in patients in stage 3&4 with low CD4 count (<200/microlitre)

## CONCLUSION

Cardiovascular abnormalities are more common and predictable complications in late stages of HIV infection.So all HIV patients with low CD4 count(<200/microlitre) should be screened for cardiac abnormalities.Early diagnosis and management of these complications is associated with increased survival rates and clinical outcomes in HIV patients.

# INTRODUCTION

Human immunodeficiency virus is a retrovirus that affects all systems in the body.Among this cardiovascular disease is one of the leading causes of non HIV related death in HIV patients. Risk factors for cardiovascular disease in HIV patients include traditional risk factors, chronic inflammation associated with HIV infection and metabolic effects of antiretroviral therapy. HIV infection itself is a independent risk factor for cardiovascular diseases.

HIV infection increases the production of various cytokines which are toxic to myocytes and thereby increases the risk of cardiovascular complications. HIV infection induced endothelial dysfunction and vasculitis are also playing an important role in pathogenesis of these complications.

Although many cardiovascular complications have been described like pulmonary hypertension, systemic hypertension, infective endocarditis and accelerated atherosclerosis in HIV patients,the most common complications include diastolic dysfunction, left ventricular systolic dysfunction ,pericardial effusion, dilated cardiomyopathy and coronary artery disease. Rapid onset congestive heart failure leads to death in HIV patients within 6 to 12 months of diagnosis.

As the disease progresses the CD4 count declines which increases the cardiovascular complications leading to death. So echocardiographic

screening should be performed in all HIV patients with low CD4 count for early detection and management of the complications.

This study was conducted to study the prevalence of cardiac complications in HIV patients and their correlation with CD4 count.

# AIMS AND OBJECTIVES

1. To assess the cardiac abnormalities such as systlolic dysfunction, diastolic dysfunction, dilated cardiomyopathy, coronary artery disease, pulmonary hypertension and infective endocarditis and their correlation with CD4 count.

2. To evaluate whether this parameter can be used as prognostic marker of disease progression in HIV patients.

# REVIEW OF LITERATURE

## HISTORY AND PROBLEM STATEMENT

AIDS(Acquired immunodeficiency syndrome), recognised as an emerging disease in early 1980s and has evolved from a mysterious illness to a global pandemic which has infected tens of million in less than twenty years. In 1981, AIDS was recognised in US and HIV virus was isolated from a patient with lymphadenopathy and it was determined that HIV was the causative agent for AIDS.

In the year 2007, it was estimated that around 33 million people are living with HIV in the world. And 2.4 million people are living with HIV in India.

According to estimates by World health organisation at the end of 2013, 35 million people were living with HIV and around 11.7 million people had access to antiretroviral therapy in low and middle income countries. Over 28 million people are eligible for antiretroviral therapy, under WHO.

# TYPES OF HIV EPIDEMICS

WHO and UNAIDS define the different types of HIV epidemics as follows.

| | |
|---|---|
| Low level epidemics | HIV prevalence has not consistently exceeded more than 5% in any defined subpopulation |
| Concentrated epidemics | HIV prevalence has consistently exceeded more than 5% in atleast one subpopulation but < 1% in pregnant women. |
| Generalised HIV in epidemics | HIV prevalence has consistently exceeded more than 5% in any defined subpopulation and > 1% in pregnant women. |

HIV PREVALENCE STATEMENT IN (SEAR) COUNTRIES,2007

| COUNTRY | ESTIMATED NUMBER OF PLHA | PERCENTAGE OF ADULT POPULATION INFECTED WITH HIV |
|---|---|---|
| BANGLADESH | 12,000 | <0.1% |
| BHUTAN | <500 | <0.1% |
| INDIA | 24,00,000 | 0.3% |
| INDONESIA | 2,70,000 | 0.2% |
| MALDIVES | <100 | 0.1% |
| MYANMAR | 2,40,000 | 0.7% |
| NEPAL | 70,000 | 0.5% |
| SRILANKA | 3,800 | <0.1% |
| THAILAND | 6,10,000 | 1.4 |

# HIV PREVALENCE IN INDIA

Based on the sentinel surveilliance data,HIV prevalence classified into three groups.

GROUP I – HIGH PREVALENCE STATES

>5% in high risk groups and 1% or > 1% in pregnant women

-Tamilnadu, Maharastra, Karnataka,

-Andhrapradesh, Manipur, Nagaland.

GROUP II - MODERATE PREVALENCE STATES

>5% in high risk groups and <1% in pregnant women

- Gujarat,Goa, Pondicherry.

GROUP III - LOW PREVALENCE STATES

<5% in high risk groups and <1% in pregnant women

-Remaining states.

## DEFINITION AND CLASSIFICATION

The current CDC(Center for disease control and prevention) classified the HIV infected person based on clinical condition and CD4 cell count .

HIV patient is said to have AIDS when the CD4 count <200/microlitre irrespective of presence of signs, symptoms and opportunistic infections.

| CD4+ T cell count (per μL) | Category A – asymptomatic/ acute HIV/ PGL | Category B – symptomatic | Category C – AIDS indicators |
|---|---|---|---|
| >500 | A1 | B1 | C1 |
| 200 – 400 | A2 | B2 | C2 |
| <200 | A3 | B3 | C3 |

CATEGORY A : consists of patients with one or more of the following conditions , but conditions enumerated under category B or C must not have occurred. These include :

| |
|---|
| Asymptomatic HIV infection |
| Generalised lymphadenopathy (present persistently) |
| Acute HIV infection with associated illness or history of acute HIV infection. |

CATEGORY B: consists of patients with one or more of the following conditions, but those under category C must not have occurred plus the condition is related to HIV or defect in cell mediated immunity. These include[11] :

| |
|---|
| ❖ Bacillary angiomatosis |
| ❖ Oral thrush |
| ❖ Vulvovaginal candidiasis recurrent/ non responsive to treatment |
| ❖ Cervical dysplasia/ carcinoma in situ |
| ❖ Fever/ diarrhoea > 1 month |
| ❖ Oral hairy leukoplakia |

| |
|---|
| ❖ >1 episode/ >1 dermatome – Herpes zoster |
| ❖ Idiopathic thrombocytopenic purpura |
| ❖ Listeria infection |
| ❖ PID like tubo ovarian abscess |
| ❖ Peripheral neuropathy |

Category c-AIDS defining illness

| |
|---|
| ❖ Invasive candidiasis (esophagus, trachea, lung or bronchi) |
| ❖ Invasive cervical malignancy |
| ❖ Coccidioidomycosis |
| ❖ Cryptococcosis |
| ❖ Chronic intestinal Cryptosporidiosis / Isospora infection |
| ❖ CMV retinitis |
| ❖ HIV encephalopathy |
| ❖ Herpes simplex infections ( bronchitis, pneumonia, esophagitis) |
| ❖ Histoplasmosis |
| ❖ Kaposi sarcoma |
| ❖ Primary CNS lymphoma |
| ❖ Burkitt's lymphoma |

| |
|---|
| ❖ Pulmonary or extrapulmonary TB |
| ❖ Mycobacterium Avium Complex infection |
| ❖ Pneumocystis carinii pneumonia |
| ❖ Progressive multifocal leukoencephalopathy (PML) |
| ❖ CNS toxoplasmosis |
| ❖ AIDS cachexia |
| ❖ Recurrent pneumonia/ Salmonella sepsis |

# HIV VIRUS

HIV virus is classified under the family of retroviridae and subfamily of lentivirus.Two subtypes of HIV virus have been identified. HIV 1 is the most common subtype in worldwide.HIV virus is easily killed by heat and it is readily inactivated by either,acetone,ethanol 20% and betapropionolactone. It is relatively resistant to ionizing radiation and UV light

## MORPHOLOGY

Spherical in shape and enveloped virus

90-120nm in size

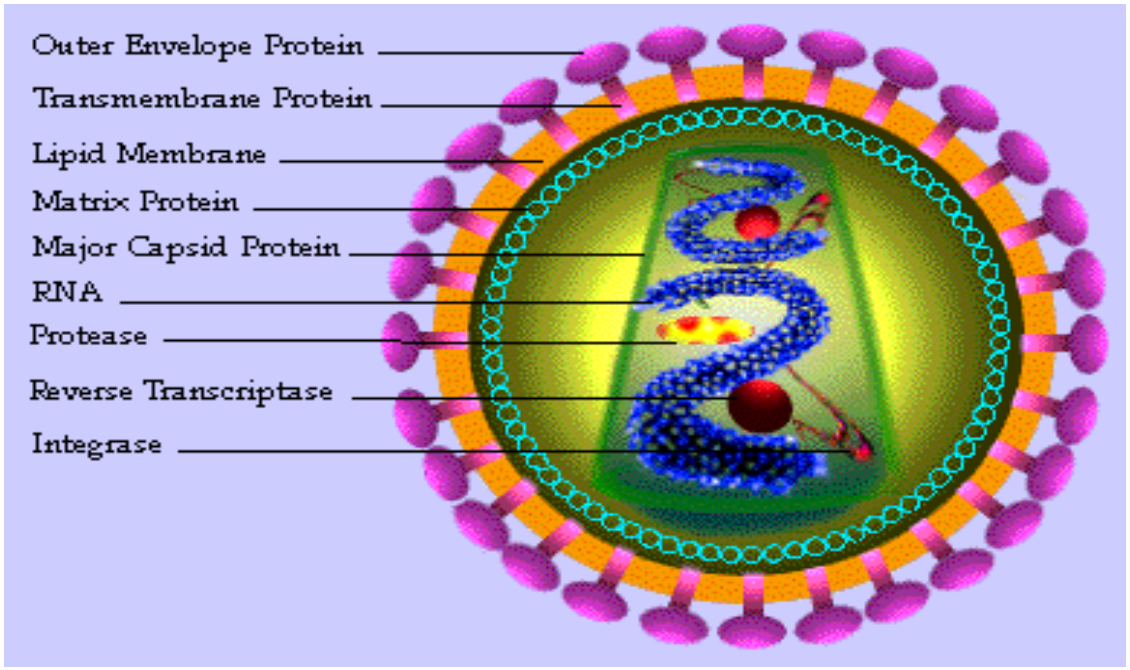
Genome contains two identical single strandard +one RNA copy and Reverse transcriptase

Three structural genes –gag,pol and env

Non-structural and regulatory genes

tat,nef,rev,vif,vpu,vpr.

STRUCTURE OF THE HIV VIRUS

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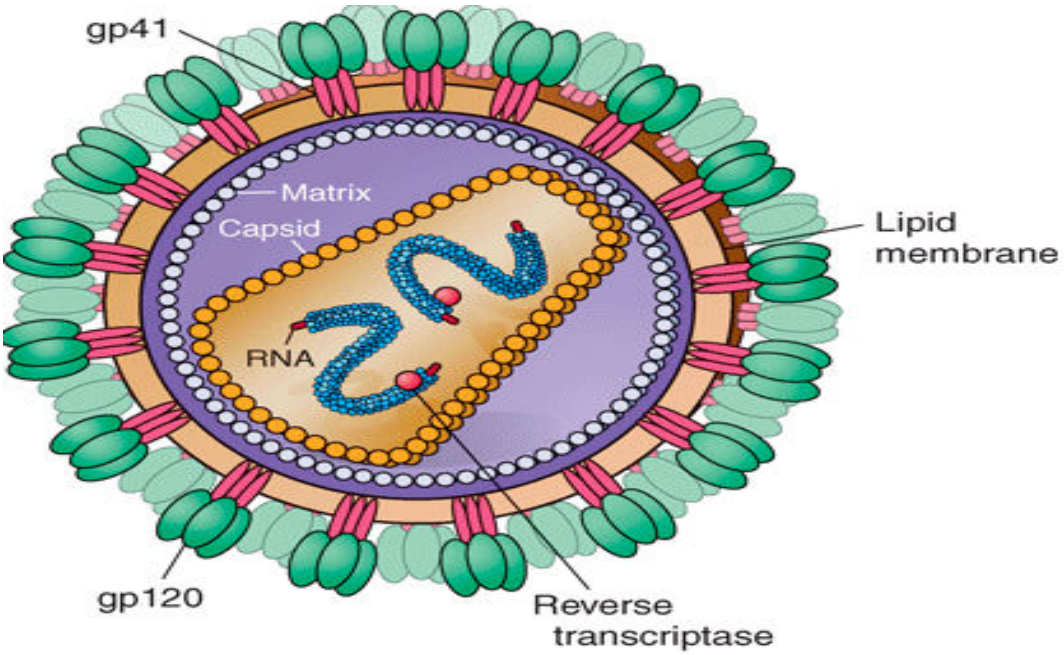



B

MAJOR ANTIGENS OF HIV

A. Envelope antigens - 1.spike antigen –gp120

2.transmembrane pedicle Ag-gp41

B. Shell antigen - Nucleocapsid protein p18

C. core antigens

1.principal core antigen p24

2.other core antigens-p15,p55

D. Polymembrane antigens-p31,p51,p66

| GENE | FUNCTION |
|---|---|
| gag | Core of virion (incuding p24 antigen) |
| pol | Protease, reverse transcriptase and integrase enzymes |
| Env | Envelope glycoproteins |
| tat, rev, nef, vif, vpr, vpu | Regulates viral gene replication and host cell modification to enhance viral growth |

## GROUPS

- 4 groups - group M (major), group O (outlier),group N and group P
- Group M is further subclassified into subtypes. Includes 9 subtypes : A, B, C, D, F, G, H, J and K
- Sometimes patients are infected with more than one subtype which recombine to give rise to CRFs (circulating recombinant forms). Examples include , CRF01_AE and CRF02_AG
- Subtype A and F are further sub classified into sub – sub – types such as A1, A2 and F1, F2.
- The geographic distribution of these different strains is widely distributed.A, B, C, D, G and CRF01_AE,CRF_AG are by far the common strains globally.While subtype C is the most prevalent strain.
- There are numerous implications to this genetic diversity such as :

1. Wide diversity (subtypes, circulating recombinant forms)
2. Continuous viral evolution
3. Different rates of disease progression
4. Varied response to therapy &
5. Development of resistance
6. Inability to develop vaccine against wide range of strains

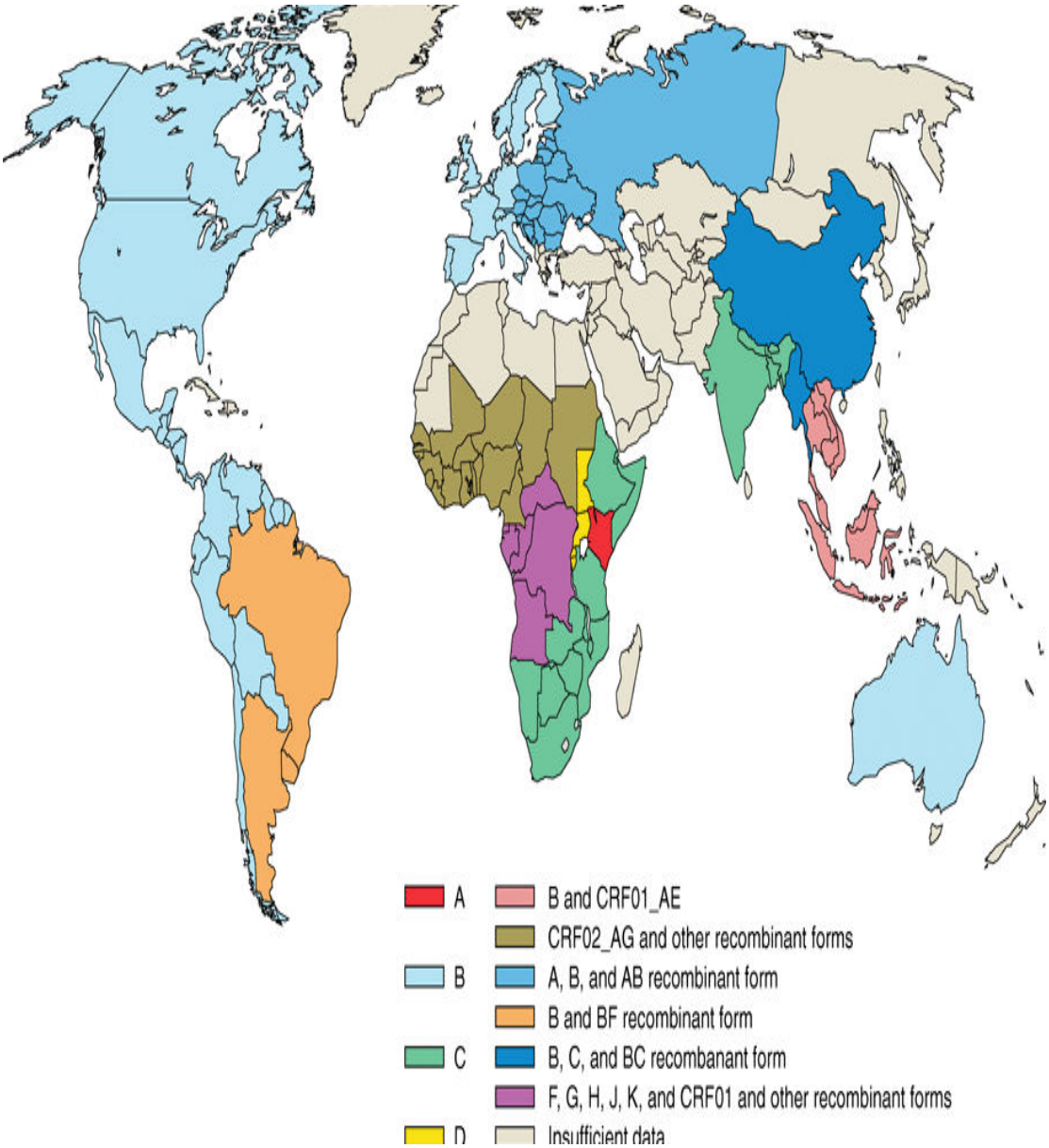
GEOGRAPHIC DISTRIBUTION OF HIV &SUBTYPES

| | | |
|---|---|---|
| 1. | Sub-Saharan Africa | Subtype C (most common)<br>Subtype B and G, CRFO2_AG |
| 2. | India | Subtype C |
| 3. | China | Subtypes B, C and<br>BC recombinant forms |
| 3. | Southeast Asia | CRF01_AE |
| 4. | North America and some parts of South America | Subtype B |
| 5. | Australia | Subtype B |
| 6. | Western Europe | Subtype B |
| 7. | Eastern Europe | Subtype A,B and<br>AB recombinant forms |

New emerging strains:

| | |
|---|---|
| Thai B. Indian C. | southern China* |
| CRF03_AB | Former soviet union |
| CRF14_BG | Spain* Portugal* |
| BF recombinant forms | South America |
| CRF35_AD | Afghanistan and Iran* |

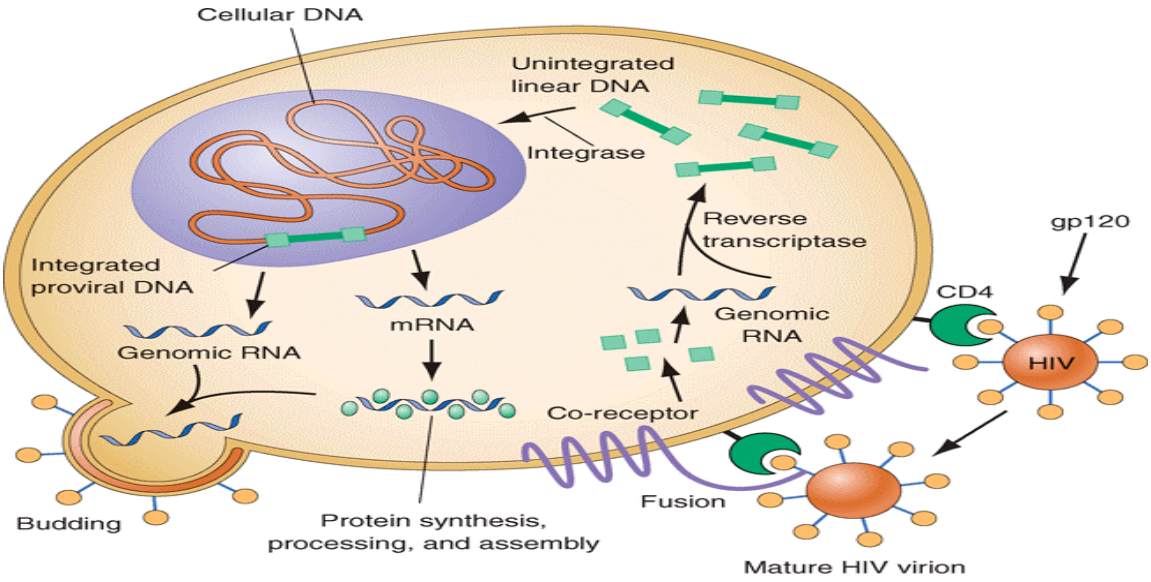
GEOGRAPHIC DISTRIBUTION OF HIV &SUBTYPES



# REPLICATION CYCLE

HIV virus enters into the body through blood or tissues of infected person. After entering the virus binds with host cell (CD4 lymphocyte) by using the envelope antigens gp120 and gp41.Binding of HIV to the host cell can also be mediated by the HIV coreceptors CXCR4(for Tcell trophic HIV strains) and CCR5(for macrophage trophic strains).

After the fusion of HIV with the host cell membrane HIV genome is uncoated and internalised into the cell.Then the virus reverse transcriptase mediates the transcription of HIV RNA into double strandard DNA which is incorporated into the host cell genome which leads to formation of proviruses.

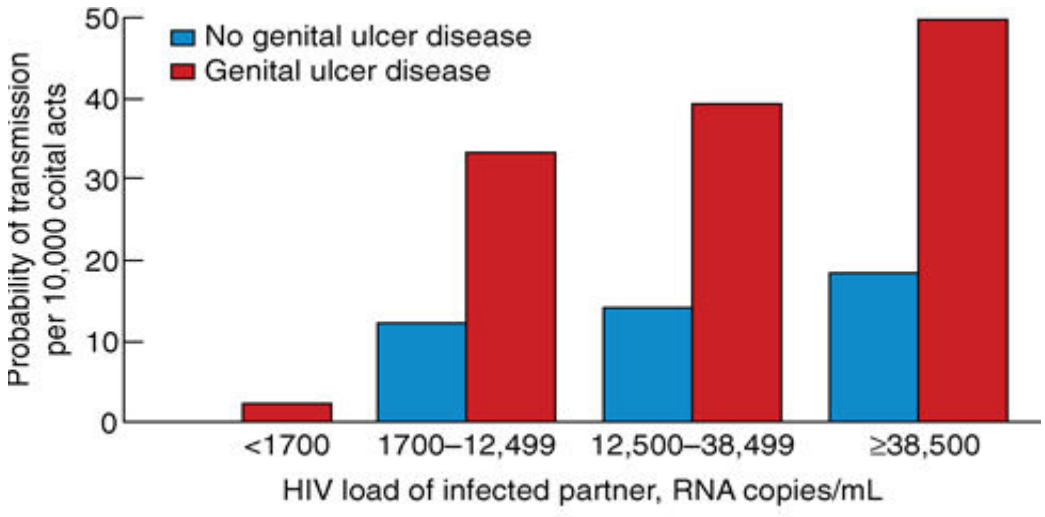


TRANSMISSION OF HIV

HIV can be transmitted through sexual,blood and blood products and maternal-fetal transmission.

SEXUAL TRANSMISSION

- Can be through homosexual or heterosexual route
- Male to female transmission rate is higher than female to male transmission rate .Increased risk of heterosexual transmission in the presence of genital ulcer.



- Unprotected receptive anal intercourse increased the rate of transmission because of thin fragile rectal mucous membrane.
- Oral sex is associated with decreased risk of HIV transmission compare to vaginal and anal sex .
- Uncircumcised males are more prone to develop HIV infection because of the foreskin contains plenty of langerhan cells , CD4 T cells and macrophages which are the targets of HIV

## TRANSMISSION BY BLOOD AND BLOOD PRODUCTS

The first case of HIV infection transmitted through the blood products was reported in 1982. HIV virus can be transmitted by transfusion of contaminated white blood cells, platelets and clotting factors.

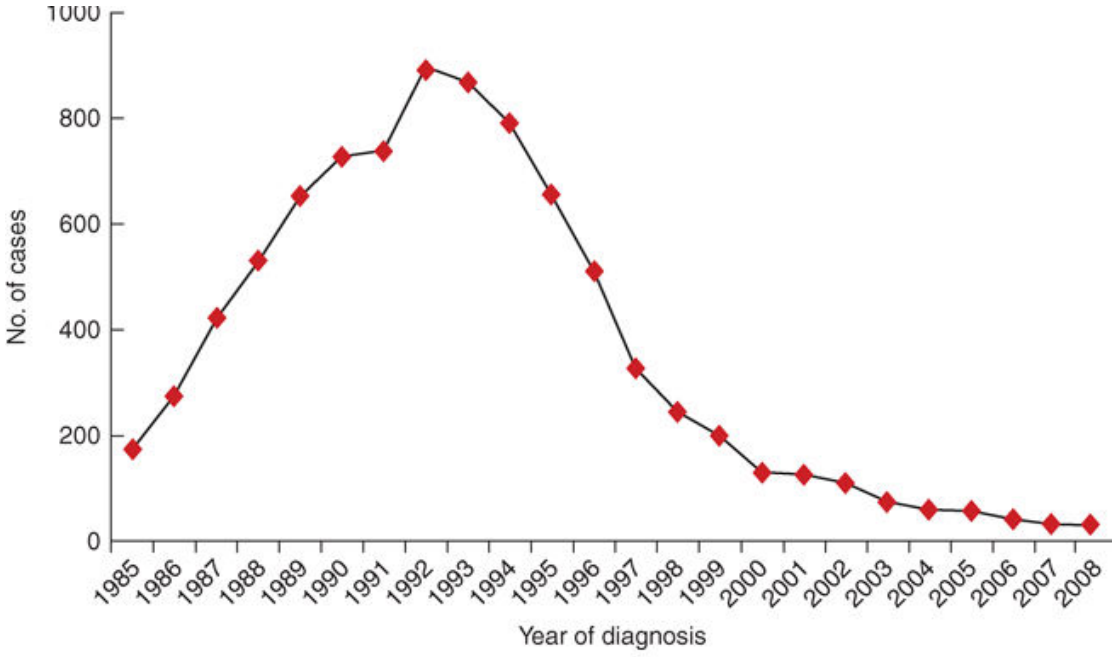
Transfusion of hyperimmune gammaglobulin ,hepatitisB Ig,HepB vaccine and Rh Ig will not transmit the infection.Any skin piercing including injection ,ear pricking,tattoing and acupuncture can also transmit the infection.

MOTHER TO FETUS/INFANT TRANSMISSION

- Maternal to fetus transmission occurs during pregnancy,during delivery and by breast feeding
- Low maternal CD4 count is associated with high rate of transmission
- Prolonged second stage of labour also increase the risk of HIV transmission

In the absence of prophylactic ART to the mother during pregnancy, risk of mother to fetus transmission is around 10% to 25% in industrialised countries, 20% to 25% in developing countries.With prophylactic ART, rate of transmission decreases by 5%.

Graph showing the number of perinatally acquired cases in children



## TRANSMISSION BY OTHER BODY FLUIDS

- Saliva contains so many antiviral factors such as IgA , IgG And IGM mucins , thrombospondin 1, secretory lecukocyte protease inhibitor(SLPI) which inhibits the replication of HIV and increases the clearance by the host.
- Transmission of HIV by human bite is very rare.
- Exposure to body fluids such as sweat, urine and tears will not transmit the HIV infection

## MODES OF HIV TRANSMISSION

| | |
|---|---|
| SEXUAL ROUTE | 87% |
| MOTHER TO CHILD | 5% |
| BLOOD AND BLOOD PRODUCTS | 2% |
| INJECTION DRUG USE | 2% |
| UNKNOWN | 4% |

## CLINICAL FEATURES OF HIV INFECTION

AIDS ( Acquired immuno deficiency syndrome) is a fatal illness characterised by multisystem involvement and development of various opportunistic infections leading to death

Clinical manifestation of HIV infection have been classified into 3 broad categories

1. Acute HIV syndrome
2. Asymptomatic stage
3. Symptomatic disease

## ACUTE HIV SYNDROME

Around 50% to 70% of the individuals will develop acute HIV infection after 3 to 6 weeks of primary infection. Most common manifestations include fever, pharyngitis, headache, nausea, vomiting and diarrhoea. Symptoms will persist for several weeks and gradually subside. Neurology and dermatologic manifestations also occur in acute HIV syndrome

Systemic symptoms:

Cutaneous manifestations 1.Mucocutaneous ulcer

2.Erythematous maculopapular rash

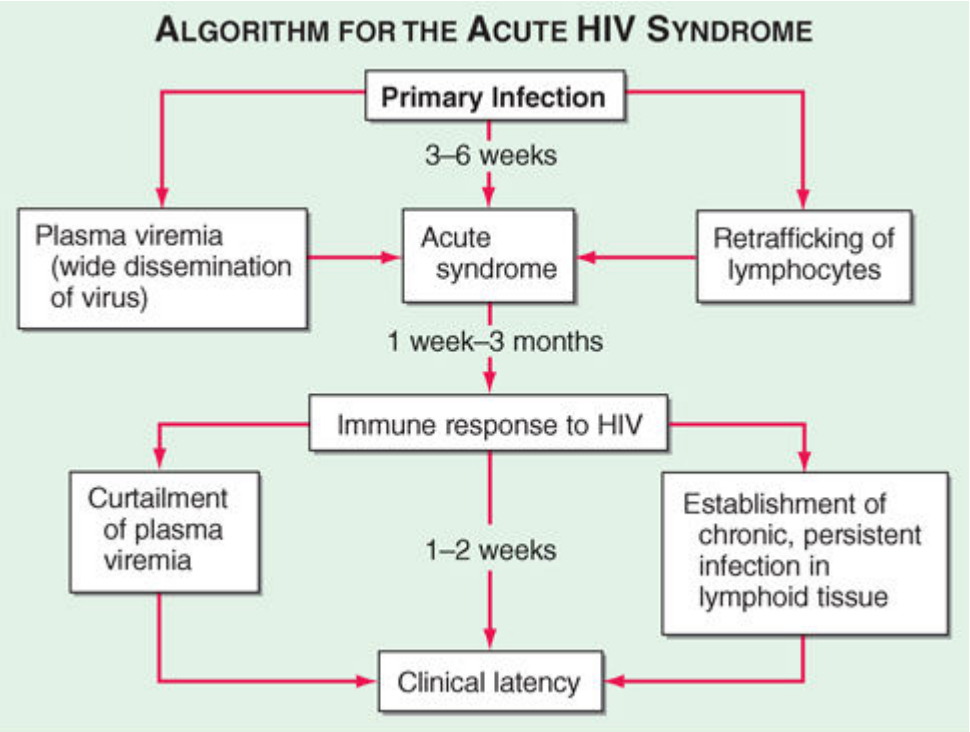
| | |
|---|---|
| Fever | Pharyngitis |
| Myalgia | Arthralgia |
| Weight loss | Nausea |
| Vomiting | Diarrhea |
| Headache | Retro orbital pain |
| Lymphadenopathy | |

Neurological manifestations:

| | |
|---|---|
| Encephalitis | Aseptic meningitis |
| Acute transverse myelitis | Peripheral neuropathy |
| Acute demyelinating Encephalomyelitis | |

Approximately around 10% of HIV patients will have fulminant course even after the disappearance of signs and symptoms.

If antiretroviral therapy (ART) is initiated during the acute HIV infection, small percentage of patients may revert to a negative ELISA test. But after discontinuation of the treatment rapidly they will reseroconvert to positive test.

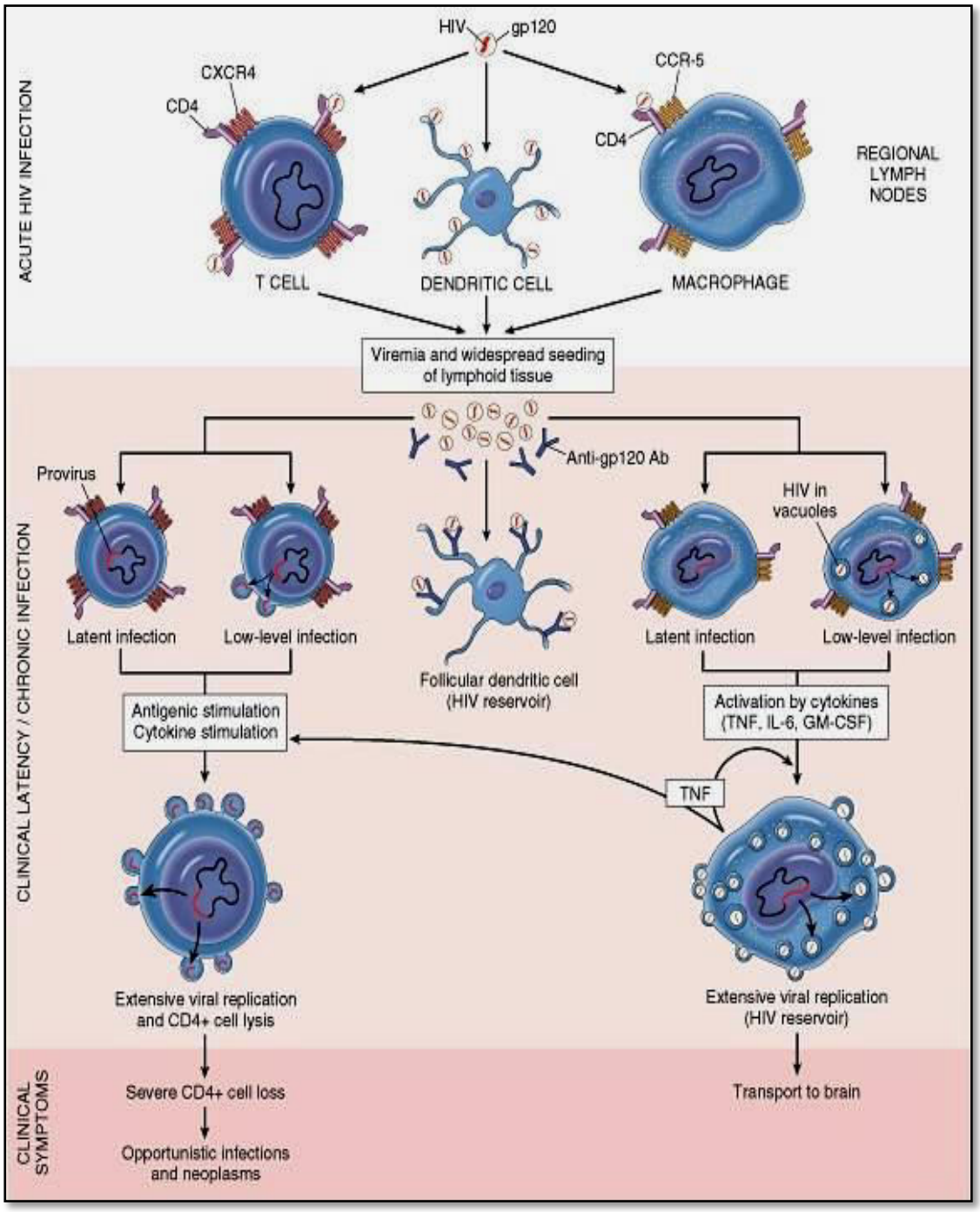



## ASYMPTOMATIC STAGE

During the asymptomatic stage antibodies to HIV is present in the serum but no signs and symptomps of the disease. Duration of the asymptomatic stage varies from months to years.During this period rate of fall of CD4 count is 50/microlitre/year.

## SYMPTOMATIC DISEASE

During the course of illness, signs and symptoms appear at any stage of illness.Symptoms depends upon the rate of fall of CD4 count.As the CD4 count decreases,opportunistic infection increases leading to fatal complications.




NATURAL HISTORY OF THE DISEASE IN HIV INFECTION

## RESPIRATORY SYSTEM INVOLVEMENT

Most common manifestation of pulmonary disease is pneumonia. HIV patients have six fold increase in incidence of pneumococcal pneumonia.Pneumocysti carini pneumonia occurs in patients with CD4 count <200/microlitre.Classical chest xray finding is dense perihilar infiltrate which is unusual in HIV patients.

Mycobacterium avium complex infection is seen in patients with CD4 count<50/microlitre.Fungal infections can also cause pneumonia in HIV patients. Two forms of Idiopathic pneumonia(Lymphoid interstitial pneumonia &Nonspecific interstitial pneumonia) have been recognized and are seen in 1% of adult HIV patients.It is due to polyclonal activation of lymphocytes.Transbronchial biopsy is diagnostic in 50% of cases and the disease is usually self limited.

Sinus infection is also common in HIV patients .Maxillary sinus is most commonly involved.Common organisms causing sinusitis in HIV infection are H.influenza and Staph aureus. Fungal infection like mucormycosis in HIV infection progresses very slowly and responds to amphotericinB

## DISEASE OF OROPHARYNX AND GIT

Gastrointestinal manifestations in HIV infections are most commonly due to secondary infections , Kaposi sarcomas, and lymphomas. And they occur in patients with CD 4 count <300 /micro litre. Most common oral infections include thrush,hairy leukoplakia and aphthous ulcers.

Oesophagitis in HIV is due to Candida,CMV,HSV Infections. HSV ulcers are usually multiple while CMV ulcer is usually solitary. Achlorhydria is also common in HIV infection but other gastric problems are rare.

Diarrheal illness in HIV is caused by bacterial infections like Salmonella, Shigella and Campylobacter spp, fungal infections like Penicillosis , Histoplasmosis,Coccididomycosis,and Parasitic infections such as Cryptosporidia,Microspora &Isospora belli.

CMV colitis was one of the common manifestations in pre ART era, but after the introduction of ART its incidence have been decreased. Patients with gastro intestinal manifestations should be screened for ophthalmic evaluation for CMV retinitis.

Some patients with HIV infections may develop a chronic diarrheal syndrome called AIDS or HIV enteropathy for which no cause other than HIV infection can be identified. Rectal lesions due to reactivation of herpes simplex are also more common in HIV infection.

## DISEASES OF KIDNEY & GENITOURINARY SYSTEM

Diseases of genitourinary system are due to direct consequences of HIV infection or due to neoplasm or opportunistic infections or drug toxicities. HIV associated nephropathy (HIVAN) can be an early manifestation of HIV infection. Proteinuria is the most common finding in this disorder. Renal biopsy is diagnostic of HIVAN.

Drug causing renal toxicities in HIV infection are Amphotericin, pentamidine,adefovir,cidofovir and foscarnet. Renal stones are caused by Indinavir in 10% of cases.Condylomata lata a form of secondary syphilis most commonly seen in HIV patients.

Vulvovaginal candidiasis is common problem in females with HIV infections and symptoms include pruritus and dysuria. Microscopic examination of vaginal discharge for psuedohyphae in 10% KOH. Fluconazole is used in treatment of severe form of disease.

## RHEUMATOLOGIC & IMMUNOLOGICAL DISEASES :

Drug allergies are the most common significant allergic reactions occurring in around 65% of patients receiving Trimethoprim-Sulphamethoxazole for pneumocystitis carnii pneumonia.

Anaphylaxis in HIV is usually rare due to ART except Abacavir which can cause fatal allergic reactions. HLA B-57 strongly associated with allergic reactions due to abacavir.

The one auto immune disease that occur in increased frequency in HIV Infections is a variant of Primary Sjogren's syndrome in which salivary gland is infiltrated with CD8 T cells. In Sjogren's syndrome CD4 T cell infiltrates are more prominent.

Reactive arthritis also occurs in one third of HIV patients and well responds to standard therapy. HIV or AIDS associated arthropathy is characterised by sub acute oligo arthritis developing over a period of over one to six weeks and lasting for six weeks to six months. It usually involves large joints.

Another type of arthritis also called as painful articular syndrome which involves the large joints and affects 10% of AIDS patients, presenting as a acute severe sharp pain in the affected joint. It affects primarily the knee,elbow & ankle joints and lasts for 2-24 hours.

In very few patients some rare clinical manifestations like leucocytoclastic vasculitis, CNS angiitis and polymyositis have been reported.

DERMATOLOGICAL MANIFESTATIONS:

Dermatological manifestations occurs in around 10% of HIV patients .It will vary from simple skin rash to cutaneous malignancies. The most common non neoplastic problems are seborrheic dermatitis, folliculitis and opportunistic infections .

Seborrheic dermatitis occurs in around 50% OF HIV patients and causative organism is Pityrosporum ovale.Folliculitis is the next most prevalent dermatological abnormalities seen in 20% of HIV patients.

Reactivation of Herpes zoster is seen in 10 -20% of HIV patients. This reactivation syndrome of varicella-zoster virus indicates a modest decline in immune function and may be the first indication of clinical immunodeficiency.. The clinical manifestations of reactivation zoster in HIV-infected patients, although indicative of immunologic compromise, are not as severe as those seen in other immunodeficient conditions.

Thus, while lesions may extend over several dermatomes, involve the spinal cord, and/or be associated with frank cutaneous dissemination, visceral involvement has not been reported. In contrast to patients without a known underlying immunodeficiency state, patients with HIV infection tend to have recurrences of zoster with a relapse rate of 20%.Valacyclovir, acyclovir or famciclovir is the treatment of choice. Foscarnet may be of value

in patients with acyclovir-resistant virus. Infections with HSV is associated with recurrent oro labial genital and peri anal lesions as a part of recurrent reactivation syndrome.

Allergic reactions like steven johnson syndrome, toxic epidermal necrolysis can occur in HIV infections due to sulpha drugs and abacavir and protease inhibitor like ambrenavir, darunavir, fosamprenavir and tipranavir. Zidovudine therapy is associated with elongation of the eye lashes and bluish discoloration of the nails and they are more common in American and African patients.

Other rare cutaneous problems include eosinophilic pustular folliculitis, icthyosis and psoriasis.

## HEPATOBILIARY MANIFESTATIONS.

HCV infection is more common and 10 fold increase of death in HIV infection when compared to general population.Granulomatous hepatitis is one of the worst complication seen in HIV patients and the causative organisms are mycobacterium avium complex and fungal infections.

Hepatic mass also caused by tuberculosis,pertussis,hepatitis or fungal infections like C.immitis and H.capsulatum may be seen and in HIV patients.Nucleoside reverse transcriptors also cause hepatitis which is fulminant in some patients.Indinavir can also cause hyperbilirubinemia.

Pentamidine and didanosine are the important causes of pancreatitis in HIV patients.Biliary tract disease-papillary stenosis and sclerosing cholangitis have also been reported in HIV patients.

## DISEASES OF ENDOCRINE SYSTEM AND METABOLIC DISORDERS

HIV lipodystrophy is a common metabolic problem in patients receiving Antiretro viral therapy and develops in 30-75% of patients.It can develop anytime from 6 weeks to several years after initiation of ART.

Characteristic features of lipodystrophy are

- Increased total cholesterol,
- Increased triglycerides,
- Increased apolipoprotein B,
- Hyperinsulinemia,
- Hyperglycemia and
- Fat redistribution -truncal obesity&peripheral wasting.

Next to lipodystrophy the other common metabolic abnormality in HIV patients is hyponatremia .The important causes include syndrome of inappropriate antidiuretic hormone secretion (SIADH)due to pulmonary and CNS lesion,due to adrenal gland involvement by HIV infection itself and by CMV,cryptococcosis and histoplasmosis and due to drug toxicity by Antiretroviral therapy.

Thyroid gland is most common gland involved in HIV infection and the most common abnormality is subclinical hypothyroidism.Grave's disease can also occur 9 to 48 months after initiation of HAART.

Around 50% of HIV patients develops hypogonadism and erectile dysfunction.Testicular dysfunction can also be due to ganciclovir therapy. Avascular necrosis of hip and shoulder,osteoporosis have also been developed in HIV infection.

## DISEASE OF HEMATOPOIETIC SYSTEM

Hematolgical abnormalities seen in HIV infection include anemia,leukopenia,thrombocytopenia which may be due to HIV infection, nutritional, drug induced, secondary infections and neoplasms.Zidovudine and dapsone are two drugs most commonly associated with anemia.

In some patients generalised lymphadenopathy may be the first presentation.Monoclonal gammapathy of unknown significance(MGUS) have been reported in 3% of HIV infection.

Thrombocytopenia in HIV infection may be due to associated HCV infection, cirrhosis and thrombotic thrombocytopenic purpura. Incidence of venous thromboembolism in HIV infection is 1% per year. Causes of bone marrow suppression in HIV patients include infections like mycobacterium , fungus, parvovirus B19 and lymphomas and drugs like zidovudine, dapsone, ganciclovir , interferon alpha, trimethoprim sulfmethoxazole , pyrimethamine and foscarnet

The incidence of venous thromboembolic disease such as deep-vein thrombosis or pulmonary embolus is approximately 1% per year in patients with HIV infection. This is approximately 10 times higher than that seen in an age-matched population.

Among the factors associated with clinical thrombosis are age over 45, history of an opportunistic infection, lower CD4 count, and estrogen use. Abnormalities of the coagulation cascade including decreased protein S activity, increase in factor VIII, anticardiolipin antibodies, or lupus-like anticoagulant have been reported in more than 50% of patients with HIV infection. The clinical significance of this increased propensity toward thromboembolic disease is likely reflected in the observation that elevations in d-dimer are strongly associated with all-cause mortality in patients with HIV infection.

OCULAR MANIFESTATIONS(50%)

Ocular manifestations occur in 50% of patients in late stage of HIV infection.Cotton wool spots are the most common fundus finding and these are due to retinal ischemia.

CMV retinitis is one of the dangerous ophthalmic complication of HIV infection and occurs in patients with CD4 count <100/microlitre.So all patients with CD4 count <100/microlitre ophthalmic screening for CMV retinitis should be done.

Acute retinal necrosis syndrome or progressive outer retinal necrosis is a rapidly progressing bilateral necrotizing retinitis and the patient may present with keratitis and iritis.It is most often associated with HSV or

varicella infection.Syphilitic uveitis and kaposi sarcoma of eyelids and conjunctiva are rarely seen in HIV infection.

NEUROLOGICAL MANIFESTATIONS

Neurological problems in HIV infection is due to direct consequence of the virus or secondary to opportunistic infections like toxoplasmosis ,cryptococcosis,CMV infection or mycobacterial infection.

Cryptococci neoformans is the most common cause of meningitis in HIV infection cccurs in patients with CD4 count less than 100/microlitre.Diagnosis is confirmed by identification of organism in CSF by Indian ink examination.

HIV associated dementia may be initial AIDS defining illness in 3% of cases.Around 25% of patients with HIV infection will develop clinically significant encephalopathy in late stages of HIV infection and it progresses slowly over months.It should be diagnosed after ruling out the other causes of encephalopathy.A major feature of this entity is the development of dementia, defined as a decline in cognitive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty in reading, or increased difficulty in performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue.

In contrast to "cortical" dementia (such as Alzheimer's disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a "subcortical dementia" characterized by defects in short-term memory and executive function.

In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence.

Behavioral problems include apathy, irritability, and lack of initiative, with progression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This is in contrast to the finding of somnolence in patients with dementia due to toxic/metabolic encephalopathies

The precise cause of HIV-associated dementia remains unclear,although the condition is thought to be a result of a combination of direct effects of HIV on the CNS and associated immune activation.

Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harbouring virus in the CNS. Histologically,

the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor, language, and judgment are most severely affected.

Combination antiretroviral therapy is of benefit in patients with HIV-associated dementia. Improvement in neuropsychiatric test scores has been noted for both adult and pediatric patients treated with antiretrovirals. The rapid improvement in cognitive function noted with the initiation of cART suggests that at least some component of this problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects.Therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully.

Seizures may be initial manifestion in some patients with HIV infection. The seizure threshold is often lower in patients with advanced HIV infection due to the presence of electrolyte abnormalities.

Causes of Seizures in Patients with HIV Infection

| |
|---|
| ❖ HIV encephalopathy |
| ❖ Cerebral toxoplasmosis |
| ❖ Cryptococcal meningitis |
| ❖ Primary central nervous system lymphoma |
| ❖ Progressive multifocal leukoencephalopathy |

Spinal cord disease is seen in 20% of patients with HIV infection.Three main types of spinal cord disease are vacuolar myelopathy, pure sensory ataxia,&paresthesia/dysesthesia. Other neurological manifestations present in HIV infection are progressive multifocal leukoencephalopathy, primary CNS lymphoma,kaposi sarcoma,aseptic meningitis, peripheral neuropathy(AIDP&CIDP) and myopathy.

# WASTING SYNDROME IN HIV INFECTION

Generalised wasting is an AIDS-defining condition; it is defined as involuntary weight loss of >10% associated with intermittent or constant fever and chronic diarrhea or fatigue lasting >30 days in the absence of a defined cause other than rarely seen today with the earlier initiation of antiretrovirals.

A constant feature of this syndrome is severe muscle wasting with scattered myofiber degeneration and occasional evidence of myositis. Glucocorticoids may be of some benefit; however, this approach must be carefully weighed against the risk of compounding the immunodeficiency of HIV infection. Androgenic steroids, growth hormone, and total parenteral nutrition have been used as therapeutic interventions with variable success.

## IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

In some patients following inititation of ART , paradoxical worsening of preexisting , untreated or partially treated opportunistic infections occur due to Type 4 hypersensitive reactions. This is known as immune reconstitution inflammatory syndrome (IRIS). Signs and symptoms may appear at any time from two weeks to two years after initiation of ART and the symptoms include fever, localised lymphadenitis, pulmonary infiltrates, uveitis, sarcoidosis, grave's disease and raised ICT. It can be fatal in few patients and steroids can be used in treatment of IRIS.

## CHARACTERISTICS OF IRIS

- Paradoxical worsening of the clinical condition following initiation of ART.
- Occurs weeks to months following initiation of ART.
- Most common in patients starting therapy with CD4 count <50/microlitre
- Frequently seen in patients with tuberculosis.
- Can be fatal.

OPPORTUNISTIC INFECTIONS IN HIV INFECTION IN RELATION TO CD4 COUNT

CD4 Count < 500 / microlitre :

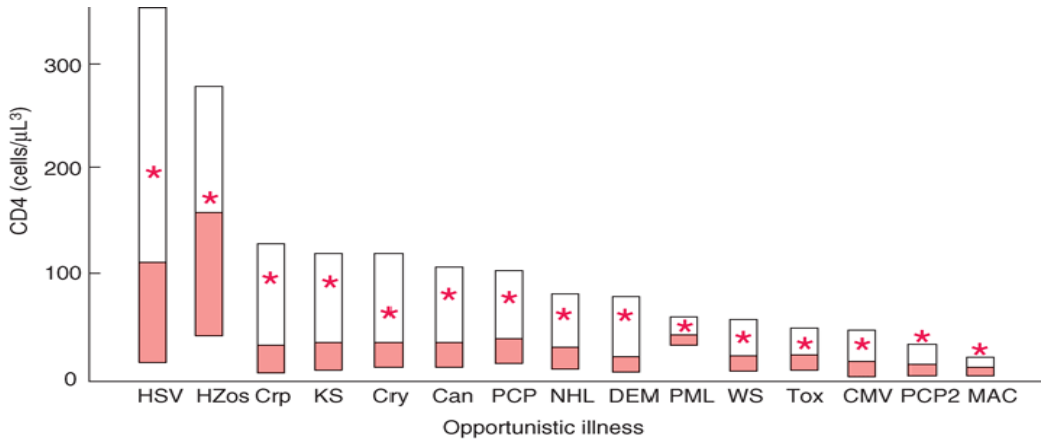
- Bacterial infections like TB,Herpes simplex
- Herpes Zoster,Vaginal Candidiasis
- Hairy leukoplakia,Kaposi sarcoma

CD4 Count <200 / microlitre :

- Pneumocystosis,Toxoplasmosis
- Coccidiomycosis,Cryptosporidiosis

CD4 Count < 50 / microlitre :

- Disseminated MAC infection,Histoplasmosis
- CMV Retinitis,CNS Lymphoma



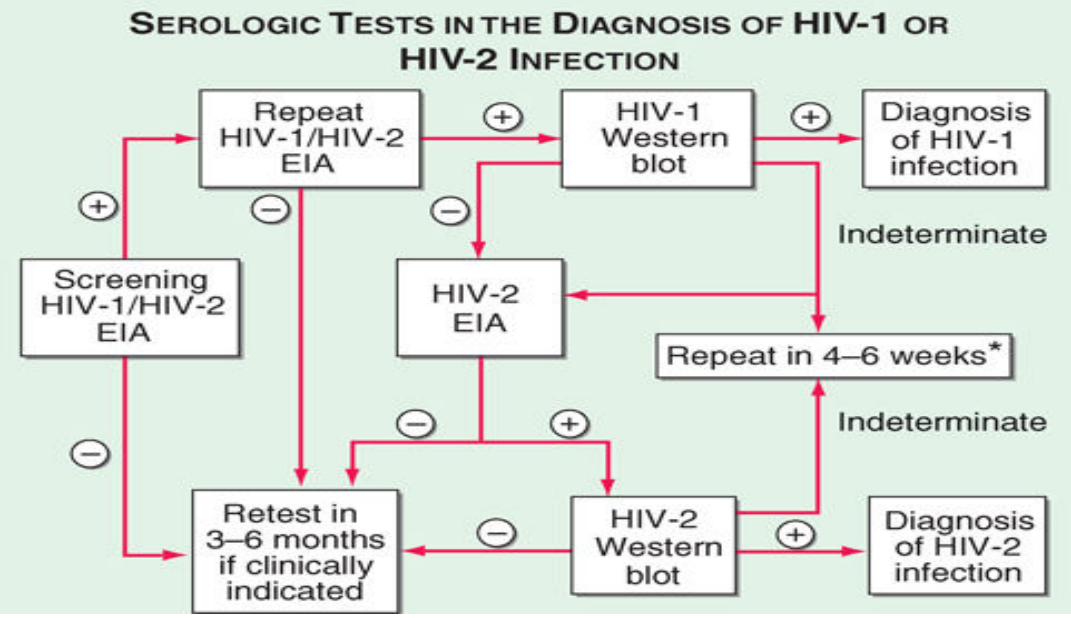
LABORATORY DIAGNOSIS OF HIV INFECTION

Diagnosis of HIV infection based on demonstration of antibodies to virus or direct demonstration of HIV or one of its components .Antibodies to HIV in the blood appears generally 3-12 weeks of infection .

ELISA(ENZYME LINKED IMMUNOSORBENT ASSAY) TEST

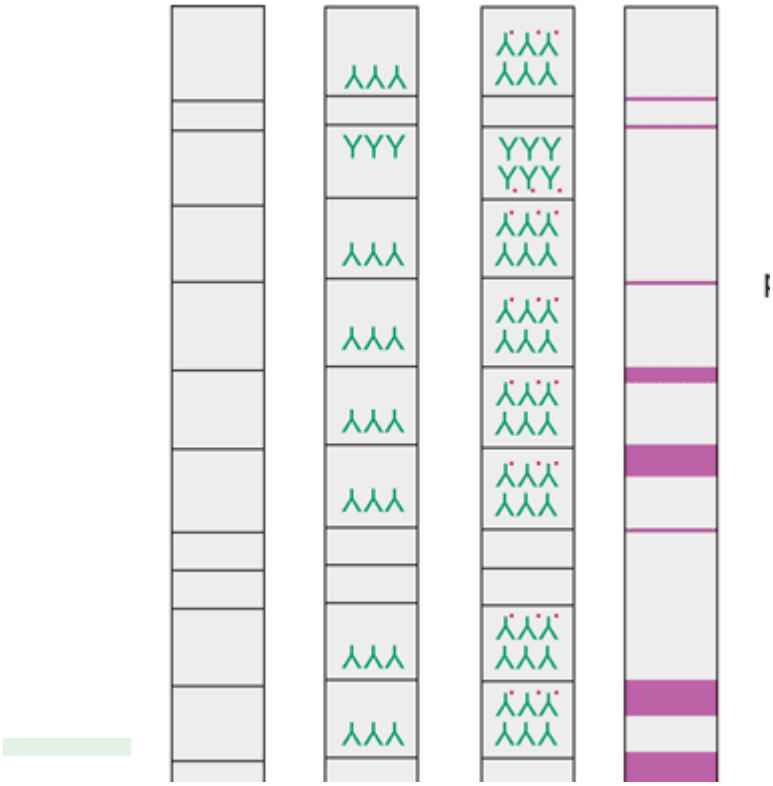
It is the best screening test for HIV infection.This test is also known as enzyme immunoassay.Results of this test is graded as positive(highly reactive), intermediate (partially reactive) and negative (nonreactive).

If results are intermediate it should be repeated within 4-6 wks ELISA test is positive usually within 22 days of infection.



WESTERN BLOT TEST

This is a highly specific test for detection of HIV infection.It is based on detection of specific antibody to viral core protein p24 and envelope glycoprotein p41. Results of this test is also graded as positive(highly reactive),intermediate (partially reactive) and negative (nonreactive). If results are intermediate it should be repeated within 4-6 weeks



WESTERN BLOT TEST

## TESTS FOR DIRECT DETECION OF HIV COMPONENTS

Following laboratory tests are used for direct detection of HIV and its components.

1.p24 capture assay-Positive in 50% of patients; detects down to 15 pg/mL of p24 protein

2.HIV RNA detection by PCR- Reliable to 40 copies/mL of HIV RNA

3. HIV RNA detection by bDNA- Reliable to 50 copies/mL of HIV RNA

4.HIV RNA detection by NASBA(Nucleic Acid Sequence Based Amplification)- Reliable to 80 copies/mL of HIV RNA

## TESTS FOR MONITORING OF PATIENTS WITH HIV INFECTION

1.CD4 T cell count

2.HIV RNA estimation

3.Complete blood count

4.HIV resistance testing

5.Co-receptor tropism arrays.

6.Beta2 microglobulin

## PRINCIPLES OF MANAGEMENT OF HIV INFECTION

Various guidelines have been described in the management of HIV infection.Treatment plan should be based on plasma CD4 count and HIV RNA level.Main goal of treatment should be aimed at suppression of viral replication.

Most effective therapy for HIV infection is combination ART.All pregnant women should be treated with ART to reduce to the materno-fetal transmission.cART will not cure the disease,but prolong the life and quality of HIV patients.

1. Ongoing HIV replication leads to immune system damage and progression to AIDS.

2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.

3. Rates of disease progression differ among individuals, and treatment decisions should be individualized based on plasma HIV RNA levels and CD4+ T cell counts.

4. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.

5. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents that the patient has already received.

6. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.

7. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the patient.

8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.

9.Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the patient to be compliant.

# INITIAL EVALUATION OF PATIENT WITH HIV INFECTION

- History&Physical examination
- Complete hemogram
- Liver and renal function tests
- Blood sugar&Lipid profile
- CD4 count
- HIV RNA level
- Screening for Hepatitis A,B&C,syphilis&tuberculosis
- Pretest counseling

## INDICATIONS FOR INITIATION FOR ANTIRETROVIRAL THERAPY

1.Acute infection syndrome

2. Chronic infection

A. Symptomatic disease (including HIV-associated nephropathy)

B. Asymptomatic disease 1. CD4+ T cell count <500/

2. Pregnancy

3. Postexposure prophylaxis

## INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY

- Less than a 10 fold reduction in plasma HIV RNA by 4 weeks following the initiation of therapy
- A reproducible significant increase (defined as threefold greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
- Persistently declining CD4+ T cell numbers
- Clinical deterioation&Side effect

## POSTEXPOSURE PROPHYLAXIS

Postexposure prophylaxis is a necessary secondary preventive measure in health care workers and and those who are exposed to risk of HIV infection. Post exposure prophylaxis should be initiated as soon as possible within the first few hours and not later than 72hours of exposure.Two NRTI'S used for 4 weeks for less severe exposure and two NRTI'S plus other group of drugs.

MONITORING THE EFFICACY OF ART :

- Clinical improvement – gain in weight, decrease in occurrence & severity of HIV related infections
- Increase in total lymphocyte count
- Improvement in biological markers of HIV – CD4 count & RNA

PREVENTIVE MEASURES IN HIV INFECTION :

Health Education regarding safe sex practice,avoidance of IV drug abuse and tattooing is most important measure in preventing HIV transmission.All blood donors should be screened for HIV infection to prevent blood borne infections.

Avoiding unnecessary injections and use of sterilised disposable needle & syringes are also an effective measures in preventing HIV transmission.

Pregnant women with HIV infection should be advised to avoid pregnancy to reduce the mother to fetus transmission.

CLASSIFICATION OF ANTI RETROVIRAL DRUGS

NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

| DRUGS | DOSE | COMMON SIDE EFFECTS |
|---|---|---|
| ZIDOVUDINE | 200mg tds or<br>300 mg bd | Anaemia, neutropenia, lactic acidosis, cardio toxicity |
| DIDANOSINE | 200mg bd | Peripheral neuropathy, pancreatitis, hepatitis. |
| ZALCITABINE | 0.75mg tds | Peripheral neuropathy, aphthous ulcers, hepatitis. |
| STAVUDINE | 40mg bd | Peripheral neuropathy, pancreatitis, hepatitis. |
| LAMIVUDINE | 150mg bd | Rash and peripheral neuropathy |
| EMTRICITABINE | 200 qid | Skin discoloration and hepato toxicity. |
| ABACAVIR | 300 bd | Rash, fever. |
| TENOFOVIR | 300 qid | Gastrointestinal distress. Renal toxicity. |

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

| DRUGS | DOSE | COMMON SIDE EFFECTS |
|---|---|---|
| NEVIRAPINE | 200mg od | Skin rash, hepatotoxicity. |
| DELAVIRIDINE | 400 mg tds | Skin rash, hepatotoxicity |
| EFAVIRENZ | 600 mg od | Skin rash, neurological disturbances |
| EDRAVIRINE | 200 mg bd | Skin rash. |
| RILIPIVIRINE | 25 mg qid | Dizzinesss,nausea,vomiting, neurological disturbances |

PROTEASE INHIBITORS

| DRUGS | DOSE | COMMON SIDE EFFECTS |
|---|---|---|
| SAQUINAVIR | 1000mg bd | GI disturbances, dyslipidemia, PR and QT interval prolongation |
| RITONAVIR | 600 mg bd | GI disturbances, dyslipidemia, hepatitis |
| INDINAVIR | 800 mg tds | Dyslipidemia, renal stones. |
| NELFINAVIR | 750 mg tds | GI disturbances, dyslipidemia, |
| AMBRANAVIR | 1200 mg bd | GI disturbances, dyslipidemia, renal stones. |
| LOPINAVIR | 400mg /100mg bd | GI disturbances, dyslipidemia, PR and QT interval prolongation |
| ATAZANAVIR | 400 mg qid | GI disturbances, dyslipidemia, PR and QT interval prolongation, skin rash. |
| TIPRANAVIR | 500 mg bd | GI disturbances, dyslipidemia, skin rash, hepatitis, intracranial hemorrhage |
| DARUNAVIR | 600 mg bd | GI disturbances, dyslipidemia, skin rash, hepatitis. |

ENTRY INHIBITORS

| DRUGS | DOSE | COMMON SIDE EFFECTS |
|---|---|---|
| ENFUVIRTIDE | 90 mg sc bd | Skin rash, local injection reaction, bacterial pneumonia |
| MARAVIROC | 150 to 600 mg bd | Hepatotoxicity, skin rash, gastro intestinal disturbances, musculoskeletal symptoms. |

INTEGRASE INHIBITORS

| DRUGS | DOSE | COMMON SIDE EFFECTS |
|---|---|---|
| RALTEGAVIR | 400mg bd | GI disturbances, muscle weakness, rhabdomyolysis. |
| ELVITEGRAVIR | Under trial | Under trial. |

# CARDIOVASCULAR ABNORMALITIES IN HIV PATIENTS

HIV infection is the one of the leading cause of acquired heart disease throught the world. Cardiovascular abnormalities are the most common cause of death in HIV patients Various heart diseases have been reported in approximately 40% of autopsy cases and during life by echocardiography in around 25% of patients with AIDS.Initially cardiomyopathy was the predominant cardiac complication,but after the introduction of HAART coronary artery disease and other atherosclerotic vascular disease are becoming the the most common cardiac complication in HIV patients. But often these are underdiagnosed.

HIV tends to persist in reservoir cells(dendritic cells) of myocardium and cerebral cortex even after antiretroviral therapy.These cells are playing a major role in development of pathogenesis of cardiac manifestations.

Cardiac complications occur in late stage of the disease with low CD4count .The most common cardiovascular complications in HIV patients include systolic and diastolic dysfunction,pericardial effusion and dilated cardiomyopathy.

Other less common complications include infective endocarditis, nonbacterial thrombotic endocarditis, pulmonary hypertension,vasculitis, accelerated atherosclerosis and coronary artery disease and arrhythmias .

Various mechanisms have been described in pathogenesis of cardiac complications in HIV patients.

The possible mechanisms include

1.AIDS related myocarditis

Reservoir cells(dendritic cells) in myocardium cause release of various cytokines in respose to HIV infection and leads to progressive tissue damage.

2.Autoimmunity

Cardiac specific autoantibodies have been reported in upto 30% of HIV related cardiac abnormalities.HIV has a direct effect on potentiating effect on leukocyte interaction with cardiovascular tissues leading to ECM degradation,myocyte hypertrophy and replacement fibrosis.Antibodies to highly cardiac specific protein Beta myosin have been found higher levels in HIV patients with myocardial disease than those without HIV infection.

3.Nutritional deficiencies

Deficiencies of selenium,betacarotene,vitamin Bgroup A&E,zinc and magnesium have been implicated in pathogenesis.

4.Drug toxicity

Anti retroviral therapy NRTI'S and anticancer therapy doxorubicin used for Kaposi sarcoma are most commonly associated with cardiotoxicity

Zidovudine causes diffuse destruction of cardiac mitochondrial structures and inhibition of mitochondrial DNA replication.Lactic acidosis due to mitochondrial dysfunction also aggravates the myocardial dysfunction.

5.Opportunistic infections

Infections have been implicated in pathogenesis of cardiac involvement in HIV infection include Toxoplasmosis,Cryptococcosis, Cytomegalovirus, Candida spp, Pneumocytis carinii ,Microsporidium spp,Histoplasma capsulatum,atypical mycobacterium and aspergillus.

## LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

HIV patients with left ventricular dysfunction can be asymptomatic or may present with features of heart failure .Patients with encephalopathy are more likely to die of heart failure than those without encephalopathy .Myocarditis is the most important factor implicated in the pathogenesis of left ventricular dysfunction.

HIV infection increases the various cytokine release like TNF alpha which causes myocardial damage and dilated cardiomyopathy which is also an important cause of LV systolic dysfunction.Various opportunistic infections are also playing a major role in the pathogenesis of left ventricular dysfunction

Nutritional deficiencies like selenium and vitamin B12 also associated with myocardial dysfunction.Levels of carnitine ,growth hormone and thyroid hormones are also altered in HIV infection which leads to LV dysfunction.

Echocardiography is used in assessing the wall thickness ,ejection fraction and fractional shortening .Diuretics,beta blockers and angiotensin converting enzyme (ACE) inhibitors are used in managing the patients with LV systolic dysfunction .

## DIASTOLIC DYSFUNCTION

Left ventricular diastolic dysfunction seems to be a common cardiac disorder in HIV-infected patients and is often associated with myocardial hypertrophy.

The pathogenesis of HIV associated diastolic dysfunction is likely multifactorial.First although it remains controversial, several studies suggest that hypertension is associated with antiretroviral use ,including prolonged duration of antiretroviral therapy and treatment with protease inhibitors .

HIV has a direct effect on cardiac myocytes and causes myocyte hypertrophy and replacement fibrosis which is the important factor in pathogenesis of diastolic dysfunction.Indivividual with HIV infection have high rates of inflammation which may predispose HIV patients to diastolic dysfunction.

Diastolic dysfunction occurs due to noncompliance of ventricle. Most of patients with diastolic dysfunction present with exertional dyspnoea.

Diagnosis can be confirmed by Echocardiography. Betablockers are the mainstay of treatment.

# DILATED CARDIOMYOPATHY

Dilated cardiomyopathy was first described in HIV infection in 1986. Incidence of dilated cardiomyopathy in HIV infection is <8%.Most of them are asymptomatic or may present with signs of failure.The increasing occurrence of HIV associated cardiomyopathy detected by autopsy studies and by echocardiographic fidings strongly suggests that a careful cardiologic evaluation should be made to detect early involvement of the heart in HIV patients. Direct action of HIV on myocardial tissue or release of the proteolytic enzymes are an important causes of dilated cardiomyopathy.

Various opportunistic infections ,Antiretroviral therapy like zidovudine and doxorubicin used in management of Kaposi sarcoma are related with cardiotoxicity and lead to development of dilated cardiomyopathy.Diagnosis of dilated cardiomyopathy can be made by ECG findings like nonspecific intraventricular conduction defects,RBBB &LBBB.Echocardiogarm is useful in assessing dilation of cardiac chambers ,hypokinesia, and the LV ejection fraction .Diuretics,beta blockers ,angiotensin converting enzyme (ACE) inhibitors and mineralocorticoid receptor antagonists are used in treating the patients with dilated cardiomyopathy with heart failure.

# PERICARDIAL EFFUSION

Incidence of pericardial effusion in HIV infection is 11%. Aymptomatic pericardial effusions are more common and some times pericardial effusion itself is suggestive of HIV infection.So HIV infection should be suspected in young patients with pericardial effusion or tamponade.Clinically significant effusions are usually caused by bacterial or viral or malignant disease.Unusual infections like nocardia,and herpes simplex infections can also cause pericardial effusion in association with cytomegalo virus infection.

Various mechanisms have been described in the pathogenesis of pericardial effusion in HIV infection.

Possible mechanisms include

1.Opportunistic infections

2.Malignancies-kaposi sarcoma and lymphoma

3.Capillary leak syndrome due to cytokine release

4.Uremic pericarditis due to HIV associated nephropathy

Usual manifestations of pericardial effusions include chest pain and breathing difficulty.

If patient develops pericardial tamponade hypotension,muffled heart sounds and elevated jugular venous pulse will be present.This is also known as Beck’s traid.

Diagnosis

1.ECG-low voltage QRS complex

2.CXR PA view – cardiomegaly

3.Echocardiogarm-RA&RV collapse in pericardial tamponade

4.Pericardial fluid analysis-gram stain/culture/malignant cells

Spontaneous resolution occurs in 40% of case of pericardial effusion.Pericardiocentesis should be done if patient develops cardiac tamponade.

INFECTIVE ENDOCARDITIS

Incidence of infective endocarditis in HIV population is 6%.Most common bacterial infections causing infective endocarditis in HIV patients are staphylococcus and salmonella species.Other organisms include aspergillus and candida species

Fulminant course of infective endocarditis occurs in late stages of disease in poorly nourished patients. Blood culture and echocardiogram are used in diagnosis of infectious endocarditis.IV antibiotics are according to culture&sensitivity are used in management.

Operative indications

1.Hemodynamically stable patients

2.Blood culture positivity after appropriate IV antibiotics.

3.Severe valvular deformity

## CARDIOVASCULAR MALIGNANCIES

Cardiovascular malignancies in HIV infection are usually metastatic diasease and occurs in advanced diaease.Kaposi sarcoma occurs in 35% of AIDS patients.It is also known as angiosarcoma.Human herpes virus 8 (HHV8) is the causative organism of Kaposi sarcoma.It occurs most commonly in homosexuals.Kaposi sarcoma is an endothelial neoplasm with a predilection in the heart for subpericardial fat around the coronary arteries.Symptomps are due to pericardial effusion associated with epicardial location of the tumour.Pericadial fluid in Kaposi sarcoma is typically serosanguinous without infection or malignant cells.

## PRIMARY CARDIAC MALIGNANCY

Primary cardiac malignancy in HIV patients is generally caused by cardiac lymphoma .Non Hodgkin lymphomas are 25 to 60 times more common in HIV patients.Cardiac lymphomas are the first manifestation of AIDS in 4% of patients.Cardiac lymphomas are associated with rapid progression of tamponade.Pericardial fluid analysis shows malignant cells but can be histologically normal.Although systemic chemotherapy with or without radiotherapy is beneficial, prognosis is poor

## ACCELERATED ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Human immunodeficiency virus infection may independently predispose to AMI(acute myocardial infarction) via combination of endothelial dysfunction,a heightened pro-inflammatory state,dyslipidemia and thrombosis.

Similarly,protease inhibitor therapy has the potential to induce an adverse metabolic phenotype that involves a similar pathogenic response that increase the risk of AMI particular during prolonged treatment.

The exact pathogenic role of HIV independent of associated modifiable and nonmodifiable risk factors is difficult to determine but may be important as a contributory factor in an already vulnerable patient.

HIV associated lipodystrophy is serious complication and patients with this syndrome are more prone to develop coronary artery disease and early recognition and treatment is effective measure in preventing coronary artery disease in patients with HIV infection.Chances of restenosis are also high after PCI because of accelerated atherosclerosis in HIV patients.

## PULMONARY HYPERTENSION

Incidence of pulmonary hypertension in HIV infection is 0.5%.Cause of pulmonary hypertension in HIV infection is multifactorial and poorly understood.Genetic factors such as increased frequency of HLA-DR6& DR52 and activation of alpha receptors have also been implicated in the pathogenesis of HIV associated pulmonary hypertension.

Left ventricular dysfunction due to global left ventricular dilation can result in mitral valve regurgitation which leads to development of secondary pulmonary hypertension.

## SYSTEMIC HYPERTENSION(SHT)

Incidence of Systemic hypertension before initiation was 20 to 25%.But after the introduction of ART incidence have been increased because of metabolic complications related with protease inhibitors.Posssible mechanisms include HIV induced vasculitis, endothelial dysfunction and atheromatous changes due to Antiretro viral therapy.

## RHYTHM DISORDERS&AUTUNOMIC DYSFUNCTION

Rhythm disturbances and sudden cardiac death are common in HIV infection and account for 20% of cardiac related deaths in HIV

infection.These rhythm disturbance are due to drugs like pentamidine and ganciclovir or associated electrolyte disturbances.

INDICATIONS FOR ECHOCARDIOGRAPHIC ASSEESSMENT OF HIV POSITIVE PATIENTS.

1.Possible baseline assessment at the time of diagnosis

2.Clinical manifestion of possible cardiac involvement

- Unexplained dyspnea,Pedal edema
- Raised JVP,Third & Fourth heart sound
- Cardiomegaly in Chest X-RAY

3.Viral infections

- Cytomegalo Virus,Epstein barr virus,
- Coxsackie virus,Adenovirus

4.History of Pre existing heart diseases

- LV systolic dysfunction due to all cause
- Valvular heart hisease
- Suspicion of infective endocarditis in i.v drug abusers

5.High Risk HIV Patients with

- Wasting,encephalopathy,CD4count <100/AIDS
- Potentially cardiotoxic medication
- Multiple Hospitalizations

6.Possible Monitoring every 1-2 years of asymptomatic HIV positive patients

7.Frequent assessment of HIV Positive Patients with Cardiovascular involvement

# CARDIOVASCULAR COMPLICATIONS OF DRUGS USED IN HIV INFECTION

| CLASS | DRUGS | SIDE EFFECTS |
|---|---|---|
| NRTI'S | Abacavir,tenofovir zidovudine,lamivudine,didanosine,zalcitabine | Lactic acidosis, hypotension,cardiomyopathy |
| NNRTI'S | Delaviridine, efavirenz, nevirapine | Myocardial ischemia,arrhythmias |
| Antibiotics | Erythromycin,clarithromycin, trimethoprim/sulfamethoxazole,rifampicin | Orthostatic hypotension,QT prolongation and Ventricular tachycardias |
| Antifungals | AmphotricinB ketoconazole,itraconazole | Hypertension,cardiomyopathy, Arrhythmias |

| | | |
|---|---|---|
| Antiviral agents | Foscarnet,ganciclovir | Reversible heart failure,ventricular tachycardias,hypotension |
| Antiparasitic agents | Pentamidine | Hypotension,ventricular arrhythmias |
| Chemotherapy agents | Vincristine,doxorubicin | Myocardial infarction ventricular arrhythmias,cardiomyopathy |

# MATERIALS AND METHODS

## PARTICIPANTS

200 HIV positive patients >12years of age coming to ART centre,Govt.Rajaji Hospital, Madurai.

## STUDY POPULATION :

This study was conducted among 200 HIV positive patients coming to ART centre, Govt.Rajaji Hospital, Madurai. CD4 count, ECG and Echocardiograrm were done in all the participants of the study. Cases were classified as HIV patients into four groups depending upon the CD4 cell count >500 stage1),CD4 cell count 200 – 500 (stage 2), and 50-200(stage 3) and <50 stage 4.

## Inclusion criteria

- Age >12 yrs
- Newly diagnosed HIV patients
- Patients on ART therapy

**Exclusion criteria:**

**Patients with**

- Valvular heart disease.
- Coronary artery disease.
- Congenital heart disease
- Rheumatic heart disease
- Thyroid disorders
- Pregnant women

**DATA COLLECTION:**

A detailed history with detailed clinical examination was done for the HIV positive individuals. The blood samples of people belonging to study groups were tested for CD4 cell count. ECG and echocardiogram were done in study group**.**

LABORATORY INVESTIGATIONS

Blood samples were collected from the study group and CD4 counts were obtained by flow cytometry. Here the cells were conjugated to monoclonal antibodies against CD3 and CD4 cell surface markers. These cells were then made to pass through a flow chamber and subjected to intersection by a LASER beam. The flourescent signals obtained from the LASER beam intersecting the cells were analysed and data

obtained helped delineate the different cell sub populations based on their cluster differentiation.12 lead ECG and Echocardiogram were done in study group.

## DATA ANALYSIS

The final data was entered onto Microsoft excel sheet 2007 version and statistical analysis was done using SPSS software and chi – square test. The results were considered very significant with p value $< 0.01$ and significant with p value $<0.05$.

## STUDY PROTOCOL:

- All cases were classified into 3 categories based on CD4 cell count
- 12 lead ECG and Echocardiogram were done in study group.

**Design of study:**

Prospective analytical study

**Period of study:**

5months (APRIL 2014 TO AUGUST2014)

**Collaborating departments:**

- ✓ Department of Medicine**,**
- ✓ Department of Cardiology
- ✓ Regional ART centre

**Ethical clearance** :Obtained

**Consent** :Individual written and informed consent.

**Analysis** :Statistical analysis-chi square test

**Conflict of interest** : NIL

**Financial support** : NIL

## OBSERVATION AND RESULTS

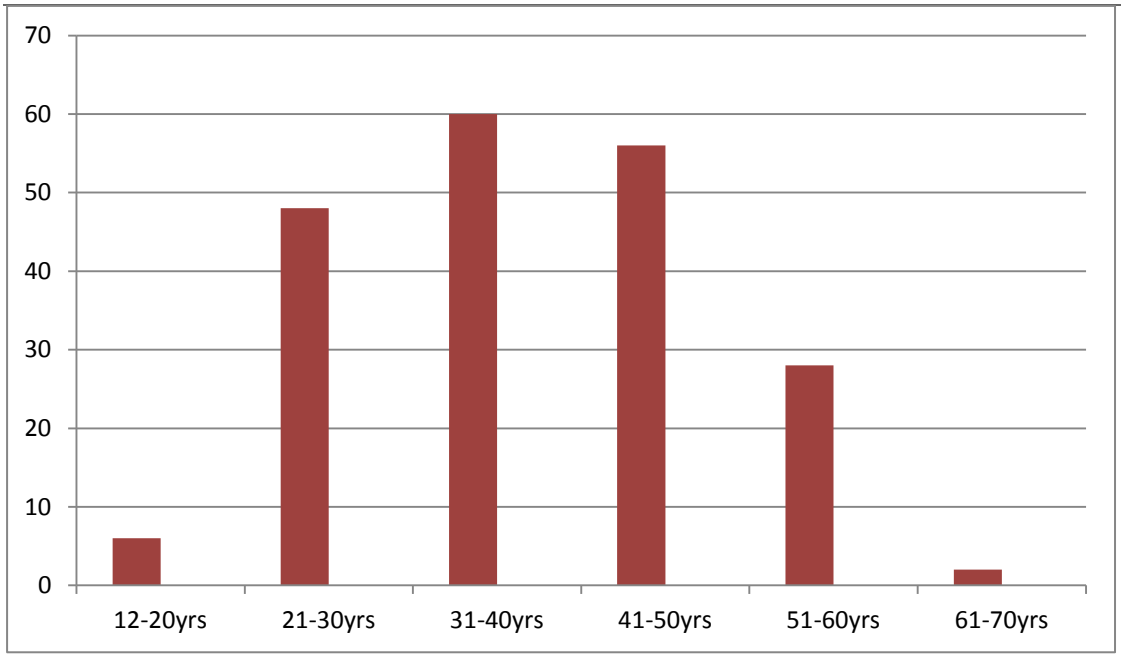
Table 1

Age distribution of the study population (n=200)

| AGE GROUP | FREQUENCY | PERCENTAGE |
|---|---|---|
| 12-20 | 6 | 3% |
| 21-30 | 48 | 24% |
| 31-40 | 60 | 30% |
| 41-50 | 56 | 28% |
| 51-60 | 28 | 14% |
| 61-70 | 2 | 1% |
| TOTAL | 200 | 100% |

Comments: About 54% of study population were in the age group of 21-40 years and 42% of study populalation were in the age group of 41-60 years

Chart1:Age distribution in the study population




Comment: Most of study population were in the age group of 21 to 50years

Table 2

Gender distribution in the study population(n=200)

| GENDER | FREQUENCY | PERCENTAGE |
|---|---|---|
| MALE | 109 | 54.5% |
| FEMALE | 91 | 45.5% |
| TOTAL | 200 | 100% |

Comments: Males and females were almost equal in the study population

Table3

Distribution of the study population according to ART status(n=200)

| ART STATUS | FREQUENCY | PERCENT |
|---|---|---|
| ON ART | 160 | 80% |
| NEWLY DIAGNOSED | 40 | 20% |
| TOTAL | 200 | 100% |

Comment:Most of the study population were on ART.

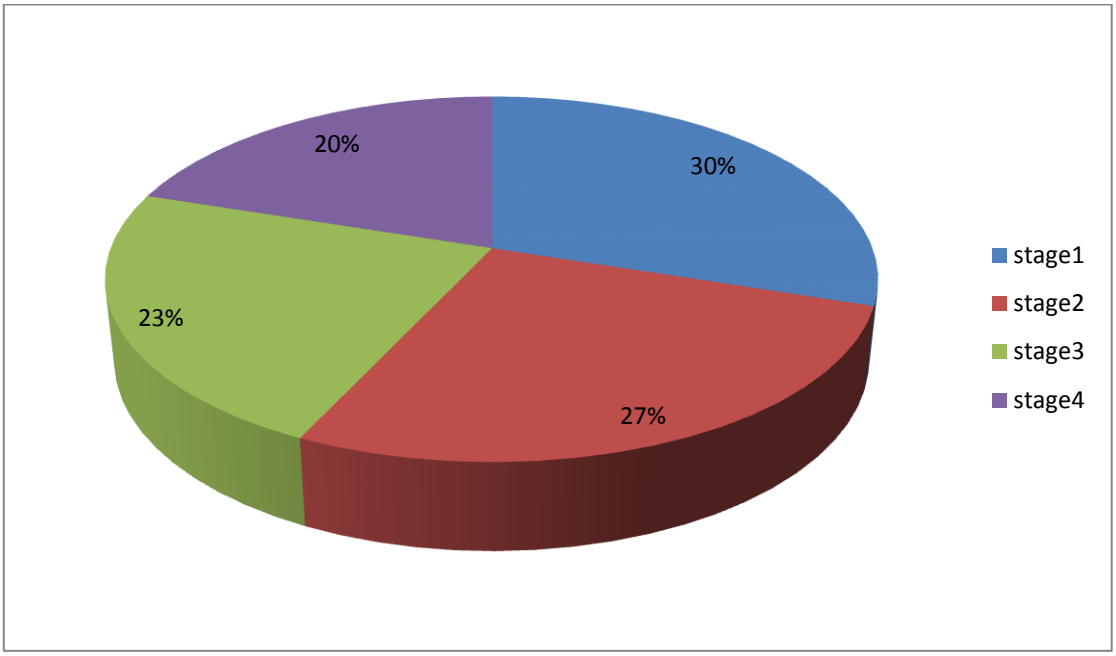
Table4

Staging of CD4 count in the study population(n=200)

| CD4 C0UNT | FREQUENCY | PERCENT |
|---|---|---|
| STAGE 1: >500 | 60 | 30% |
| STAGE 2: 200-500 | 54 | 27% |
| STAGE 3: 50-200 | 46 | 23% |
| STAGE 4: <50 | 40 | 20% |
| TOTAL | 200 | 100% |

Comments: About 57% of population in the study group were stage 1& 2 and about 43% of population in the study group were stage 3 & 4.

Chart2:CD4 count staging in the study population




Comments: About 57% of the study population were in stage 1&2 and 43% of study population in stage 3&4 .

Table 5

Prevalence of ECG abnormalities in the study population (n=200)

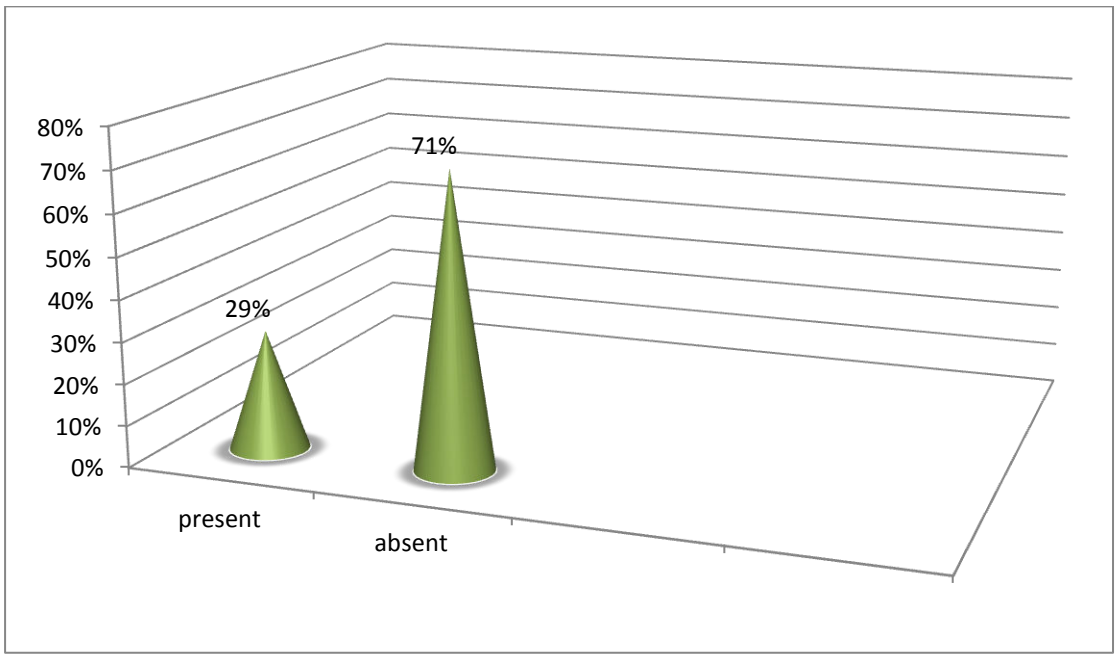
| ECG ABNORMALITIES | FREQUENCY | PERCENTAGE |
|---|---|---|
| PRESENT | 58 | 29% |
| ABSENT | 142 | 71% |
| TOTAL | 200 | 100 |

ECG abnormalities in the study population

| ECG ABNORMALITIES | FREQUENCY | PERCENTAGE |
|---|---|---|
| Poor progression of R wave | 26 | 13% |
| Low voltage QRS | 18 | 9% |
| RBBB | 10 | 5% |
| LBBB | 4 | 2% |
| TOTAL | 58 | 29% |

Comments:ECG abnormalities were present in 29% of the study population ant most common finding was poor progression of R wave.

Chart3:Prevalence of ECG abnormalities in study population (n=200)




Comments : ECG abnormalities were present in about 29% of study population .

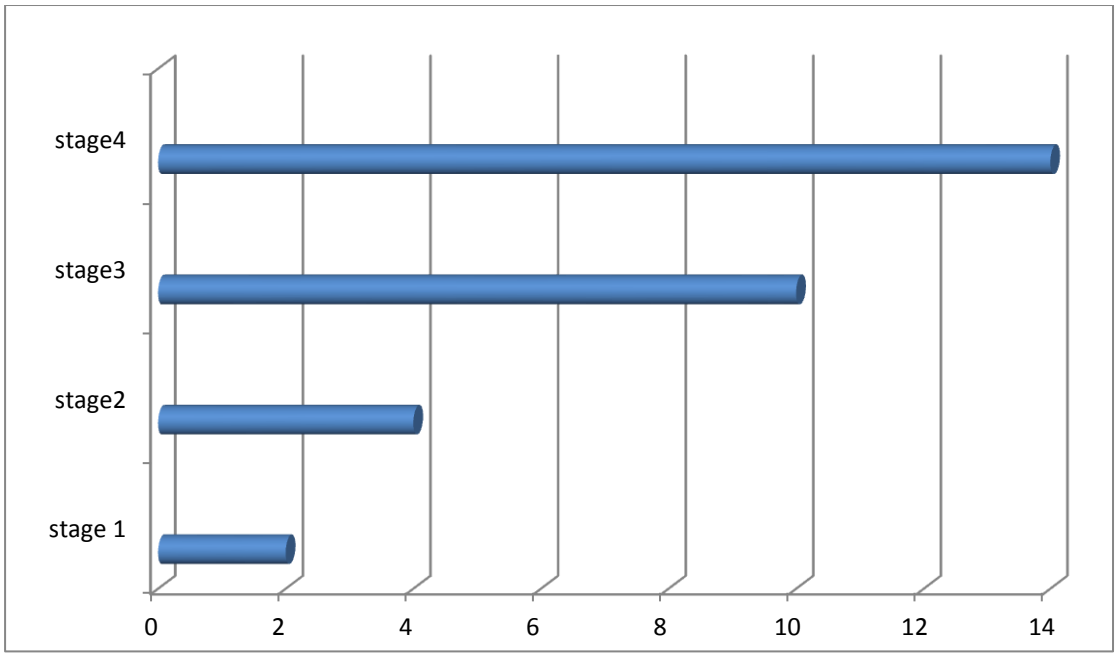
Table6

Prevalence of pericardial effusion in the study population(n=200)

| PERICARDIAL EFFUSION | FREQUENCY | PERCENTAGE |
|---|---|---|
| PRESENT | 30 | 15% |
| ABSENT | 170 | 85% |
| TOTAL | 200 | 100% |

Comments: Pericardial effusion was present in around 15% of study population.P value is <0.001 signnificant .

Chart4:CD4 count staging and pericardial effusion in the study group




P value;<0.012 significant

Comments: The difference in proportions of pericardial effusion in stage 1&2 and stage 3&4 is statistically significant and prevalence of pericardial effusion showed a close association with decreasing CD4 count.

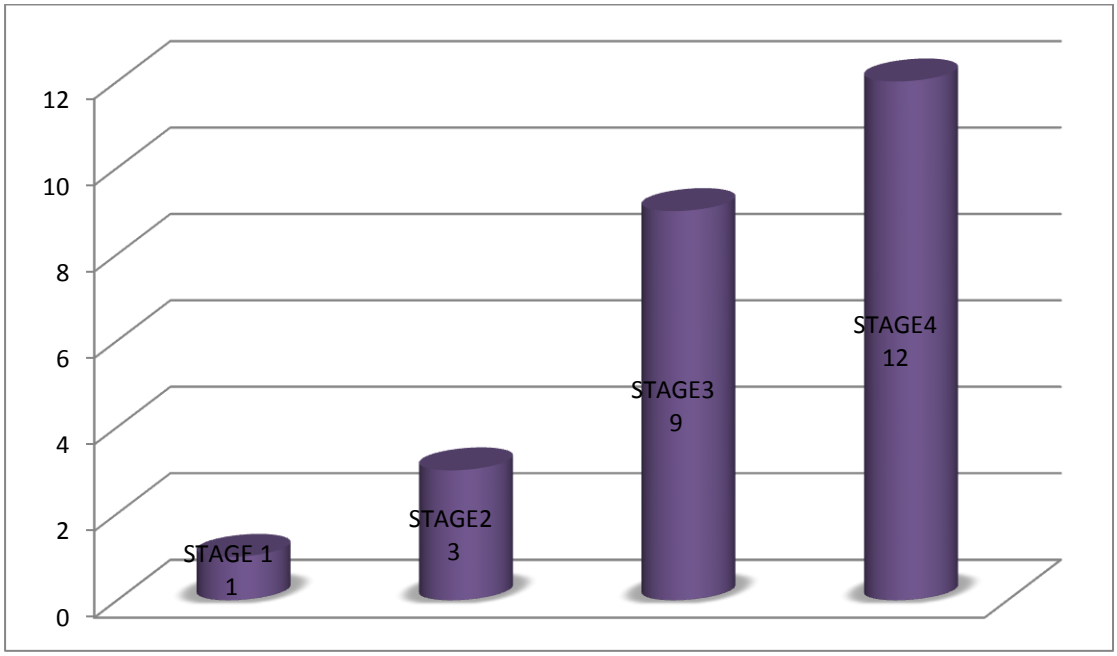
Table 7

Prevalence of systolic dysfunction in the study group(n=200)

| SYSTOLIC DYSFUNCTION | FREQUENCY | PERCENTAGE |
|---|---|---|
| PRESENT | 26 | 13% |
| ABSENT | 174 | 87% |
| TOTAL | 200 | 100% |

Comment: Systolic dysfunction was present in around 13% of study population.P value is <0.001 significant.

Chart5:CD4 count staging and systolic dysfunction in the study group(n=200)




P value <0.018 significant. Comments:The difference in proportions of systolic dysfunction in stage 1&2 and stage 3&4 is statistically significant and prevalence of systolic dysfunction showed a close association with decreasing CD4 count.

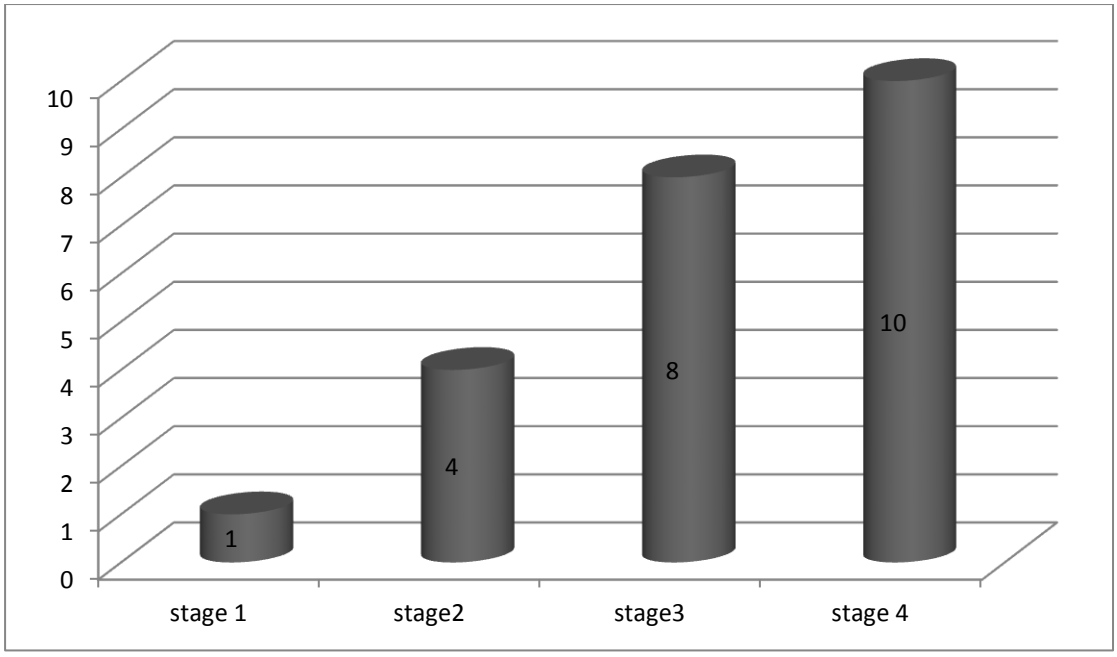
Table 8

Prevalence of diastolic dysfunction in the study population(n=200)

| DIASTOLIC DYSFUNCTION | FREQUENCY | PERCENTAGE |
|---|---|---|
| PRESENT | 23 | 11.5% |
| ABSENT | 187 | 88.5% |
| TOTAL | 200 | 100% |

Comment: Diastolic dysfunction was present in around 11.5% of study population.P value is <0.001 significant

Chart6:CD4 count staging and diastolic dysfunction in the study group(n=200)




P value <0.046significant

Comments: The difference in proportions of diastolic dysfunction in stage 1&2 and stage 3&4 is statistically significant and prevalence of diastolic dysfunction showed a close association with decreasing CD4 count

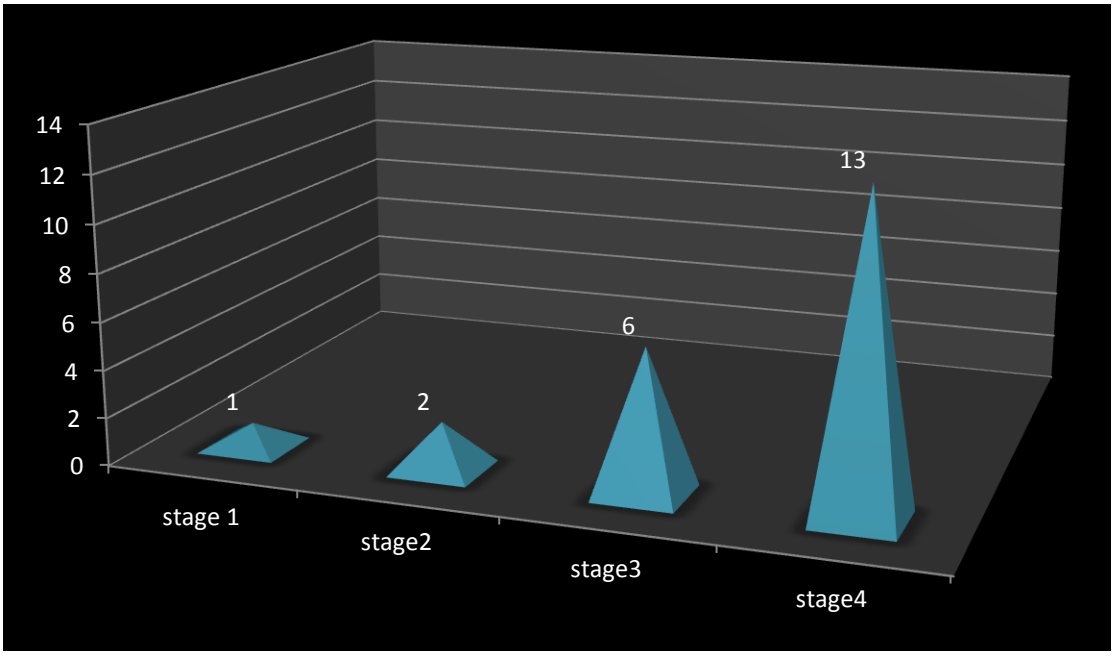
Table 9

Prevalence of dilated cardiomyopathy in the study population (n=200)

| DCM | FREQUENCY | PERCENTAGE |
|---|---|---|
| PRESENT | 18 | 9% |
| ABSENT | 182 | 91% |
| TOTAL | 200 | 100% |

Comment:Dilated cardiomyopathy was present in around 9% of study population.P value is <0.001 significant

Chart 7:Prevalence of dilated cardiomyopathy in the study population




P value <0.023 significant

Comments: The difference in proportions of dilated cardiomyopathy in stage 1&2 and stage 3&4 is statistically significant and prevalence of dilated cardiomyopathy showed a close association with decreasing CD4 count

Table10

Prevalence of other abnormalities in the study population(n=200)

| OTHER ABNORMALITIES | FREQUENCY | PERCENTAGE |
|---|---|---|
| RWMA | 3 | 1.5% |
| INFECTIVE ENDOCARDITIS | 1 | O.5% |
| PULMONARY HYPERTENSION | 4 | 2% |
| TOTAL | 8 | 4% |

Comments:Prevalence of other cardiac abnormalities were present in 4% of the study population

Table 11

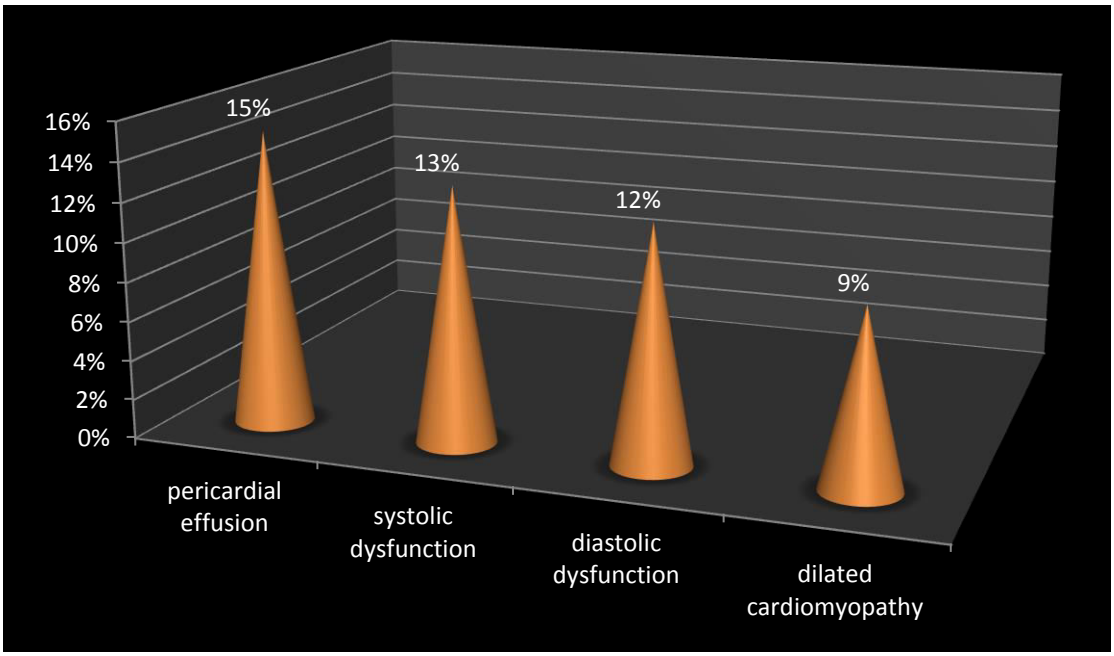
Correlation of various cardiac abnormalities and CD4 count

| Cardiac abnormalities | stage1 | stage 2 | stage 3 | Stage4 | Total | P value |
|---|---|---|---|---|---|---|
| Pericardial effusion | 2 | 4 | 10 | 14 | 30 | 0.012 |
| Systolic dysfunction | 2 | 3 | 9 | 12 | 26 | 0.018 |
| Diastolic dysfunction | 1 | 4 | 8 | 10 | 23 | 0.046 |
| Dilated cardiomyopathy | 1 | 3 | 6 | 8 | 18 | 0.023 |
| RWMA | 0 | 1 | 1 | 1 | 3 | 0.453 |
| Infective endocarditis | 0 | 0 | 1 | 0 | 1 | 0.665 |
| Pulmonary hypertension | 1 | 2 | 1 | 0 | 4 | 0.836 |

COMMENTS:

- All the cardiac abnormalities were prevalent in stage 3&4 and the p value is significant
- There was a statistically significant positive linear correlation between the CD4 count and cardiac abnormalities.i.e decrease in CD4 count had a corresponding increasing cardiac abnormalities.

Chart 8:Prevalence of cardiac abnormalities in the study population




Comments:Pericardial effusion was the most common abnormality seen in the study population and all the abnormalities had statistically significant p value <0.001

# DISCUSSION

Cardiovascular abnormalities are more common in HIV infection in late stages of disease .This study was conducted in 200 HIV patients including newly diagnosed and patients on ART attending ART clinic,Government Rajaji Hospital,Madurai.The study population were divided into 4 groups according to CD4 count.About 54% of study population were in the age group of 21-40 years and 42% of study populalation were in the age group of 41-60 years.

Around 70% of study population were on ART and 30% of the study population were newly diagnosed.Gender distribution were also almost equal in the study group.ECG and Echocardiography were performed in the study population.

In this study most of the patients with HIV infection had echocardiac abnormalities which were clinically quiescent.This suggests that echocardiographic screening is important tool for diagnosing subclinical cardiac abnormalities.

Pericardial effusion was the most commonly observed finding in HIV patients.It was seen in around 15% of cases and among that most of the cases were in stage 3&4(CD4 count<200) with the spectrum ranging from asymptomatic mild effusion to massive pericardial effusion.

Pericardial effusion is the most common cardiac problem associated with shortened survival . Causes of pericardial effusion in HIV infection include tuberculosis,secondary infections ,malignancy and part of generalised effusive process. Echocardiography is the diagnostic procedure and pericardiocentesis is needed in symptomatic patients.

Systolic dysfunction was present in 13% of patients with the p value <0.001.Most of patients were aymptomatic and had mild LV systolic dysfunction and were in stage 3&4.Only few patients were asymptomatic. Systolic dysfunction is an important cause of morbidity and mortality and symptomatic heart failure occur in 6% patients with advanced illness. Causes include myocarditis ,dilated cardiomyopathy and coronary artery disease.

Diastolic dysfunction was also most commonly observed finding in this study.It was seen in 12% of patients with p value<0.001and majority of the patients had were in stage 3&4 and most of the patients had exertional dyspnea.Diastolic dysfunction is due to ventricular filling abnormalities due to noncompliance of the ventricle.

Dilated cardiomyopathy (DCM) was found in 9% of the patients in the study group with the p value <0.001and most of the cases were in stage 3&4.

Most common causes of DCM in HIV infection include myocarditis,opportunistic infections,nutritional and drug induced especially zidovudine.

Other cardiac abnormalities seen in the study group were regional wall motion abnormality (RWMA),infective endocarditis (IE) and pulmonary hypertension (PHT) which were statistically not significant. From this study we conclude that all cardiac abnormalities occur in late stage of HIV patients with low CD4 count .As the CD 4 count decreases cardiovascular abnormalities increases.So echocardiographic screening is mandatory in HIV patients with CD4 count<500/micrlitre.

Eventhough decrease in CD4 count well correlates with the cardiac abnormalities,this study had some limitations.Because there may be some confounding factors like smoking ,alcohol and substance abuse ,diabetes mellitus,hypertension and dyslipidemia which can also cause these cardiac manifestations.

Although the exact mechanism of the pathogenesis of cardiovascular abnormalities in HIV is multifactorial and poorly understood,progression of cardiac problems in HIV infection can be reduced by effective antiretroviral therapy .

# SUMMARY

HIV infection is most oftenly associated with cardiac abnormalities.This study was conducted in 200 HIV patients including newly diagnosed and patients on ART and the study population were divided into 4 groups according to CD4 count.About 54% of study population were in the age group of 21-40 years and 42% of study populalation were in the age group of 41-60 years.

Around 70% of study population were on ART and 30% of study population were newly diagnosed.Gender distribution were also almost equal in the study group.ECG and Echocardiography were performed in the study population.

Systolic dysfunction(13%) and diastolic dysfunction(12%) pericardial effusion(PE) (15%) and dilated cardiomyopathy(DCM)(9%) were most prevalent in the study group and the p value was <0.001,statistically significant and were seen most commonly in HIV patients receiving antiretroviral therapy

Other abnormalities like infective endocarditis(IE), regional wall motion abmormality(RWMA) and pulmonary hypertension(PHT) were seen in only few patients which were statistically not significant.

These cardiac abnormalities were more prevalent in stage 3 and 4 with CD4 count <200/microlitre.There is a positive linear correlation between prevalence of Systolic and diastolic dysfunction, pericardial effusion(PE) and dilated cardiomyopathy(DCM) with a fall in the CD4 count

# CONCLUSION

Cardiovascular abnormalities are more common and predictable complications in late stages of HIV infection.This study was done.

- To highlight the various cardiovascular abnormalities occurring in HIV infection.
- Many of these abnormalities are associated with increased morbidity and mortality .
- Pericardial effusion ,systolic and diastoloic dysfunction,and dilated cardiomyopathy are the most common cardiac abnormalities occurring in significant number of HIV patients with low CD4 count. So these parameters can also be used as predictors of disease progression.
- So all HIV patients with low CD4 count(<200/microlitre) should be screened for cardiac abnormalities.Early diagnosis and management of these complications is associated with increased survival rates and clinical outcomes in HIV patients .

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PROFORMA

Name: Age / Sex: Occupation:

**Presenting complaints:**

H/o chest pain, H/o palpitation, H/o breathing difficulty, H/o pedal edema, H/o syncope,

**Past History:**

H/o DM,HT,CKD,CVD, Drug intake, CAD, Thyroid disorders

**Clinical Examination:**

**General Examination:**

Consciousness, pallor, jaundice,cyanosis, clubbing,pedal edema,lymphadenopathy

**Vitals:** Pulse Rate: Blood Pressure: Respiratory Rate:

**Systemic examination**: CVS: RS:

ABDOMEN: CNS:

**Laboratory investigations:**

CD4 count,ECG&Echocardiogram

MASTER CHART

| S.no | Age/sex | CD4count/microlitre | ECG changes | Pericardial eff | systolic dysfunctio | Diastolic dysfunction | DCM | RWMA | Infective endocarditis | Pulm hypertension |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 51/m | 678 | - | - | - | - | - | - | - | - |
| 2 | 19/f | 1720 | - | - | - | - | - | - | - | - |
| 3 | 21/m | 518 | - | - | - | + | | - | - | - |
| 4 | 51/m | 548 | + | - | - | - | - | - | - | - |
| 5 | 42/f | 1047 | - | - | - | - | - | - | - | - |
| 6 | 18/f | 910 | - | - | - | - | - | - | - | - |
| 7 | 21/f | 1200 | + | - | - | - | - | - | - | - |
| 8 | 53/m | 612 | - | - | + | - | - | - | - | - |
| 9 | 20/f | 42 | + | - | - | + | - | - | - | - |
| 10 | 38/f | 527 | - | - | - | - | - | - | - | - |
| 11 | 58/f | 57 | - | + | - | - | - | - | - | - |
| 12 | 30/f | 214 | + | - | - | - | - | - | - | + |
| 13 | 54/m | 647 | + | - | - | - | - | - | - | - |
| 14 | 20/m | 85 | - | + | - | | - | - | - | - |
| 15 | 24/m | 1590 | - | - | - | - | - | - | - | - |
| 16 | 21/f | 77 | + | - | - | - | - | - | - | - |
| 17 | 37/f | 98 | - | - | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 23/f | 612 | - | - | - | - | - | - | - | - |
| 19 | 53/f | 36 | + | - | + | - | - | - | - | - |
| 20 | 54/f | 148 | - | - | - | - | - | - | - | - |
| 21 | 45/m | 749 | - | - | - | - | - | - | - | - |
| 22 | 53/f | 160 | - | + | - | - | - | - | - | - |
| 23 | 36/f | 890 | + | - | - | - | - | - | - | - |
| 24 | 54/m | 40 | - | - | + | - | - | - | - | - |
| 25 | 59/m | 114 | + | - | - | - | - | - | - | - |
| 26 | 36/m | 102 | - | - | - | - | - | - | - | - |
| 27 | 55/m | 396 | - | - | - | - | - | - | - | - |
| 28 | 25/m | 26 | - | - | - | - | - | - | - | - |
| 29 | 47/f | 368 | + | - | - | + | - | - | - | - |
| 30 | 56/m | 103 | - | - | - | - | - | - | - | + |
| 31 | 23/f | 32 | - | - | - | - | - | - | - | - |
| 32 | 56/m | 690 | + | - | - | - | - | - | - | - |
| 33 | 26/m | 37 | + | - | - | - | - | - | - | - |
| 34 | 37/m | 707 | - | - | - | - | - | + | - | - |
| 35 | 39/f | 848 | - | - | - | - | - | - | - | - |
| 36 | 21/m | 59 | - | - | - | - | - | - | - | - |
| 37 | 35/f | 480 | - | - | - | - | - | - | - | - |
| 38 | 57/m | 960 | - | - | - | - | - | - | - | - |
| 39 | 40/m | 414 | + | + | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 43/m | 710 | - | - | - | - | - | - | - | - |
| 41 | 36/m | 998 | - | - | - | - | - | - | - | - |
| 42 | 39/m | 108 | - | - | - | - | - | - | - | - |
| 43 | 54/f | 414 | + | - | - | - | - | - | - | - |
| 44 | 23/f | 319 | - | - | - | - | + | - | - | - |
| 45 | 38/m | 26 | - | - | - | - | - | - | - | - |
| 46 | 34/m | 112 | - | - | - | - | - | - | - | - |
| 47 | 45/m | 714 | - | - | - | - | - | - | - | - |
| 48 | 40/f | 28 | - | - | - | - | - | - | - | - |
| 49 | 46/f | 122 | + | + | - | - | - | - | - | - |
| 50 | 39/m | 41 | - | - | - | + | - | - | - | - |
| 51 | 17/f | 29 | - | - | - | - | - | - | - | - |
| 52 | 24/f | 142 | + | - | - | - | - | - | - | - |
| 53 | 57/f | 69 | + | - | - | - | - | - | - | - |
| 54 | 40/m | 804 | - | - | - | - | - | - | - | - |
| 55 | 33/m | 40 | - | - | - | + | - | - | - | - |
| 56 | 40/f | 109 | - | + | - | - | - | - | - | - |
| 57 | 26/f | 78 | - | - | - | - | - | - | - | - |
| 58 | 42/f | 312 | + | - | - | - | - | - | - | - |
| 59 | 38/m | 39 | - | - | - | + | - | - | - | - |
| 60 | 24/m | 314 | + | - | - | - | - | - | - | - |
| 61 | 45/m | 647 | - | + | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 62 | 39/m | 298 | - | - | - | - | - | - | - | - |
| 63 | 56/m | 947 | + | - | - | - | - | - | - | + |
| 64 | 32/f | 418 | - | - | - | + | - | - | - | - |
| 65 | 56/m | 22 | - | - | + | - | - | - | - | - |
| 66 | 33/m | 936 | - | - | - | - | - | - | - | - |
| 67 | 38/m | 29 | - | - | - | - | - | - | - | - |
| 68 | 61/m | 290 | - | - | - | - | + | - | - | - |
| 69 | 57/f | 712 | - | - | - | - | - | - | - | - |
| 70 | 58/f | 110 | - | + | - | - | - | - | - | - |
| 71 | 51/m | 777 | - | - | - | - | - | - | - | - |
| 72 | 33/f | 78 | - | - | - | - | - | - | - | - |
| 73 | 56/f | 92 | - | - | - | - | - | - | + | - |
| 74 | 40/f | 38 | - | - | + | - | - | - | - | - |
| 75 | 25/f | 128 | - | - | - | - | - | - | - | - |
| 76 | 37/f | 814 | + | + | - | - | - | - | - | - |
| 77 | 22/f | 1812 | - | - | - | - | - | - | - | - |
| 78 | 27/m | 43 | - | - | - | - | - | - | - | - |
| 79 | 57/m | 137 | - | - | - | - | - | - | - | - |
| 80 | 50/f | 113 | + | - | - | - | + | - | - | - |
| 81 | 51/f | 24 | - | - | - | - | - | - | - | - |
| 82 | 35/f | 1047 | - | - | + | - | - | - | - | - |
| 83 | 36/m | 129 | - | - | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 84 | 59/f | 35 | + | - | - | + | - | - | - | - |
| 85 | 30/f | 629 | + | - | - | - | - | - | - | - |
| 86 | 37/m | 147 | - | + | - | - | - | - | - | - |
| 87 | 60/m | 110 | - | - | - | - | - | + | - | - |
| 88 | 35/m | 25 | - | - | + | - | - | - | - | - |
| 89 | 51/m | 639 | - | - | - | - | - | - | - | - |
| 90 | 36/f | 117 | - | - | - | - | - | - | - | - |
| 91 | 29/m | 818 | - | - | - | - | - | - | - | - |
| 92 | 27/f | 268 | - | - | - | + | - | - | - | - |
| 93 | 26/m | 276 | + | - | - | - | - | - | - | - |
| 94 | 60/m | 854 | - | - | - | - | - | - | - | - |
| 95 | 32/m | 32 | - | - | - | - | - | - | - | - |
| 96 | 52/m | 400 | - | - | - | + | - | - | - | - |
| 97 | 35/m | 408 | - | - | - | + | - | - | - | - |
| 98 | 31/m | 719 | - | - | - | - | - | - | - | - |
| 99 | 27m/ | 49 | - | - | - | - | - | - | - | - |
| 100 | 50/m | 153 | - | - | - | - | - | - | - | - |
| 101 | 31/f | 675 | - | - | - | - | - | - | - | - |
| 102 | 34/m | 1032 | - | - | - | - | - | - | - | - |
| 103 | 40/m | 245 | - | - | - | - | - | - | - | - |
| 104 | 26/m | 57 | - | - | - | - | - | - | - | - |
| 105 | 42/f | 178 | - | - | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 106 | 32/m | 891 | - | - | - | - | - | - | - | - |
| 107 | 46/m | 234 | + | - | - | - | - | - | - | - |
| 108 | 28/m | 1126 | - | - | - | - | - | - | - | - |
| 109 | 48/f | 897 | - | - | - | - | - | - | - | - |
| 110 | 53/m | 675 | - | - | - | - | - | - | - | - |
| 111 | 35/m | 648 | - | - | - | - | + | - | - | - |
| 112 | 33/m | 486 | - | - | - | + | - | - | - | - |
| 113 | 27/f | 68 | + | - | - | + | + | - | - | - |
| 114 | 55/m | 701 | - | - | - | + | - | - | - | - |
| 115 | 19/m | 28 | - | - | - | + | - | - | - | - |
| 116 | 33/f | 32 | + | - | - | - | - | - | - | - |
| 117 | 54/m | 80 | - | - | + | - | + | - | - | - |
| 118 | 27/m | 240 | - | - | - | - | - | - | - | - |
| 119 | 62/m | 100 | - | - | - | - | - | - | - | - |
| 120 | 56/f | 40 | - | - | + | - | - | - | - | - |
| 121 | 32/m | 316 | - | - | - | - | - | - | - | - |
| 122 | 42/m | 23 | - | + | - | - | - | - | - | - |
| 123 | 47/m | 260 | - | + | - | - | - | - | - | - |
| 124 | 34/f | 196 | - | - | - | - | - | - | - | - |
| 125 | 31/f | 114 | + | - | + | - | + | - | - | - |
| 126 | 47/f | 512 | - | - | - | - | - | - | - | - |
| 127 | 27/m | 209 | - | - | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 128 | 26/m | 72 | - | + | - | - | - | - | - | - |
| 129 | 48/f | 419 | - | - | + | - | - | - | - | - |
| 130 | 45/f | 227 | - | - | - | + | - | - | - | - |
| 131 | 37/m | 1314 | - | - | - | - | - | - | - | - |
| 132 | 40/f | 454 | - | - | - | - | - | - | - | - |
| 133 | 35/f | 69 | + | - | - | - | - | - | - | - |
| 134 | 39/f | 1012 | + | - | - | - | - | - | - | - |
| 135 | 28/f | 34 | - | - | + | - | - | - | - | - |
| 136 | 57/m | 139 | - | - | + | - | - | - | - | - |
| 137 | 41/f | 39 | - | - | - | - | - | - | - | - |
| 138 | 36/f | 406 | + | - | + | - | - | - | - | - |
| 139 | 27/f | 1678 | - | - | - | - | - | - | - | - |
| 140 | 39/m | 476 | - | - | - | + | - | - | - | - |
| 141 | 58/f | 49 | - | - | + | - | - | - | - | - |
| 142 | 37/m | 39 | - | - | - | - | - | - | - | - |
| 143 | 30/f | 898 | - | - | - | - | - | - | - | - |
| 144 | 42/m | 496 | - | - | - | - | - | - | - | - |
| 145 | 37/f | 308 | - | - | - | - | - | - | + | - |
| 146 | 40/m | 1012 | - | - | - | - | - | - | - | - |
| 147 | 29/m | 61 | - | - | - | - | - | - | - | - |
| 148 | 38/m | 176 | + | - | - | - | + | - | - | - |
| 149 | 36/m | 35 | - | - | + | - | - | - | - | - |

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|---|---|---|---|---|---|---|---|---|---|---|
| 150 | 50/m | 650 | + | - | + | - | + | - | - | - |
| 151 | 30/f | 30 | - | - | + | - | - | - | - | - |
| 152 | 27/f | 300 | + | - | - | - | - | - | - | - |
| 153 | 54/m | 26 | - | + | - | - | - | - | - | - |
| 154 | 37/m | 34 | - | - | - | - | - | - | - | - |
| 155 | 28/f | 728 | - | - | - | - | - | - | - | - |
| 156 | 46/f | 1509 | - | - | - | - | - | - | - | - |
| 157 | 28/m | 94 | - | - | - | - | - | - | - | - |
| 158 | 43/m | 41 | + | - | - | + | - | - | - | - |
| 159 | 36/f | 59 | - | - | - | - | - | - | - | - |
| 160 | 34/m | 1065 | - | - | - | - | - | - | - | - |
| 161 | 46/f | 897 | + | - | - | - | - | - | - | - |
| 162 | 29/m | 219 | - | + | - | - | - | - | - | - |
| 163 | 39/m | 46 | - | - | + | - | - | - | - | - |
| 164 | 45/f | 38 | - | - | - | - | - | - | - | - |
| 165 | 35/f | 244 | + | - | - | - | - | - | - | - |
| 166 | 22/m | 92 | - | - | - | - | - | - | - | - |
| 167 | 59/f | 560 | - | - | - | - | - | - | - | - |
| 168 | 40/f | 24 | - | - | + | - | - | - | - | - |
| 169 | 27/m | 77 | - | + | - | - | - | - | -- | - |
| 170 | 39/f | 949 | - | - | - | - | - | - | -- | - |

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|---|---|---|---|---|---|---|---|---|---|---|
| 171 | 45/m | 249 | - | - | - | - | - | - | - | + |
| 172 | 47/f | 369 | - | - | - | - | - | - | - | - |
| 173 | 34/f | 75 | - | - | + | - | - | - | - | - |
| 174 | 40/m | 340 | - | - | - | + | - | - | - | - |
| 175 | 28/m | 481 | - | - | + | - | - | - | - | - |
| 176 | 22/f | 68 | + | - | - | - | - | - | - | - |
| 177 | 34/m | 1412 | - | - | - | - | - | - | - | - |
| 178 | 43/m | 380 | - | - | - | - | - | - | - | - |
| 179 | 25/m | 679 | - | + | - | - | - | - | - | - |
| 180 | 42/f | 1208 | - | + | - | - | - | - | - | - |
| 181 | 39/f | 194 | + | - | + | - | + | - | - | - |
| 182 | 33/f | 838 | - | - | - | - | - | - | - | - |
| 183 | 29/m | 146 | - | - | + | - | - | - | - | - |
| 184 | 37/m | 914 | - | - | - | - | - | - | - | - |
| 185 | 22/f | 1844 | - | - | - | - | - | - | - | - |
| 186 | 60/f | 184 | + | - | - | - | + | - | - | - |
| 187 | 28/f | 1345 | - | - | - | - | - | - | - | - |
| 188 | 51/m | 612 | - | - | - | - | - | - | - | - |
| 189 | 25/f | 124 | - | - | - | - | - | - | - | - |
| 190 | 52/m | 568 | - | - | - | - | - | - | - | - |
| 191 | 38/m | 26 | - | - | + | - | + | - | - | - |
| 192 | 32/m | 517 | - | - | - | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 193 | 56/m | 49 | - | + | - | - | - | - | - | - |
| 194 | 53/f | 678 | - | - | - | - | - | - | - | - |
| 195 | 34/m | 890 | + | - | - | - | - | - | - | - |
| 196 | 31/f | 1149 | - | - | - | - | - | - | - | - |
| 197 | 54/m | 197 | - | - | - | - | - | - | - | + |
| 198 | 22/f | 80 | - | + | - | - | - | - | - | - |
| 199 | 25/m | 982 | - | - | - | - | - | - | - | - |
| 200 | 55/m | 1119 | - | - | - | - | - | - | - | - |

Ref.No.4459/E1/5/2014

Madurai Medical College,
Madurai -20. Dated: 27.05.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020. Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for May 2014 –
Approved list – reg.

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The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 12th May 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai. The following members of the Ethics Committee have attended the meeting.

| | | |
|---|---|---|
| 1.Dr.V.Nagarajan,M.D.,D.M(Neuro)<br>Ph: 0452-2629629<br>Cell No.9843052029<br>nag9999@gmail.com. | Professor of Neurology<br>(Retired)<br>D.No.72, Vakkil New Street,<br>Simmakkal, Madurai -1 | Chairman |
| 2.Dr.Mohan Prasad, MS.M.Ch.<br>Cell.No.9843050822 (Oncology)<br>drbkcmp@gmail.com | Professor & H.O.D of Surgical<br>Oncology (Retired)<br>D.No.32, West Avani Moola Street,<br>Madurai.-1 | Member<br>Secretary |
| 3.Dr.K.Parameswari, MD(Pharmacology)<br>Cell No.9994026056<br>drparameswari@yahoo.com. | Director of Pharmacology<br>Madurai Medical College. | Member |
| 4.Dr.S.Vadivel Murugan, MD.,<br>(Gen.Medicine)<br>Cell No.9566543048<br>svadivelmurugan_2007@rediffmail.com. | Professor & H.O.D of Medicine<br>Madurai Medical College | Member |
| 5. Dr.L.Santhanalakshmi, MD (Physiology)<br>Cell No.9842593412<br>dr.l.santhanalakshmi@gmail.com. | Vice Principal, Prof. & H.O.D.<br>Institute of Physiology<br>Madurai Medical College | Member |
| 6.Dr.A.Sankaramahalingam, MS.,<br>(Gen. Surgery)<br>Cell.No.9443367312<br>chandruhospitalmdu@gmail.com | Professor & H.O.D. Surgery<br>Madurai Medical College.<br>Madurai | Member |
| 7.Mrs.Mercy Immaculate<br>Rubalatha. M.A., Med.,<br>Cell.No.9367792650<br>lathadevadoss86@gmail.com | 50/5, Corporation Officer's<br>Quarters, Gandhi Museum Road,<br>Thamukam, Madurai-20. | Member |
| 8.Thiru.Pala.Ramasamy, B.A.,B.L.,<br>Cell.No.9842165127<br>palaramasamy2011@gmail.com | Advocate,<br>D.No.72,Palam Station Road,<br>Sellur, Madurai-20. | Member |
| 9.Thiru.P.K.M.Chelliah, B.A.,<br>Cell No.9894349599<br>pkmanden@gmail.com | Businessman,<br>21 Jawahar Street,<br>Gandhi Nagar, Madurai-20. | Member |

The following project was approved by the committee

| Name of the PG Student | Course | Name of the project | Remarks |
|---|---|---|---|
| Dr.G.Chinna Mariappan drcm86@yahoo.com. | PG in MD., (General Medicine) Govt. Rajaji Hospital & Madurai Medical College, Madurai | Study of Cardiac Abnormalities in HIV patients and their correlation with CD4 count. | Approved |

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the E thical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Chairman
Ethical Committee

Member Secretary
for Ethical committee

DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai- 20.

To
The above Applicant
-thro. Head of the Department concerned

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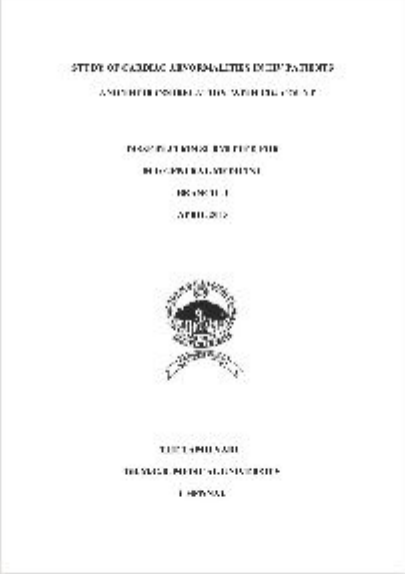

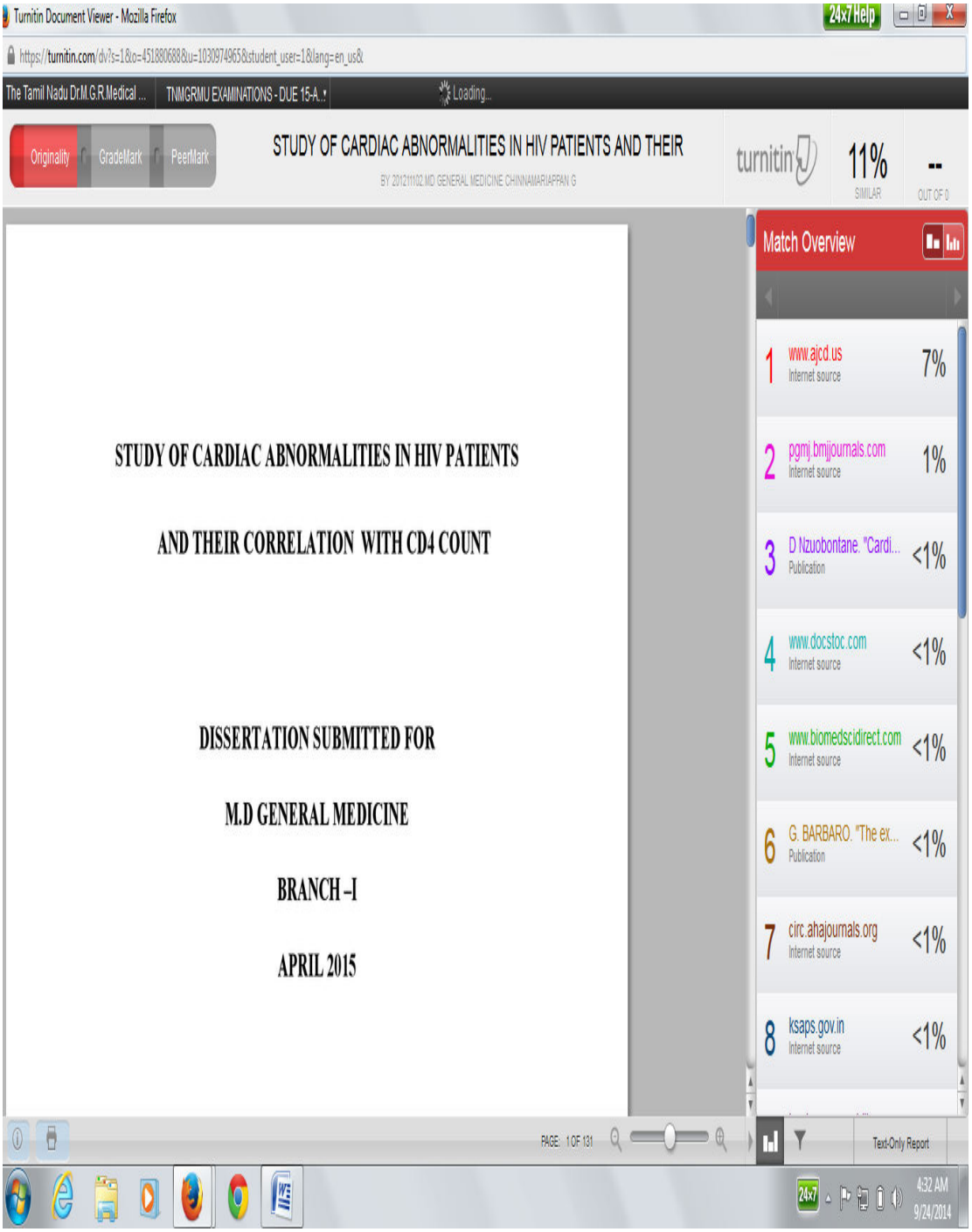
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